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Proposal for a

REGULATION OF THE EUROPEAN PARLIAMENT AND OF THE COUNCIL

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

Proposal for a

DIRECTIVE OF THE EUROPEAN PARLIAMENT AND OF THE COUNCIL

amending Directive 2001/83/EC on the Community code relating to medicinal products for human use

Proposal for a

DIRECTIVE OF THE EUROPEAN PARLIAMENT AND OF THE COUNCIL

amending Directive 2001/82/EC on the Community code relating to veterinary medicinal products

(presented by the Commission)

EXPLANATORY MEMORANDUM

I. GENERAL CONSIDERATIONS AND OBJECTIVES

1. On 1 January 1995, new Community procedures concerning the authorisation and surveillance of medicinal products came into force, superseding various procedures based on voluntary cooperation between the relevant national authorities¹. The European Agency for the Evaluation of Medicinal Products (the Agency) plays a central role in this system. Its aims include pooling the scientific expertise of Member States in order to ensure a high degree of protection for public health, ensuring free movement of pharmaceuticals, and making certain that Europeans have access to new generations of medicinal products.

Five years on, these goals are still relevant. But both the international and the European stakes have changed. Science is progressing radically, and new therapies are on the horizon. The existing legislation must therefore be adapted and thought must be given to a basic outline for the procedures for authorising the products to be placed on tomorrow's market.

Regulation (EEC) No 2309/93 provided for possible changes to these procedures. Its Article 71 states: "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 [medicinal products for human use] and in Chapter IV of Directive 81/851/EEC [medicinal products for veterinary use]".

On the basis of the provisions in Article 71 of Regulation No 2309/93, Cameron McKenna and Andersen Consulting were asked to carry out an audit of the Agency's procedures and operations. The results of this work are analysed and developed in the Commission report on the operation of Community procedures for authorising the placing of medicinal products on the market (COM...).

2. Given the experience acquired between 1995 and 2000 and the analysis of the comments by the various parties concerned (competent authorities of the Member States, pharmaceutical companies, doctors' and pharmacists' organisations and patient and consumer associations), it appeared necessary for the Commission to adapt certain provisions of Regulation (EEC) 2309/93. The word "adapt" should be emphasised, as although some procedures and administrative provisions must be amended or replaced by new ones, neither the general principles nor the basic structure of the "centralised" procedure and, therefore, the Agency, as established by the founding act of 1993, are called into question.

The functioning of the Single Market in the pharmaceuticals field and the maintenance of a high level of public health protection remain the two main, inseparable objectives of this legislation and any proposed amendment must be judged in this light. The legislation will be of growing benefit to patients by providing them with faster access to increasingly innovative medicinal products, whilst guaranteeing a high level of safety, and to the pharmaceutical industry – the

¹ Directives 93/39/EEC, 93/40/EEC, 93/41/EEC and Regulation (EEC) No 2309/93.

source of this innovation through its investment in research and development – by allowing it to become more competitive, since it will endeavour to benefit as effectively as possible from Community integration.

3. Another new dimension to be considered since the 1993 context is the enlargement of the European Union. As in other areas, the future enlargement obviously raises the question of whether certain procedural arrangements for the regulation of medicinal products are appropriate and particularly whether it will be possible in a context designed in 1993 for 12 states for 20, 25 or 28 Member States to conduct scientific debates and take decisions effectively. For example, it is imperative that the procedure by which the Commission takes decisions under the centralised procedure, the composition of the scientific committees and the Agency's Management Board should be reviewed, as should their internal rules of procedure, in order to maintain (or even increase) efficiency and transparency.
4. The amendments linked to accommodating the enlargement of the Community should therefore be set against the ever present need to maintain and strengthen the internal market and to prevent any undermining of the progress achieved so far, particularly since 1995. Moreover, in this field, where the immense technical and scientific progress of the future will be inconceivable without the globalisation of research and development and to some extent the assessment rules, there is no alternative to integrating the management of resources and taking decisions at Community level.
5. Consequently, alongside the considerations linked to the experience of six years of implementation of the centralised procedure and the operating of the Agency, account should also be taken of the current progress of applied sciences in the pharmaceutical field (particularly in the field of biotechnology) and also probable future developments (for example, the increased development of the technologies underlying gene therapy, current developments in pharmacogenomics and xenogenic somatic therapy trials). These considerations should also be viewed in the light of ever-increasing globalisation, in particular between the world's three major pharmaceutical "regions", namely Europe, North America and Japan. Globalisation in research and development, which is still limited primarily to the new, potentially very innovative medicinal products, is doubtless the result of the internal strategies of big pharmaceutical companies, but it also reflects genuine scientific and economic necessities.
6. Furthermore, scientific globalisation must not be allowed to overshadow its counterpart, the globalisation of certain regulatory practices, in particular scientific and technical criteria for the assessment of medicinal products. The increasingly rapid spread of new technologies in R&D in the field of medicinal products now requires an adaptable regulatory environment based on stable, well-defined principles which are of a genuinely international dimension. This "global" dimension of regulatory requirements is clearly one of the main changes since the beginning of the 1990s, when the current Community system for marketing authorisation was designed. No regulatory environment for authorising medicinal products can now be considered modern, effective and sustainable if it is developed in isolation. The Commission and the Member States are already participating very actively in the

context of the ICH² and the VICH³ in international discussions on technical and scientific requirements for human and veterinary medicinal products. However, it is also very important for the regulatory framework of the Community marketing authorisation system to take due account of this new global environment in order to allow the EU to play a full role on the international stage, in particular alongside its American and Japanese partners.

7. All these regulatory and technical considerations must, of course, take account of the fact that one of the main objectives of the development and operating of the single market in medicinal products is to achieve tangible benefit to patients' health. The centralised system of authorisation has demonstrated its ability in the assessment of the quality, safety and efficacy of medicinal products. The time within which the medicinal products are made available is satisfactory, as described in the abovementioned Commission report. The average length of procedures is approximately 270 days, which is entirely comparable with the approval periods of the other major non-Community systems, such as the US "Food and Drug Administration". Furthermore, these periods have been considerably reduced for categories of medicinal products authorised under the centralised procedure compared with the situation prior to 1995, when the same medicinal products were mostly covered by the concertation procedure set up by Directive 87/22/EEC⁴.

Although the adoption of Regulation (EC) 141/2000 of the European Parliament and of the Council on orphan medicinal products⁵ helped improve the conditions of access by patients to certain new medicinal products, there is still scope under the centralised procedure to further increase the availability of new treatments. The introduction of an accelerated authorisation procedure for certain medicinal products of major interest to public health because of their innovative nature or because they fall into a category where there are few alternative therapies, and the introduction of a conditional authorisation allowing early marketing of the medicinal products as soon as the results of the studies available show there are significant benefits for patients, will allow European citizens to benefit as early as possible from research.

8. However, it would not be possible to introduce these new provisions to the detriment of patient safety, the need for market surveillance and the strengthening of pharmacovigilance. The analysis of the risk/benefit balance for any new medicinal product must remain the basis for any administrative decision regarding it, irrespective of the authorisation procedure applied. Although the provisions in force have provided a high level of safety, some of the existing procedures need to be improved to increase the overall efficiency of the pharmacovigilance and market surveillance system, particularly to take account of the emergence of new therapies and an increase in the size of the market to be monitored as a result of the forthcoming enlargement of the European Union. At the heart of this system, the Agency must be given a stronger role. The Commission's procedures for taking decisions or adopting emergency measures must also be amended in this context, in

² International Conference on Harmonisation of Technical Requirements for the Registration of Veterinary Pharmaceutical Products.

³ International Conference on Harmonisation of Technical Requirements for the Registration of Veterinary Pharmaceutical Products.

⁴ OJ L 15, 17.1.1987, p. 38. This Directive was repealed by Directive 93/41/EEC (OJ L 214, 24.8.1993, p. 40) when the Agency and the centralised procedure were created.

⁵ OJ L 18, 22.1.2000, p. 1.

order to increase speed and efficiency. In more concrete terms, it is proposed to increase the frequency of periodic safety reporting, to expand the reporting requirements for adverse reactions, in particular for serious adverse reactions, to make the use of a common international terminology for pharmacovigilance reporting more widespread, and to promote the general use of a database for this information.

9. In the veterinary field, most of the above considerations apply, subject to alterations linked to particular technical or scientific aspects. In this sector, a growing problem lies in the availability of veterinary medicinal products for certain species of animal or certain indications. Although this mainly concerns the revision of the Directive (consolidation)⁶ and the revision of Council Regulation (EEC) No 2377/90⁷, in the case of the procedures for implementing certain provisions and the definition of the field of application of the centralised procedure, the present proposal lays down exemptions or arrangements to take account of specific cases, such as certain immunological medicinal products for regional use or those used in the treatment of diseases covered by Community prophylactic measures.
10. Generally speaking, there are four main objectives to the revision of pharmaceutical legislation. They are based on the conclusions of the Commission Report which are particularly relevant to the centralised procedure and the Agency's responsibilities.

- To guarantee a high level of health protection for the people of Europe, particularly by providing patients, as swiftly as possible, with innovative and reliable products and through increased market surveillance thanks to a strengthening of monitoring and pharmacovigilance procedures. In the case of veterinary medicinal products, to improve animal health, particularly by increasing the number of medicinal products available.
- To complete the internal market in pharmaceutical products taking account of the implications of globalisation and to establish a regulatory and legislative framework that favours the competitiveness of the European pharmaceuticals sector.
- To meet the challenges of the future enlargement of the European Union.
- To rationalise and simplify the system as far as possible, thus improving its overall consistency and visibility, and the transparency of procedures and decision-making.

II. RECASTING

Even though the proposed changes do not affect the broad thrust and main lines of Regulation (EEC) No 2309/93 and are, in principle, no more than improvements made on the basis of experience gained in the operation of the system, it is nevertheless true that the text will have to undergo numerous modifications which will change its current presentation. Moreover, the adoption of the two consolidated directives in the human and veterinary health sector will mean having to replace all

⁶ OJ L
⁷ OJ L 224, 18.8.1990, p. 1.

references to all the old directives with references to the new articles in the consolidated directives. If all the articles concerned were amended, there would be a risk of ending up with a very complicated and practically unreadable proposal. Against this background, it is proposed to repeal Regulation (EEC No 2309/93 (*Article 78*)) and, for reasons of clarity, to replace it with a new act modelled on the regulation in force but enriched with all the new elements and adjustments to the consolidated directives. This represents a recasting of Regulation (EEC) No 2309/93, as a great many provisions are being amended and the regulation in force will be replaced by the new regulation.

In this connection, the grounds for this proposal follows the pattern of those for Regulation (EEC) No 2309/93, amended only on the basis of the new elements introduced into the operative provisions.

III. DETAILED CONTENT OF THE PROPOSAL

A. Centralised procedure for medicinal products for human use

1. The scope of this procedure still includes categories of medicinal products for which the procedure is obligatory and those for which it is optional. As regards substance, it is proposed to maintain the scope of the original Regulation subject to certain amendments resulting from the experience acquired over the past six years and scientific and technological progress.

This proposal lays down that the centralised procedure should remain compulsory for medicinal products resulting from biotechnical processes, in particular those using recombinant DNA technology. This definition covers gene therapy products, including the vectors used, and any medicinal product which contains a proteinaceous constituent obtained using recombinant DNA technology, whether or not the constituent is an active substance of the medicinal product. Products intended for cell therapy have to be considered as medicinal products requiring marketing authorisation if they are industrially manufactured. If cell therapy products are the result of any biotechnology process referred to in the Annex to this proposal, they will have to be authorised under the centralised procedure. The Commission refers in this respect to the interpretation of "medicinal products developed by means of biotechnological processes" given in its two Communications 94/C 82/04⁸ and 98/C 229/03⁹. The interpretation remains fully applicable to this proposal (*Article 3(1) and point 1 of the Annex*).

The main amendment proposed seeks to make this procedure also compulsory for any new active substance appearing on the Community market (*Article 3(1) and point 3 of the Annex*).

There are various arguments in favour of this field of application. For one thing, the acceptance and broad dissemination of biotechnical medicinal products is to a large extent explained by the introduction in 1995 of a Community procedure guaranteeing a common approach and a high level of expertise. For another, the cost of developing most of the molecules with high innovative potential does not allow them, from the

⁸ OJ C 82, 19.3.1994, p. 4.

⁹ OJ C 229, 22.7.1998, p. 4.

economic or sociological points of view, to be restricted to a few national markets and justifies a global, Community approach, giving them access from the outset to a continental market. In these circumstances and as regards the assessment costs, it should be remembered that the Agency had the possibility under Regulation (EC) No 297/95¹⁰ of reducing the fees linked to the authorisation or to maintaining the authorisation.

- This proposal provides for the centralised procedure to be optional for the other medicinal products which constitute therapeutic innovation. In addition, it is proposed to allow access to this procedure for medicinal products which, although "innovative", may be of benefit to society or to patients if they are authorised from the outset at Community level. This may apply in particular to certain medicinal products which cannot be supplied without a medical prescription (*Article 3(2)*).
- Finally, provision is made for Member States to have the possibility of authorising at national level the generic form of medicinal products authorised by the Community, on the condition that the harmonisation achieved at Community level is maintained. The manufacturers of these generic forms would thus henceforth have the choice between the two existing procedures (centralised and decentralised) for obtaining marketing authorisations (*Article 3(3)*).

2. Apart from the change to its name to reflect the comprehensive nature of its competence regarding medicinal products, the composition of the Scientific Committee responsible for the centralised procedure (*Article 5*) is changed (one representative per competent authority) to take account of the future enlargement. In addition, in order to maintain the necessary scientific representation, the possibility of coopting additional members has been introduced (*Article 54*). The possibilities for the Committee to create working parties or groups of experts and to delegate certain tasks to these groups are included in the legislation (*Article 50(2) and (3)*). Particular emphasis is placed on the creation of a standing working party attached to this Committee, responsible for the development and adoption of scientific opinions and providing advice to companies. The Commission considers the development of this service by the Agency of prime importance, particularly insofar as it may concern small and medium-sized businesses developing biotechnological medicinal products or firms working in the research and development of new therapies.
3. The centralised procedure itself is not changed substantially. One change is made to the appeal procedure for applicants who contest the scientific opinion of the Committee, in order to make the procedure more effective by better preserving the applicant's position (*Article 9(1) and Article 55(1), second subparagraph*). The context of the Commission's decision-making is altered. The current procedure has been highly criticised, as has already been mentioned, particularly because of its length. At present, the decision-making procedure is subject to a comitology procedure of the type III b)¹¹. It should first be noted that from the outset the

¹⁰ OJ L 35, 15.2.1995, p. 1; Regulation as last amended by Regulation (EC) No 2743/98, OJ L 345, 19.12.1998, p. 3.

¹¹ Within the meaning of Council Decision 87/373/EEC, OJ L 197, 18.7.1987, p. 33.

Commission has always followed the Agency's opinion on highly scientific matters. Every time the Regulatory Committee has been consulted, a favourable opinion has been adopted on the Commission's draft Decision, either unanimously or by qualified majority in a very small number of cases¹². Furthermore, the vast majority of these opinions¹³ were given by written procedure without a formal meeting of the Regulatory Committee – a possibility provided for under Regulation (EEC) 2309/93. The rare cases that gave rise to a formal vote at a meeting occurred in the first few procedures, that is when the centralised Community system was at the running-in stage.

Given the industry's criticisms (see the abovementioned Commission report), in the light of the experience acquired over six years and, finally, with the adoption of a new "Comitology" Decision by the Council on 28 June 1999 (1999/468/EC)¹⁴, it has proved necessary to reassess the decision-making procedure.

The preamble to the new Council Decision (recital 7) lays down that the regulatory procedure should be applied for measures of general scope, which is clearly not the case when a particular economic operator is granted a marketing authorisation for a specific medicinal product. Furthermore, experience has shown that decision-making in this specific context does not necessarily give rise to a particular problem likely to suspend or delay the taking of a decision. The Commission therefore proposes applying a consultation procedure to the taking of a decision within the meaning of Decision 1999/468/EEC, when the draft submitted by the Commission follows the Agency's scientific opinion, or applying a management procedure within the meaning of this Decision in all the other cases. In both cases, the deadlines are adapted in order to shorten the consultation phase with the Member States (*Articles 10 and 77*).

4. To meet patients' legitimate wish to have the swiftest possible access to certain innovative therapies with a major impact on public health, the proposal introduces two new ways of obtaining marketing authorisation. On the one hand, the applicant may apply for an accelerated assessment and decision, which therefore has priority over other procedures. The applicant must justify the request from the point of view of public health and the Scientific Committee may agree or refuse to give it priority. In any event, the usual assessment criteria based on the quality, safety and efficacy of the medicinal products must be met. This refers in particular, but not exclusively, to medicinal products to treat cancer, HIV infection, etc. (*Article 13(6)*). The second procedure introduced concerns the specific case of certain medicinal products which are likely, according to the studies available, to be of considerable benefit to patients, since the risk/benefit balance is favourable given the pathology – often serious – for which they are recommended. This proposal provides for the granting of a provisional authorisation of one year, subject to strict conditions and annual reassessment. The framework for the implementation of this provision will have to be drawn up in detail, following the opinions of scientists based on the experience acquired in non-member countries and the Member States. It is proposed that the

¹² Five opinions by qualified majority, 257 unanimous opinions on 1 May 2001.

¹³ 253 opinions given by written procedure out of a total of 262 opinions given on 1 May 2001 in the field of medicinal products for human use.

¹⁴ OJ L 184, 17.7.1999, p. 23.

Commission should determine this framework in an implementing regulation adopted under the Regulatory Committee procedure (*Article 13(4)*).

5. As in the decentralised procedure and the proposals made in the general context of legislation on marketing authorisation, this proposal abolishes the five-yearly renewal of marketing authorisations. This is combined with the strengthening of pharmacovigilance procedures and an increase in the frequency at which updated safety reports must be submitted (*Article 13(1) and Articles 15 to 24*). Two comments should be made in this respect. To reduce the administrative burden on the Agency, to ensure greater market transparency and to take into account the withdrawal of the obligation to renew authorisation on a five-yearly basis, this proposal lays down that any marketing authorisation which does not result in the actual marketing of the medicinal product concerned during two consecutive years ceases to be valid (*Article 13(2) and (3)*). The strengthening of pharmacovigilance and market surveillance will bring with it greater efficiency and speed up the administration's decision-making and sanction processes (*Article 18(2) ff*).

B. Centralised procedure for medicinal products for human use

1. Most of the abovementioned points reappear in identical form in the part of the proposal concerning veterinary medicinal products. This is true for the provisions concerning generic medicinal products for veterinary use (*Article 3(3)*), the composition and procedures applicable to the Scientific Committee competent in the veterinary field ("Committee for Veterinary Medicinal Products") particularly as regards the creation of expert groups (*Article 54 and Article 50(2) and (3)*), the procedure for appealing against the scientific opinion of the Scientific Committee (*Article 31(1) and Article 55(1), second subparagraph*), and provisions concerning the Commission's Decisions (*Article 32 and Article 77*). The abolition of the five-yearly renewal of authorisation and the invalidity clauses concerning authorisation (*Article 35(1) to (3)*) and the provisions to strengthen pharmacovigilance and market surveillance (*Articles 37 to 46*) are introduced in parallel to those proposed for the human sector.

Finally, provision is also made for applicants to propose an accelerated assessment of their case, whereby the Agency gives it priority. Applicants have to justify such a request from the point of view of therapeutic needs and animal health. The Scientific Committee will accept or reject the request on the basis of the details provided by the applicant. In any event, standard criteria linked to the quality, safety and efficacy of the medicinal products must be fulfilled (*Article 35(5)*).

2. Nevertheless, there are some provisions of a specific nature. Provision is made for the application of the centralised procedure to be adapted to the specific context in which certain veterinary medicinal products are used. For instance, given the "regional" distribution of certain infectious diseases, it seems appropriate to provide for special administrative measures, such as the taking over of responsibility for the translations, by the agency, in order to facilitate the authorisation of medicinal products to treat these diseases (*Article 69*). On the other hand, it is useful to allow authorisation under the centralised procedure for immunological medicinal products used for diseases subject to Community prophylactic measures (*Article 3(2)*), whether or not the substances used are new.

C. Provisions concerning the Agency and general provisions

1. The amendments to the provisions concerning the Agency concern on the one hand its responsibilities and on the other the adaptation of its administrative and scientific structures to its new tasks and the future enlargement of the Union. The principles governing the Agency, its administrative structure and its overall operating methods are not changed, since experience has shown that the choices made in 1993 were satisfactory.
2. The proposal gives the Agency additional tasks, most of them going beyond the assessment of medicinal products. For instance, provision is made for it to increase and systematically develop the scientific advice it provides for companies at the research and development phases of new medicinal products, well before the authorisation procedures for placing them on the market (*Article 51(l)*). This aspect, already mentioned above, is of prime importance to the Commission, particularly in the context of new therapies and medicinal products resulting from biotechnological processes. The purpose is to help and stimulate pharmaceutical research in Europe and thus allow European patients to benefit earlier from more effective medicinal products. The emergence of new fields of research (pharmacogenomics, gene therapy and cell therapy, including xenogenic somatic therapy, etc.) together with the burgeoning of small and medium-sized businesses in these fields makes it essential to create a genuine partnership between the industry and the authority responsible for assessing future medicinal products, respecting the areas of competence of each party.

The Agency has already developed this type of service and the results are encouraging. This proposal aims to strengthen the Agency's expertise in this field (*Article 50(3)*) by creating a standing working party in order to allow greater use of this type of service.

3. It is also proposed that the Agency should participate in implementing, at Community level, the programmes set up by certain pharmaceutical firms for the compassionate use of human medicinal products covered by this Regulation (*Article 73*). Compassionate use is defined in this context as a firm making a medicinal product available, on its own responsibility, to certain groups of patients prior to authorisation but subject to specific conditions. Clearly such availability must reflect - at least potentially - major benefits as regards survival, quality of life or improving the prognosis for the patient concerned. Such compassionate use is therefore reserved for medicinal products intended for the treatment of serious, often fatal, pathologies, for which the treatment available is non-existent, rare or involves serious side-effects. By definition, compassionate use takes place before or during the assessment procedure for the granting of market authorisation. It ends with the result of this procedure. Finally, although some patients have access to medicinal products which are being developed through their participation in clinical trials, compassionate use as referred to here concerns the availability of a medicinal product outside such trials.

The proposal does not provide for replacing or harmonising either the Member States' legislation on this subject or any of the criteria that would determine which medicinal products should or may be covered by an early availability programme for certain patients. Its aim is simply to ensure greater equity between European patients as regards access to these programmes. It is therefore proposed

that the scientific and material conditions under which the medicinal product would be made available to patients be established at Community level. Thus, when compassionate use is considered for a particular medicinal product, the Agency must be notified (*Article 73(2)*) and the Committee for Human Medicinal Products may adopt recommendations concerning the conditions for use, distribution and the choice of patients targeted (*Article 73(3)*). These recommendations must then be implemented in accordance with the national legislation of the Member States.

4. As regards *international scientific cooperation*, this proposal aims to allow the Agency to increase and develop its technical and scientific support for the Member States and the Commission, particularly through multilateral discussions on technical harmonisation (*Article 51(h)*). In this context, to meet a need expressed by the World Health Organisation and following repeated requests by pharmaceutical companies exporting medicinal products not intended for the Community markets to non-member countries, the proposal gives the Agency the task of carrying out a scientific assessment of these medicinal products on the basis of the criteria applied in the Community concerning quality, safety and efficacy. However, this assessment will be carried out only on the recommendation of the World Health Organisation confirming the needs expressed by certain non-member countries or international organisations (*Article 52*).
5. Finally, this proposal inserts an article in Regulation (EEC) No 2309/93 aimed at preventing or solving potential conflicts between the scientific opinions of the Agency and scientific opinions given by other scientific bodies, Community or otherwise (*Article 53*). This Article is similar to Article 29 of the Commission proposal establishing the European Food Authority¹⁵. It should be noted that this provision in no way seeks to resolve differences between the scientific opinions of the Agency and those of the national authorities competent in the field of medicinal products. Such divergences of opinion should be settled under the procedures drawn up for this purpose under Community pharmaceutical law. However, Article 53 should be applied each time there is a potential conflict between the opinion given by the Agency in connection with its responsibilities regarding medicinal products and the opinions of other competent bodies outside the field of medicinal product evaluation.
6. The second category of changes made to the Agency concerns its administrative and scientific structures. Most of these changes are made with a view to the next enlargement and aim to adapt the composition of the Committees accordingly. As a result, it is proposed that the Scientific Committees should henceforth consist of one representative from each competent national authority (*Article 54(1)*). In order to preserve the expertise necessary for the proper functioning of these Committees and to maintain a broad spectrum of knowledge in highly specialised fields, it is proposed, on the one hand, to introduce the possibility of coopting additional members to the afore-mentioned committees, and on the other hand, to make more systematic use of experts - either through their direct nomination by the Committee members (*Article 54(1)*) or by including them on the list of the Agency's accredited experts (*Article 55(2)*). In this context, in order to rationalise and increase the potential expertise of the Committees, greater use of specialised working parties by the Committees is provided for (*Article 50(2)*) with the possibility of delegating

¹⁵ COM(2000) 716 final; OJ C 96 E, 27.3.2001, p. 247.

certain tasks to these groups (*Article 54(5)*) The proposal incorporates in the Agency's administrative and legal structure the Committee on Orphan Medicinal Products created by Regulation (EC) 141/2000 and anticipates the establishment of a Committee on Herbal Medicinal Products, whose activities are described in the proposal for a specific directive which the European Parliament and the Council will be called upon to discuss alongside this proposal (*Article 50 points c and d*).

The composition of the Agency's Management Board is changed to take account of the structure proposed by the Commission when the latest agencies and authorities on foodstuffs, maritime safety and air safety were set up. The Management Board consists of four representatives appointed by the Council of Ministers, four appointed by the Commission, four appointed by the European Parliament and four representatives of patients and the industry appointed by the Commission (*Article 58*).

To increase the technical consistency of the overall Community system of evaluating medicinal products and market surveillance and to optimise the way the Agency performs its duties, it is proposed that an Advisory Board should be set up under the Executive Director, comprising all the national authorities or agencies competent in the field of human and veterinary medicinal products (*Article 59*).

7. Finally, it is proposed to amend certain general provisions of the 1993 Regulation and to introduce new ones in order to solve some problems which appeared in its implementation and to restore the legal certainty essential for the proper functioning of the procedures. This involves in particular specifying the responsibilities of the Management Board regarding the definition of the transparency rule (*Article 69*), laying down certain marketing conditions for medicinal products authorised by the Community (*Article 72*), specifying the Agency's role as the authority responsible for checking that such medicinal products are distributed in a parallel fashion (*Article 51 (m)*) and specifying the procedures for the Agency's use of service providers (*Article 55(4)*).

D. Legal basis

This proposal is based on Article 95 and Article 152.4(b) of the EC Treaty. Article 95, which prescribes use of the co-decision procedure described in Article 251, is the legal basis for achieving the aims set out in Article 14 of the Treaty, which include the free movement of goods (*Article 14(2)*), in this case human and veterinary medicinal products. While taking account of the fact that any regulations on the manufacture and distribution of medicinal products, including veterinary medicinal products, must be fundamentally aimed at safeguarding public health, this aim must be achieved by means that do not impede the manufacture and free movement of medicinal products within Community. Since the Amsterdam Treaty came into force, all legislative provisions adopted by the European Parliament and the Council – except for directives adopted on the basis of executive powers vested in the Commission – and aimed at aligning the provisions on medicinal products have been adopted on the basis of that Article, since the differences between the national legislative, regulatory and administrative provisions on medicinal products tend to hinder intra-Community trade and therefore directly affect the operation of the internal market. The intervention of the Community legislator is therefore justified with a view to preventing or eliminating these obstacles.

The proposal contains all the provisions of Regulation (EEC) No 2309/93, which established the Agency and created a centralised authorisation procedure for medicinal products. The Regulation had already authorised the necessary transfer of responsibilities to Community level and legally and technically set up the Agency.

The Regulation which is the subject of this proposal and is a recasting of the previous regulation, pursues the objectives of adapting certain procedures and reforming the composition of the component bodies of the Agency, without altering the basic principles contained in the original Regulation, as well as maintaining consistency between the two consolidated directives. Certain new responsibilities for the Agency have also been introduced which can be inferred or derive from the powers already attributed to the Agency in 1993.

This proposal will increase cohesion and improve the functioning of the Community medicinal product market in the light of the six years of experience.

Furthermore, Article 152.4 b) mentions henceforth explicitly the measures having as their direct objective public health protection in the veterinary and phytosanitary sectors. The present proposal contains a number of measures in the veterinary field having as an objective public health protection. Before the adoption of the Treaty of Amsterdam, which institutionalised a new public health policy by granting legislative responsibilities to Community institutions, legislative instruments in this field were adopted on the basis of ex Articles 100 and 235 of the EC Treaty (for want of specific responsibilities at the time of their introduction) – which is no longer necessary in this area, given the existence of an ad hoc legal basis.

E. Administrative and legislative simplification

This proposal takes due account of the immense amount of work carried out on consolidating the directives in the field of Community legislation on medicinal products for human use (31 consolidated texts) and veterinary medicinal products (11 consolidated texts). It also introduces provisions to speed up and rationalise the decision-making procedures relating to marketing authorisations for medicinal products.

F. Consultations held prior to the drafting of the proposal

The Commission commissioned an external consultant to carry out an audit, as stated at the start of this explanatory memorandum. Many consultations, meetings and hearings were held with all the interested parties. The Commission also received many reports and working documents from these parties, particularly from patients' associations and European federations of the pharmaceutical industry, pharmacists and distributors. All of these documents and the analyses of them are included in the Commission's report to the European Parliament and the Council on the operating of the marketing authorisation procedures in the Community, mentioned earlier.

Proposal for a

REGULATION OF THE EUROPEAN PARLIAMENT AND OF THE COUNCIL

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

(Text with EEA relevance)

THE EUROPEAN PARLIAMENT AND THE COUNCIL OF THE EUROPEAN UNION,

Having regard to the Treaty establishing the European Community, and in particular Article 95 and Article 152(4)(b) thereof,

Having regard to the proposal from the Commission¹,

Having regard to the Opinion of the Economic and Social Committee²,

Having regard to the Opinion of the Committee of the Regions³,

In accordance with the procedure referred to in Article 251 of the Treaty⁴,

Whereas:

- (1) Council Regulation No 2309/93 of 22 July 1993 laying down Community procedures for the authorisation and supervision of medicinal products for human and veterinary use and establishing a European Agency for the Evaluation of Medicinal Products⁵ provides, in Article 71, that within six years of the entry into force of the Regulation the Commission is to publish a general report on the experience acquired as a result of the operation of the procedures laid down in the Regulation.
- (2) In the light of the Commission's report⁶ on the experience gained, it has proved necessary to improve the operation of the authorisation procedures for the placing of medicinal products on the market in the Community and to amend certain administrative aspects of the European Agency for the Evaluation of Medicinal Products.

¹ OJ L

² OJ L

³ OJ L

⁴ OJ L

⁵ OJ L 214, 24.8.1993, p. 1; Regulation as amended by Commission Regulation (EC) No 649/98 (OJ L 88, 24.3.1998, p. 7).

⁶ COM(2001) final.

- (3) It emerges from the conclusions of that report that the amendments to be made to the centralised procedure set up by Regulation (EEC) No 2309/93 consist of corrections to some of the operating procedures and adaptations to take account of the probable development of science and technology and the future enlargement of the European Union. It also emerges from the report that the general principles previously established which govern the centralised procedure should be maintained.
- (4) Moreover, since the European Parliament and the Council have adopted Directive 2001/83/EC of 23 October 2001 on the Community code relating to medicinal products for human use⁷ and Directive 2001/82/EC of 23 October 2001 on the Community code relating to veterinary medicinal products⁸, the updating of all the references contained in Regulation (EEC) No 2309/93 to the codified directives has to be undertaken.
- (5) For the sake of clarity, it is necessary to replace the said Regulation with a new regulation.
- (6) It is appropriate to preserve the Community mechanism, set up by the repealed Community legislation, for concertation prior to any national decision relating to a high-technology medicinal product.
- (7) Experience gained since the adoption of Council Directive 87/22/EEC⁹ of 22 December 1986 has shown that it is necessary to create a centralised authorisation procedure that is compulsory for high-technology medicinal products, particularly those resulting from biotechnical processes, in order to maintain the high level of scientific evaluation of these medicinal products in the European Union and thus to preserve the confidence of patients and the medical professions in the evaluation. This is particularly important in the context of the emergence of new therapies, such as gene therapy and associated cell therapies, and xenogenic somatic therapy. This approach should be maintained, particularly with a view to ensuring the effective operation of the internal market in the pharmaceutical sector.
- (8) With a view to harmonising the internal market for new medicinal products, this procedure should also be made compulsory for any medicinal product which is intended to be administered to humans or animals and contains an entirely new active substance, that is, one that has not yet been authorised in the Community.
- (9) As regards medicinal products for human use, optional access to the centralised procedure should also be provided for in cases where use of a single procedure produces added value for the patient. This procedure should remain optional for medicinal products which, although not belonging to the abovementioned categories, are nevertheless a therapeutic innovation. It is also appropriate to allow access to this procedure for medicinal product which, although not innovative, may be of benefit to society or to patients if they are authorised from the outset at Community level, such as certain medicinal products which cannot be supplied without a medical prescription. This option may be extended to generic medicinal products authorised by the Community, provided that this in no way undermines either the harmonisation

⁷ OJ L

⁸ OJ L

⁹ OJ L 15, 17.1.1987, p. 38; Directive repealed by Directive 93/41/EEC (OJ L 214, 24.8.1993, p. 40).

achieved when the reference medicinal products was evaluated or the results of that evaluation.

- (10) In the field of veterinary medicinal products, administrative measures should be provided for in order to take account of the specific features of this field, particularly those due to the regional distribution of certain diseases. The field of application of the centralised procedure should also include medicinal products used within the framework of Community provisions regarding prophylactic measures for epizootic diseases.
- (11) In the interest of public health, it is necessary that authorisation decisions under the centralised procedure be taken on the basis of the objective scientific criteria of quality, safety and efficacy of the medicinal product concerned, to the exclusion of economic and other considerations. However, Member States should be able exceptionally to prohibit the use on their territory of medicinal products for human use which infringe objectively defined concepts of public policy and public morality. Moreover, a veterinary medicinal product may not be authorised by the Community if its use would contravene the rules laid down by the Community within the framework of the Common Agricultural Policy.
- (12) Provision should be made whereby the quality, safety and efficacy criteria provided for by Directives 2001/83/EC and 2001/82/EC apply to medicinal products authorised by the Community.
- (13) The Community should have the means to carry out a scientific assessment of the medicinal products presented in accordance with the centralised Community authorisation procedures. Moreover, with a view to ensuring the effective harmonisation of administrative decisions taken by Member States with regard to medicinal products presented in accordance with centralised authorisation procedures, it is necessary to endow the Community with the means to resolve disagreements between Member States concerning the quality, safety and efficacy of medicinal products.
- (14) It is thus appropriate to establish a European Agency for the Evaluation of Medicinal Products (hereinafter referred to as the "Agency").
- (15) The structure and operation of the set of bodies making up the Agency should be designed in such a way as to take into account the need constantly to renew scientific expertise, the need for cooperation between Community and national institutions, the need for adequate representation of civil society, and the future enlargement of the European Union.
- (16) The chief task of the Agency should be to provide Community institutions and Member States with the best possible scientific opinions so as to enable them to exercise the powers regarding the authorisation and supervision of medicinal products conferred on them by Community legislation in the field of medicinal products. Only after a single scientific evaluation procedure addressing the quality, safety and efficacy of high-technology medicinal products has been conducted by the Agency, applying the highest possible standards, should marketing authorisation be granted by the Community, by means of a rapid procedure ensuring close cooperation between the Commission and Member States.

- (17) In order to ensure close cooperation between the Agency and the scientists operating in Member States, provision should be made so that the Management Board is composed in such a way as to guarantee that the competent authorities of the Member States are closely involved in the overall management of the Community system for authorising medicinal products by creating an Advisory Board responsible to the Executive Director of the Agency.
- (18) Exclusive responsibility for preparing the Agency's opinions on all questions concerning medicinal products for human use should be vested in a Committee for Medicinal Products for Human Use. As far as veterinary medicinal products are concerned, such responsibility should be vested in a Committee for Veterinary Medicinal Products . As regards orphan medicinal products, the task should fall to the Committee on Orphan Medicinal Products set up under Regulation (EC) No 141/2000 of the European Parliament and of the Council of 16 December 2000 on orphan medicinal products¹⁰. [Lastly, as regards herbal medicinal products, this responsibility should be vested in the Committee on Herbal Medicinal Products set up under Directive 2001/83/EC].
- (19) The creation of the Agency will make it possible to reinforce the scientific role and independence of the committees, particularly through the setting-up of a permanent technical and administrative secretariat.
- (20) The field of activity of the Scientific Committees should be enlarged and their operating methods and composition modernised. Scientific advice for future applicants seeking marketing authorisation should be provided more generally and in greater depth. Similarly, structures allowing the development of advice for companies should be put in place. The Committees should be able to delegate some of their evaluation duties to standing working parties open to experts from the scientific world appointed for this purpose, whilst retaining total responsibility for the scientific opinions issued. The appeal procedures should be amended to provide a better guarantee for applicants' rights.
- (21) The number of members of the Scientific Committees participating in the centralised procedure should be established with a view to ensuring that the Committees remain of efficient size after the enlargement of the Union.
- (22) It is also necessary to reinforce the role of the Scientific Committees in such a way as to enable the Agency to have an active presence in the context of the international scientific dialogue and to develop certain activities that will be necessary, in particular regarding international scientific harmonisation and technical cooperation with the World Health Organisation.

¹⁰ OJ L 18, 22.1.2000, p. 1.

- (23) Furthermore, in order to create greater legal certainty it is necessary to define the responsibilities regarding the transparency rules for the Agency's work, to set certain conditions for the marketing of medicinal products authorised by the Community, to confer on the Agency powers to monitor the distribution of medicinal products authorised by the Community and to specify the sanctions and the procedures for implementing them in the case of failure to observe the provisions of this Regulation and the conditions contained in the authorisations issued under the procedures it establishes.
- (24) It is also necessary to take measures for the supervision of medicinal products authorised by the Community, and in particular for the intensive supervision of undesirable effects of these medicinal products within the framework of Community pharmacovigilance activities, so as to ensure the rapid withdrawal from the market of any medicinal product presenting an unacceptable level of risk under normal conditions of use.
- (25) In order to enhance the efficiency of market surveillance, the Agency should be responsible for coordinating Member States' pharmacovigilance activities. A number of provisions need to be introduced to put in place stringent and efficient pharmacovigilance procedures, to allow the competent authority to take provisional emergency measures, including the introduction of amendments to the marketing authorisation and, finally, to permit a reassessment to be made at any time of the risk/benefit balance of a medicinal product.
- (26) It is also appropriate to entrust the Commission, in close cooperation with the Agency and after consultations with the Member States, with the task of coordinating the execution of the various supervisory responsibilities vested in the Member States, and in particular with the tasks of providing information on medicinal products, and of checking the observance of good manufacturing, laboratory and clinical practices.
- (27) It is necessary to provide for the coordinated implementation of Community procedures for the authorisation of medicinal products, and of the national procedures of Member States which have already been broadly harmonised by Directives 2001/83/EC and 2001/82/EC. It is appropriate that the operation of the procedures laid down by this Regulation be reexamined by the Commission every ten years on the basis of experience gained.
- (28) In order to meet, in particular, the legitimate expectations of patients and to take account of the increasingly rapid progress of science and therapies, accelerated assessment procedures should be set up, reserved for medicinal products of major therapeutic interest, and procedures for obtaining temporary authorisations subject to certain annually reviewable conditions. In the field of medicinal products for human use, a common approach should also be followed, whenever possible, regarding the criteria and conditions for the compassionate use of new medicinal products under Member States' legislation.
- (29) In line with the current provisions of Directives 2001/83/EC and 2001/82/EC, the term of validity of a Community marketing authorisation should be unlimited. Furthermore, any authorisation not used for two consecutive years, that is to say, one which has not led to the placing on the market of a medicinal product in the Community during that period, should be considered invalid, in order, in particular, to avoid the administrative burden linked to maintaining such authorisations.

- (30) Environmental risks may arise from medicinal products containing or consisting of genetically modified organisms. It is thus necessary to subject such products to an environmental risk-assessment procedure similar to the procedure under Directive 2001/18/EC of the European Parliament and of the Council of 12 March 2001 on the deliberate release into the environment of genetically modified organisms and repealing Council Directive 90/220/EEC¹¹, to be conducted in parallel with the evaluation, under a single Community procedures, of the quality, safety and efficacy of the product concerned.
- (31) Since most of the measures necessary for the implementation of this Regulation are measures of individual scope, they should be adopted by use of the advisory procedure provided for in Article 3 of Council Decision 1999/468/EC of 28 June 1999 laying down the procedures for the exercise of implementing powers conferred on the Commission¹², or else by use of the management procedure provided for under Article 4 of that Decision. In respect of measures of general scope within the meaning of Article 2 of that Decision, they should be adopted by use of the regulatory procedure provided for in Article 5 of that Decision,

HAVE ADOPTED THIS REGULATION:

TITLE I

DEFINITIONS AND SCOPE

Article 1

The purpose of this Regulation is to lay down Community procedures for the authorisation, supervision and pharmacovigilance of medicinal products for human and veterinary use, and to establish a European Agency for the Evaluation of Medicinal Products (hereinafter referred to as "the Agency").

The provisions of this Regulation shall not affect the powers of the Member States' authorities as regards setting the prices of medicinal products or their inclusion in the scope of the national health system or social security schemes on the basis of health, economic and social conditions. In particular, Member States shall be free to choose from the particulars shown in the marketing authorisation those therapeutic indications and pack sizes which will be covered by their social security bodies.

Article 2

The definitions laid down in Article 1 of Directive 2001/83/EC and those laid down in Article 1 of Directive 2001/82/EC shall apply for the purposes of this Regulation.

The holder of a marketing authorisation for the medicinal products covered by this Regulation should be established in the Community. The holder shall be responsible for placing those medicinal products on the market.

¹¹ OJ L 106, 17.4.2001, p. 1; Directive last amended by Regulation (EC) No .../2002 of the European Parliament and of the Council [of ... concerning the traceability of genetically modified organisms and the traceability of food products intended for human consumption, etc.].

¹² OJ L 184, 17.7.1999, p. 23.

Article 3

1. No medicinal product appearing in Annex I may be placed on the market within the Community unless a marketing authorisation has been granted by the Community in accordance with the provisions of this Regulation.
2. Any medicinal product not appearing in Annex I may be granted a marketing authorisation by the Community in accordance with the provisions of this Regulation, provided that the applicant shows that the medicinal product is a significant therapeutic, scientific or technical innovation or that the granting of authorisation in accordance with this Regulation is of interest to patients or to animal health at Community level.

Immunological veterinary medicinal products for the treatment of animal diseases subject to Community prophylactic measures may also be granted such authorisation.

3. A generic form of a medicinal product authorised by the Community may be authorised by the competent authorities of the Member States in accordance with Directive 2001/83/EC and Directive 2001/82/EC under the following conditions:
 - (a) the application for authorisation is submitted in accordance with Article 10 of Directive 2001/83/EC or Article 13 of Directive 2001/82/EC;
 - (b) the summary of the characteristics of the product is in all respects consistent with that of the medicinal product authorised by the Community; and
 - (c) the generic medicinal product is authorised under the same name in all the Member States where the application has been made.
4. After consulting the competent committee of the Agency set up under Article 49, Annex I may be re-examined in the light of technical and scientific progress, with a view to making any necessary amendments. Such amendments shall be adopted according to the procedure referred to in Article 77(2).

Article 4

1. In order to obtain the marketing authorisation referred to in Article 3, an application shall be submitted to the Agency.
2. The Community shall issue and supervise marketing authorisations for medicinal products for human use in accordance with Title II.
3. The Community shall issue and supervise marketing authorisations for medicinal products for veterinary use in accordance with Title III.

TITLE II
**AUTHORISATION AND SUPERVISION OF MEDICINAL PRODUCTS FOR
HUMAN USE**

CHAPTER 1

SUBMISSION AND EXAMINATION OF APPLICATIONS – AUTHORISATIONS

Article 5

1. A Committee for Human Medicinal Products is hereby established. The Committee shall be part of the Agency.
2. Without prejudice to Article 50 or to other tasks which Community law may confer on it, the Committee for Human Medicinal Products shall be responsible for formulating the opinion of the Agency on any matter concerning the admissibility of the files submitted in accordance with the centralised procedure, the granting, variation, suspension or withdrawal of an authorisation to place a medicinal product for human use on the market in accordance with the provisions of this Title and pharmacovigilance.
3. At the request of the Executive Director of the Agency or the Commission representative, the Committee for Human Medicinal Products shall also draw up an opinion on any scientific matter concerning the evaluation of medicinal products for human use.

Article 6

1. Each application for authorisation for a medicinal product for human use shall specifically include all the information and documents referred to in Articles 8(3), 10a and 11 of Directive 2001/83/EC, and Annex I thereto. The information and documents are to take account of the unique, Community nature of the authorisation requested, and particularly of the use of a single name for the medicinal product.

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

2. In the case of a medicinal product for human use containing or consisting of genetically modified organisms within the meaning of Article 2 of Directive 2001/18/EC, the application shall be accompanied by:
 - (a) a copy of the the competent authorities' written consent to the deliberate release into the environment of the genetically modified organisms for research and development purposes where provided for in Part B of Directive 2001/18/EC or in Part B of Directive 90/220/EEC¹³;
 - (b) the complete technical dossier supplying the information required by Annexes III and IV to Directive 2001/18/EC;

¹³ OJ L 117, 8.5.1990, p. 15.

- (c) the environmental risk assessment in accordance with the principles set out in Annex II to Directive 2001/18/EC; and
- (d) the results of any investigations performed for the purposes of research or development.

Articles 13 to 24 of Directive 2001/18/EC shall not apply to veterinary medicinal products containing or consisting of genetically modified organisms.

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

In the case of a medicinal product for human use containing or consisting of genetically modified organisms, the opinion of the Committee shall respect the environmental safety requirements laid down by Directive 2001/18/EC. During the process of evaluating applications for marketing authorisations for medicinal products for human use containing or consisting of genetically modified organisms, the necessary consultations shall be held by the rapporteur with the bodies set up by the Community or the Member States in accordance with Directive 2001/18/EC.

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

Article 7

In order to prepare its opinion, the Committee for Human Medicinal Products:

- (a) shall verify that the particulars and documents submitted in accordance with Article 6 comply with the requirements of Directive 2001/83/EC, and shall examine whether the conditions specified in this Regulation for issuing a marketing authorisation are satisfied;
- (b) may ask for a State laboratory or a laboratory designated for this purpose to test the medicinal product for human use, 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 within a specific timeperiod.

Where the Committee avails itself of the option under point (c) of the first paragraph, the time-limit laid down in the first subparagraph of Article 6 (3) 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 for Human Medicinal Products, a Member State shall forward the information showing that the manufacturer of a medicinal product or the importer from a non-member 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 pursuant to Article 6.
2. Where it considers it necessary in order to complete its examination of an application, the Committee for Human Medicinal Products may require the applicant to submit to a specific inspection of the manufacturing site of the medicinal product concerned.

The inspection shall be carried out within the time-limit laid down in the first subparagraph of Article 6(3), by inspectors from the Member State holding the appropriate qualifications, who may be accompanied by a rapporteur or an expert appointed by the Committee.

Article 9

1. The Agency shall forthwith inform the applicant when the opinion of the Committee for Human Medicinal Products is that:
 - (a) the application does not satisfy the criteria for authorisation set out in this Regulation;
 - (b) the summary of the product characteristics proposed by the applicant needs to be amended;
 - (c) the labelling or package leaflet of the product is not in compliance with Title V of Directive 2001/83/EC;
 - (d) the authorisation needs to be granted subject to the conditions provided for in Article 13(4) and (5).
2. Within 15 days of receipt of the opinion referred to in paragraph 1, the applicant may give written notice to the Agency that he/she wishes to appeal. In that case, the applicant shall forward the detailed grounds for his/her appeal to the Agency within 60 days of receipt of the opinion.

Within 60 days of receipt of the grounds for appeal, the Committee for Human Medicinal Products shall re-examine its opinion in accordance with the conditions laid down in the second subparagraph of Article 55(1). The reasons for the conclusion reached on the appeal shall be annexed to the final opinion.

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

4. If an opinion is favourable to the grant of the relevant authorisation to place the medicinal product concerned on the market, the following documents shall be annexed to the opinion:
 - (a) a draft summary of the product characteristics, as referred to in Article 11 of Directive 2001/83/EC;
 - (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 Title VI of Directive 2001/83/EC;
 - (c) the draft text of the labelling and package leaflet proposed by the applicant, presented in accordance with Title V of Directive 2001/83/EC;
 - (d) the assessment report.

Article 10

1. Within 30 days of receipt of the opinion referred to in Article 5(2), the Commission shall prepare a draft of the decision to be taken in respect of the application.

In the event of a draft decision granting marketing authorisation, the draft shall include or make reference to the documents mentioned in points (a), (b) and (c) of the first subparagraph of Article 9(4).

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

The draft decision shall be forwarded to the Member States and the applicant.

2. The Commission shall take a final decision in accordance with the procedure referred to in Article 77(3) if the draft decision accords with the Agency's opinion.

The Commission shall take a final decision in accordance with the procedure referred to in Article 77(4) if the draft decision does not accord with the Agency's opinion,

3. The Standing Committee on Medicinal Products for Human Use referred to in Article 77(1) shall adjust its rules of procedure so as to take account of the tasks incumbent upon it under this Regulation.

These adjustments shall provide that:

- (a) the opinion of the Standing Committee is to be given in writing;
- (b) each Member State is to be allowed 15 days to forward written observations on the draft decision to the Commission. However, if a decision has to be taken urgently, a shorter time-limit may be set by the Chairman according to the degree of urgency involved;
- (c) each Member State is to be permitted to require in writing that the draft decision referred to in paragraph 1 be discussed by a plenary meeting of the Standing Committee, giving its reasons in detail.

4. Where, in the opinion of the Commission, the written observations of a Member State raise important new questions of a scientific or technical nature which have not been addressed in the opinion of the Agency, the Chairman shall suspend the procedure and refer the application back to the Agency for further consideration.
5. The Commission shall adopt the provisions necessary for the implementation of paragraph 3 in accordance with the procedure referred to in Article 77(2).
6. The Agency shall disseminate the documents referred to in points (a), (b) and (c) of Article 9(4).

Article 11

1. The marketing authorisation 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 properly or sufficiently demonstrated by the applicant.

Authorisation shall likewise be refused if the particulars and documents provided by the applicant in accordance with Article 6 are incorrect or if the labelling and package leaflets proposed by the applicant are not in accordance with Title V of Directive 2001/83/EC.

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

Article 12

1. Without prejudice to Article 4(4) of Directive 2001/83/EC, a marketing authorisation which has been granted in accordance with the procedure laid down in this Regulation shall be valid throughout the Community. It shall confer the same rights and obligations in each of the Member States as a marketing authorisation granted by that Member State in accordance with Article 6 of Directive 2001/83/EC.

The authorised medicinal products for human use shall be entered in the Community Register of Medicinal Products and shall be given a number which shall appear on the packaging.

2. Notification of marketing authorisation shall be published in the *Official Journal of the European Communities*, quoting in particular the date of authorisation and the registration number in the Community Register.
3. The Agency shall publish the assessment report on the medicinal product for human use drawn up by the Committee for Human Medicinal Products and the reasons for its opinion in favour of granting authorisation, after deletion of any information of a commercially confidential nature.
4. After marketing authorisation has been granted, the holder of the authorisation shall inform the Agency of the dates of actual marketing of the medicinal product for human use in the Member States, taking into account the various presentations authorised.

The holder shall also inform the Agency if the product ceases to be marketed.

Upon request by the Agency, particularly in the context of pharmacovigilance, the marketing authorisation holder shall provide the Agency with all data relating to the volume of sales of or prescriptions for the medical product concerned at Community level.

Article 13

1. Without prejudice to paragraphs 2 and 3, authorisation shall be valid for an unlimited period.
2. Any authorisation which is not followed by the actual placing of the medicinal product for human use authorised on the Community market within two years of authorisation shall cease to be valid.
3. When an authorised medicinal product previously placed on the market is no longer actually present on the market for two consecutive years, the authorisation shall cease to be valid.
4. Following consultation with the applicant, an authorisation may be granted subject to certain specific obligations, to be reviewed annually by the Agency.

By way of derogation from paragraph 1, the authorisation shall be valid for one year, on a renewable basis.

The arrangements for granting such authorisation shall be determined by a Commission regulation adopted according to the procedure referred to in Article 77(2).

5. In exceptional circumstances, when one of the grounds referred to in Annex I to Directive 2001/83/EC applies to an application, and following consultation with the applicant, authorisation may be granted only under specific conditions. Continuation of the authorisation shall be linked to the annual reassessment of these conditions.
6. When an application is lodged for a marketing authorisation in respect of medicinal products for human use which are of major interest from the point of view of public health and in particular from the viewpoint of therapeutic innovation, the applicant may request an accelerated assessment procedure. Due reasons are to be given for the request.

If the Committee for Human Medicinal Products accepts the application, the time-limit laid down in the first subparagraph of Article 6(3) shall be reduced to 150 days.

7. When adopting its opinion, the Committee for Human Medicinal Products shall include a proposal concerning the criteria for the prescription or use of the medicinal products in accordance with Article 70 of Directive 2001/83/EC .
8. Medicinal products for human use which have been authorised in accordance with the provisions of this Regulation shall benefit from the ten-year period of protection referred to in Article 10(1) of Directive 2001/83/EC.

Article 14

The granting of authorisation shall not affect the civil and criminal liability borne by the manufacturer or the holder of the marketing authorisation by virtue of the prevailing national law of the Member States.

CHAPTER 2

SUPERVISION AND SANCTIONS

Article 15

1. After an authorisation has been issued in accordance with this Regulation, the holder of the marketing authorisation for a medicinal product for human use shall, in respect of the methods of manufacture and control provided for in points (d) and (h) of Article 8(3) of Directive 2001/83/EC, take account of technical and scientific progress and make any amendments that may be required to enable the medicinal products to be manufactured and checked by means of generally accepted scientific methods. He/she shall apply for approval for these amendments in accordance with this Regulation.
2. The holder of the marketing authorisation shall forthwith supply to the Agency, to the Commission and to the Member States any new information which might entail the amendment of the particulars and documents referred to in Articles 8(3), 10a and 11 of Directive 2001/83/EC , or in Annex I thereto, or Article 9(4) of this Regulation.

In particular, he/she shall forthwith inform the Agency, the Commission and the Member States 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 veterinary medicinal product concerned.

3. If the holder of the authorisation for placing the medicinal product for human use on the market proposes to make any alteration to the information and particulars referred to in paragraph 2, he/she shall submit the relevant application to the Agency.
4. The Commission shall, after consulting the Agency, make appropriate arrangements for the examination of variations to the terms of a marketing authorisation.

The Commission shall adopt these arrangements in the form of a regulation in accordance with the procedure referred to in Article 77(2).

Article 16

1. In the case of medicinal products for human use manufactured within the Community, the supervisory authorities shall be the competent authorities of the Member State or Member States which have granted the authorisation provided for in Article 40 of Directive 2001/83/EC in respect of the medicinal product concerned

2. In the case of medicinal products imported from non-member countries, the supervisory authorities shall be the competent authorities of the Member States in which the controls referred to in Article 51(1)(b) of Directive 2001/83/EC 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.

A Member State may request assistance from another Member State or from the Agency.

Article 17

1. The supervisory authorities shall have responsibility for verifying on behalf of the Community that the holder of the marketing authorisation for the medicinal product for human use or the manufacturer or importer from a non-member country satisfies the requirements laid down in Titles IV and XI of Directive 2001/83/EC.
2. Where, in accordance Article 122 of Directive 2001/83/EC, the Commission is informed of serious differences of opinion between Member States as to whether the holder of the marketing authorisation for the medicinal product for human use, or a manufacturer or importer established within the Community satisfies the requirements referred to in paragraph 1, the Commission may, after consultation with the Member States concerned, request an inspector from the supervisory authority to undertake a new inspection of the marketing authorisation holder, the manufacturer or the importer; the inspector in question shall be accompanied by two inspectors from Member States which are not party to the dispute and/or by two experts nominated by the Committee for Human Medicinal Products.
3. Subject to any arrangements which may have been concluded between the Community and non-member countries in accordance with Article 16(2), the Commission may, following a reasoned request from a Member State, or from the Committee for Human Medicinal Products, or on its own initiative, require a manufacturer established in a non-member country to submit to an inspection.

The inspection shall be undertaken by inspectors from the Member State who possess the appropriate qualifications and who may be accompanied by a rapporteur or expert appointed by the Committee for Human Medicinal Products. The report of the inspectors shall be made available to the Commission, the Member States and the Committee for Human Medicinal Products.

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 established on Community territory is no longer fulfilling the obligations laid down in Title IV of Directive 2001/83/EC, 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 or the Commission considers that one of the measures envisaged in Titles IX and XI of Directive 2001/83/EC should be applied in respect of the medicinal product concerned or where the Committee for Human Medicinal Products has delivered an opinion to that effect in accordance with Article 5 of this Regulation.

2. The Commission shall request the opinion of the Agency within a time-limit which it shall determine in the light of the urgency of the matter, in order to examine the reasons advanced. Whenever practicable, the holder of the authorisation for placing the medicinal product for human use on the market shall be invited to provide oral or written explanations.
3. Following an opinion by the Agency, the Commission shall adopt the necessary provisional measures, which shall be applied immediately.

A final decision shall be adopted within six months, in accordance with the procedures referred to in Article 10(2).

4. Where urgent action is essential to protect human or animal health or the environment, a Member State may, on its own initiative or at the Commission's request, suspend the use on its territory of a medicinal product for human use which has been authorised in accordance with this Regulation.

When it does so on its own initiative, it shall inform the Commission and the Agency of the reasons for its action at the latest on the next working day following the suspension. The Agency shall inform the other Member States without delay. The Commission shall immediately initiate the procedure provided for in paragraphs 2 and 3.

5. The suspensive measures referred to in paragraph 4 may be maintained in force until such time as a definitive decision has been reached in accordance with the procedures referred to in Article 10(2).
6. The Agency shall, upon request, inform any person concerned of the final decision.

CHAPTER 3

PHARMACOVIGILANCE

Article 19

For the purpose of this Chapter, Article 106(2) of Directive 2001/83/EEC shall apply.

Article 20

The Agency, acting in close cooperation with the national pharmacovigilance systems established in accordance with Article 102 of Directive 2001/83/EC, shall receive all relevant information about suspected adverse reactions to medicinal products for human use which have been authorised by the Community in accordance with this Regulation. If necessary, the Committee for Human Medicinal Products may, in accordance with Article 5 of this Regulation, formulate opinions on the measures necessary.

These measures may include amendments to the marketing authorisation granted in accordance with Article 10. They shall be adopted in accordance with the procedures referred to in Article 10(2).

The holder of the marketing authorisation and the competent authorities of the Member States shall ensure that all relevant information about suspected adverse reactions to the medicinal products authorised under this Regulation are brought to the attention of the Agency in accordance with the provisions of this Regulation.

Article 21

The holder of an authorisation to place a medicinal product for human use on the market granted by the Community in accordance with the provisions of this Regulation shall have permanently and continuously at his/her disposal an appropriately qualified person responsible for pharmacovigilance.

That qualified person shall be resident in the Community and shall be responsible for the following:

- (a) the establishment and maintenance of a system which ensures that information about all suspected adverse reactions which are reported to the personnel of the company and to medical representatives, is collected, evaluated and collated so that it may be accessed at a single point within the Community;
- (b) the preparation of the reports referred to in Article 22(3) for the competent authorities of the Member States and the Agency in accordance with the requirements of this Regulation;
- (c) ensuring that any request from the competent authorities 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;
- (d) providing the competent authorities with any other information relevant to the evaluation of the risks and benefits of a medicinal product, particularly information concerning post-authorisation safety studies.

Article 22

1. The holder of an authorisation to place a medicinal product for human use on the market shall ensure that all suspected serious adverse reactions occurring within the Community to a medicinal product authorised in accordance with the provisions of this Regulation which are brought to his/her attention by a health-care professional, are recorded and reported immediately to the Member States in whose territory the incident occurred, and in no case later than 15 days following the receipt of the information.

The holder of an authorisation to place a medicinal product on the market shall be obliged to record any other suspected serious adverse reactions which meet the notification criteria, in accordance with the guidelines referred to in Article 24, of which he/she may reasonably be expected to be aware, and to notify immediately the competent authority of the Member State on whose territory the incident occurred, no later than 15 days following receipt of the information.

2. The holder of the authorisation to place the medical product for human use on the market shall ensure that all suspected serious unexpected adverse reactions occurring in the territory of a non-member country are reported immediately to Member States and the Agency and in no case later than 15 days following the receipt of the information. The arrangements for the reporting of suspected unexpected adverse reactions which are not serious, whether in the Community or in a non-member country, shall be adopted in accordance with the procedure set out in Article 77(2).

Save in exceptional circumstances, these reactions shall be communicated in the form of a report transmitted electronically and in accordance with the guidelines referred to in Article 24.

3. The holder of the authorisation to place the medicinal product for human use on the market shall be required to maintain detailed records of all suspected adverse reactions within or outside the Community which are reported to him/her by a health-care professional.

Unless other requirements have been laid down as a condition of the granting of the marketing authorisation by the Community, these records shall be submitted, in the form of a updated periodical report on safety, to the Agency and Member States immediately upon request or at least every six months during the first two years following authorisation and once a year for the following two years. Thereafter, the records shall be submitted at three-yearly intervals, or immediately upon request.

These records shall be accompanied by a scientific evaluation.

Article 23

Each Member State shall ensure that all suspected serious adverse reactions occurring within their territory to a medicinal product for human use authorised in accordance with the provisions of this Regulation which are brought to their attention are recorded and reported immediately to the Agency and the marketing authorisation holder, and in no case later than 15 days following receipt of the information.

The Agency shall inform the national pharmacovigilance systems in accordance with Article 102 of Directive 2001/83/EC.

Article 24

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

In accordance with this guidance, holders of marketing authorisation shall use the medical terminology accepted at international level for the transmission of adverse reaction reports.

The Agency, in consultation with the Member States and the Commission, shall set up a data-processing network for the rapid transmission of data between the competent Community authorities in the event of an alert relating to faulty manufacture, serious adverse reactions and other pharmacovigilance data regarding medicinal products authorised in accordance with Article 6 of Directive 2001/83/EC.

Article 25

The Agency shall collaborate with the World Health Organisation in matters of international pharmacovigilance and shall take the necessary steps to submit to it, promptly, appropriate and adequate information regarding the measures taken in the Community which may have a bearing on public health protection in non-member countries; it shall send a copy thereof to the Commission and the Member States.

Article 26

Any amendment which may be necessary to update the provisions of this Chapter to take account of scientific and technical progress shall be adopted in accordance with the procedure referred to in Article 77 (2).

TITLE III

**AUTHORISATION AND SUPERVISION OF VETERINARY
MEDICINAL PRODUCTS**

CHAPTER 1 SUBMISSION AND EXAMINATION OF APPLICATIONS – AUTHORISATIONS

Article 27

1. A Committee for Veterinary Medicinal Products is hereby established. The Committee shall be part of the Agency.
2. Without prejudice to Article 50 and other tasks which Community law may confer on it, in particular under Council Regulation (EEC) No 2377/90¹⁴, the Committee for Veterinary Medicinal Products shall be responsible for formulating the opinion of the Agency on any question concerning the admissibility of the files submitted in accordance with the centralised procedure, the granting, variation, suspension or withdrawal of an authorisation to place a veterinary medicinal product on the market arising in accordance with the provisions of this Title and pharmacovigilance.
3. At the request of the Executive Director of the Agency or the Commission representative, the Committee for Veterinary Medicinal Products shall also draw up any opinions on scientific matters concerning the evaluation of medicinal products for veterinary use.

¹⁴ OJ L 224, 18.8.1990, p. 1.

Article 28

1. Each application for authorisation for a medicinal product for veterinary use shall specifically include all the information and documents referred to in Articles 12(3), 13a and 14 of Directive 2001/82/EC, and Annex I thereto. The information and documents are to take account of the unique, Community nature of the authorisation requested, and particularly of the use of a single name for the medicinal product.

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

2. In the case of a veterinary medicinal product containing or consisting of genetically modified organisms within the meaning of Article 2 of Directive 2001/18/EC, the application shall also be accompanied by:
 - (a) a copy of any written consent or consents of the competent authorities to the deliberate release into the environment of the genetically modified organisms for research and development purposes, where provided for in Part B of Directive 2001/18/EC or in Part B of Directive 90/220/EEC;
 - (b) the complete technical file supplying the information requested in Annexes III and IV to Directive 2001/18/EC;
 - (c) the environmental risk assessment in accordance with the principles set out in Annex II to Directive 2001/18/EC; and
 - (d) the results of any investigations performed for the purposes of research or development.

Articles 13 to 24 of Directive 2001/18/EC shall not apply to veterinary medicinal products containing or consisting of genetically modified organisms.

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

In the case of a veterinary medicinal product containing or consisting of genetically modified organisms, the opinion of the Committee shall respect the environmental safety requirements laid down by Directive 2001/18/EC. During the process of evaluating applications for marketing authorisations for veterinary medicinal products containing or consisting of genetically modified organisms, necessary consultations shall be held by the rapporteur with the bodies set up by the Community or the Member States in accordance with Directive 2001/18/EC.

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

Article 29

1. In order to prepare its opinion, the Committee for Veterinary Medicinal Products:
 - (a) shall verify that the particulars and documents submitted in accordance with Article 28 comply with the requirements of Directive 2001/82/EC and examine whether the conditions specified in this Regulation for issuing a marketing authorisation are satisfied;
 - (b) may ask for a State laboratory or 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 are satisfactory;
 - (c) may request a Community reference laboratory, State laboratory or 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 j, second indent of Article 12(3) of Directive 2001/82/EC is satisfactory and is suitable for use to reveal the presence of residue levels, particularly those above the maximum residue level accepted by the Community in accordance with the provisions of Regulation (EEC) No 2377/90;
 - (d) may request the applicant to supplement the particulars accompanying the application within a specific time-limit.

Where the Committee avails itself of the option contained in point (d) of the first subparagraph, the time-limit laid down in the first subparagraph of Article 28(3) shall be suspended until such time as the supplementary information requested has been provided. Likewise, the time-limit shall be suspended for the time allowed to the applicant to prepare oral or written explanations.

2. In those cases where the analytical method has not been subject to verification by one of the abovementioned laboratories in the framework of the procedures established by Regulation (EEC) No 2377/90, the verification shall be carried out within the framework of this Article.

Article 30

1. Upon receipt of a written request from the Committee for Veterinary Medicinal Products, a Member State shall forward the information establishing that the manufacturer of a veterinary medicinal product or the importer from a non-member country is able to manufacture the veterinary medicinal product concerned and/or carry out the necessary control tests in accordance with the particulars and documents supplied pursuant to Article 28.
2. Where it considers it necessary in order to complete its examination of the application, the Committee for Veterinary Medicinal Products may require the applicant to submit to a specific inspection of the manufacturing site of the veterinary medicinal product concerned.

The inspection, which shall be completed within the time-limit referred to in the first subparagraph of Article 28(3), shall be undertaken by inspectors from the Member State who possess the appropriate qualifications and who may be accompanied by a rapporteur or expert appointed by the Committee.

Article 31

1. The Agency shall forthwith inform the applicant if the opinion of the Committee for Veterinary Medicinal Products is that:
 - (a) the application does not satisfy the criteria for authorisation set out in this Regulation;
 - (b) the summary of the product characteristics should be amended;
 - (c) the labelling or package leaflet of the product is not in compliance with Title V of Directive 2001/82/EC;
 - (d) the authorisation should be granted subject to the conditions provided for in Article 35(4).

2. Within 15 days of receipt of the opinion referred to in paragraph 1, the applicant may provide written notice to the Agency that he/she wishes to appeal. In that case the applicant shall forward the detailed grounds for his/her appeal to the Agency within 60 days of receipt of the opinion.

Within 60 days of receipt of the grounds for appeal, the Committee for Veterinary Medicinal Products shall re-examine its opinion in accordance with the conditions laid down in the second subparagraph of Article 55(1). The conclusions reached on the appeal shall be annexed to the final opinion.

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

4. In the event of an opinion in favour of granting the relevant authorisation to place the relevant veterinary medicinal product on the market, the following documents shall be annexed to the opinion:
 - (a) a draft summary of the product characteristics, as referred to in Article 14 of Directive 2001/82/EC; where necessary, this draft shall reflect differences in the veterinary conditions pertaining in the Member States;
 - (b) the case of a veterinary medicinal product intended for administration to food-producing animals, a statement of the maximum residue level which may be accepted by the Community in accordance with Regulation (EEC) No 2377/90;
 - (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 veterinary medicinal product may be made available to users, in conformity with the criteria laid down in Directive 2001/82/EC;

- (d) the draft text of the labelling and package leaflet proposed by the applicant, presented in accordance with Title V of Directive 2001/82/EC;
- (e) the assessment report.

Article 32

1. Within 30 days of receipt of the opinion referred to in Article 27(2), the Commission shall prepare a draft of the decision to be taken in respect of the application.

In the event of a draft decision which envisages the granting of marketing authorisation, the draft shall include the documents mentioned in points (a) to (d) of Article 31(4), or shall make reference to them.

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

The draft decision shall be forwarded to the Member States and the applicant.

2. The Commission shall take a final decision in accordance with the procedure referred to in Article 77(3) if the draft decision accords with the Agency's opinion.

The Commission shall take a final decision in accordance with the procedure referred to in Article 77(4) if the draft decision does not accord with the Agency's opinion.

3. The Standing Committee for Veterinary Medicinal Products referred to in Article 77(1) shall adjust its rules of procedure so as to take account of the tasks assigned to it by this Regulation.

These adjustments shall provide that:

- (a) the opinion of the Standing Committee is to be given in writing;
- (b) each Member State is allowed 15 days to forward written observations on the draft decision to the Commission; however, if a decision has to be taken urgently, a shorter time-limit may be set by the Chairman according to the degree of urgency involved;
- (c) each Member State shall be permitted to request in writing that the draft decision referred to in paragraph 1 be discussed at a plenary meeting of the Standing Committee; that request shall give reasons in detail.

4. Where, in the opinion of the Commission, the written observations of a Member State raise important new questions of a scientific or technical nature which have not been addressed in the opinion of the Agency, the Chairman shall suspend the procedure and refer the application back to the Agency for further consideration.
5. The provisions necessary for the implementation of paragraph 3 shall be adopted by the Commission in accordance with the procedure referred to in Article 77(2).
6. The Agency shall disseminate the documents referred to in points (a) to (d) of Article 31(4).

Article 33

1. The marketing authorisation shall be refused if, after verification of the information and particulars submitted in accordance with Article 28, it appears that:
 - (a) the quality, the safety or the efficacy of the veterinary medicinal product have not been properly or sufficiently demonstrated by the applicant;
 - (b) in the case of zootechnical veterinary medicinal products and growth promoters, when the safety and welfare of the animals and/or consumer safety and benefits in terms of health have not been sufficiently taken into account;
 - (c) the waiting time 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;
 - (d) the veterinary medicinal product is presented for a use prohibited under other Community provisions.

Authorisation shall likewise be refused if the particulars and documents provided by the applicant in accordance with Article 28 are incorrect or if the labelling and package leaflets proposed by the applicant are not in accordance with Title V of Directive 2001/82/EC.

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

Article 34

1. Without prejudice to Article 71 of Directive 2001/82/EC, a marketing authorisation which has been issued in accordance with this Regulation shall be valid throughout the Community. It shall confer the same rights and obligations in each of the Member States as a marketing authorisation granted by that Member State in accordance with Article 5 of Directive 2001/82/EC.

The authorised veterinary medicinal products shall be entered in the Community Register of Medicinal Products and shall be given a number which shall appear on the packaging.

2. Notification of marketing authorisation shall be published in the *Official Journal of the European Communities*, quoting in particular the date of authorisation and the number in the Community Register.
3. The Agency shall publish the assessment report on the veterinary medicinal product drawn up by the Committee for Veterinary Medicinal Products and the reasons for its opinion in favour of granting authorisation, after deletion of any information of a commercially confidential nature.

4. After marketing authorisation has been granted, the holder of the authorisation shall inform the Agency of the dates of actual marketing of the veterinary medicinal product in the Member States, taking into account the various presentations authorised.

The holder shall also inform the Agency if the product ceases to be marketed.

Upon request by the Agency, particularly in the context of pharmacovigilance, the marketing authorisation holder shall provide the Agency with all data relating to the volume of sales of or prescriptions for the medical product at Community level, broken down by Member State.

Article 35

1. Without prejudice to paragraphs 2 and 3, authorisation shall be valid for unlimited duration.
2. Any authorisation which is not followed by the actual placing of the veterinary medicinal product authorised on the Community market within two years of authorisation shall cease to be valid.
3. When an authorised veterinary medicinal product previously placed on the market is no longer actually present on the market for two consecutive years, the authorisation for the product shall cease to be valid.
4. In exceptional circumstances and following consultation with the applicant, authorisation may be granted only under specific conditions. Continuation of the authorisation shall be linked to the annual reassessment of these conditions. Such exceptional decisions may be adopted only for objective and verifiable reasons.
5. When an application is lodged for a marketing authorisation in respect of veterinary medicinal products of major interest, particularly from the point of view of animal health and from the viewpoint of therapeutic innovation, the applicant may request an accelerated assessment procedure. Due reasons are to be given for the request.

If the Committee for Veterinary Medicinal Products accepts the application, the time-limits laid down in the first subparagraph of Article 28(3) shall be reduced to 150 days.

6. When adopting its opinion, the Committee for Veterinary Medicinal Products shall include a proposal concerning the conditions for the prescription or use of the veterinary medicinal products.
7. Veterinary medicinal products which have been authorised in accordance with the provisions of this Regulation shall enjoy the periods of protection referred to in Articles 13 and 13a of Directive 2001/82/EC.

Article 36

The granting of authorisation shall not affect the civil and criminal liability borne by the manufacturer or the holder of the marketing authorisation by virtue of the prevailing national law of the Member States.

CHAPTER 2

SUPERVISION AND SANCTIONS

Article 37

1. After an authorisation has been issued in accordance with this Regulation, the holder of the marketing authorisation shall, in respect of the methods of production and control provided for in points (d) and (i) of Article 12(3) of Directive 2001/82/EC, take account of technical and scientific progress and make any amendments that may be required to enable the medicinal products to be manufactured and checked by means of generally accepted scientific methods. He/she shall apply for approval for these amendments in accordance with this Regulation.
2. The competent authority in a Member State or the Agency may require the marketing authorisation holder to provide substances in sufficient quantities for the performance of tests to detect the presence of residues of the veterinary medicinal products concerned in foodstuffs of animal origin.
3. At the request of the competent authority of a Member State or the Agency, the holder of the marketing authorisation shall provide his technical expertise to facilitate the implementation of the analytical method for detecting residues of veterinary medicinal products by the Community reference laboratory or, where appropriate, national reference laboratories appointed in accordance with Council Directive 96/23/EC¹⁵.
4. The holder of the marketing authorisation shall forthwith supply to the Agency, the Commission and the Member States any new information which might entail the amendment of the particulars and documents referred to in Articles 12(3), 13a and 14 of Directive 2001/82/EC, and in Annex I thereto, and in Article 31(4) of this Regulation.

He/she shall forthwith inform the Agency, the Commission and the Member States 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 veterinary medicinal product concerned.
5. If the holder of the authorisation for placing the veterinary product on the market proposes to make any alteration to the information and documents referred to in paragraph 4, he/she shall submit the relevant application to the Agency.
6. The Commission shall, after consulting the Agency, make appropriate arrangements for the examination of variations to the terms of a marketing authorisation.

The Commission shall adopt these arrangements in the form of a regulation in accordance with the procedure laid down in Article 77(2).

¹⁵ OJ L 125, 23.5.1996, p. 10.

Article 38

1. In the case of veterinary medicinal products manufactured within the Community, the supervisory authorities shall be the competent authorities of the Member State or Member States which have granted the authorisation provided for in Article 44 of Directive 2001/82/EC in respect of the manufacture of the medicinal product concerned.
2. In the case of veterinary medicinal products imported from non-member countries, the supervisory authorities shall be the competent authorities of the Member States in which the controls referred to in Article 55(2) of Directive 2001/82/EC 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.

A Member State may request assistance from another Member State or the Agency.

Article 39

1. The supervisory authorities shall have responsibility for verifying on behalf of the Community that the holder of the marketing authorisation for the veterinary medicinal product or the manufacturer or importer established on Community territory satisfies the requirements laid down in Titles IV and VIII of Directive 2001/82/EC .
2. Where, in accordance Article 90 of Directive 2001/82/EC, the Commission is informed of serious differences of opinion between Member States as to whether the holder of the marketing authorisation for the veterinary medicinal product or a manufacturer or importer established within the Community satisfies the requirements referred to in paragraph 1, the Commission may, after consultation with the Member States concerned, request an inspector from the supervisory authority to undertake a new inspection of the marketing authorisation holder, the manufacturer or the importer; the inspector in question shall be accompanied by two inspectors from Member States which are not party to the dispute and/or by two experts nominated by the Committee.
3. Subject to any arrangements which may have been concluded between the Community and non-member countries in accordance with Article 38(2), the Commission may, upon receipt of a reasoned request from a Member State, the Committee for Veterinary Medicinal Products, or on its own initiative, require a manufacturer established in a non-member country to submit to an inspection.

The inspection shall be undertaken by inspectors from the Member State who possess the appropriate qualifications and who may, if need be, be accompanied by a rapporteur or expert appointed by the Committee for Veterinary Medicinal Products. The report of the inspectors shall be made available to the Commission, the Member States and the Committee for Veterinary Medicinal Products.

Article 40

1. Where the supervisory authorities or the competent authorities of any other Member State are of the opinion that the manufacturer or importer established on Community territory is no longer fulfilling the obligations laid down in Title VII of Directive 2001/82/EC, 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 or the Commission considers that one of the measures envisaged in Title VIII of Directive 2001/82/EC should be applied in respect of the veterinary medicinal product concerned or where the Committee for Veterinary Medicinal Products has delivered an opinion to that effect in accordance with Article 27 of this Regulation.

2. The Commission shall request the opinion of the Agency within a time-limit which it shall determine in the light of the urgency of the matter, in order to examine the reasons advanced. Whenever practicable, the holder of the authorisation for placing the medicinal product on the market shall be invited to provide oral or written explanations.
3. Following an opinion by the Agency, the Commission shall adopt the necessary provisional measures, which shall be applied immediately.

A final decision shall be adopted within six months, in accordance with the procedures referred to in Article 32(2).

4. Where urgent action is essential to protect human or animal health or the environment, a Member State may, on its own initiative or at the Commission's request, suspend the use on its territory of a veterinary medicinal product which has been authorised in accordance with this Regulation.

When it does so on its own initiative, it shall inform the Commission and the Agency of the reasons for its action at the latest on the next working day following the suspension. The Agency shall inform the other Member States without delay. The Commission shall immediately initiate the procedure provided for in paragraphs 2 and 3.

5. The suspensive measures referred to in paragraph 4 may be maintained until such time as a definitive decision has been reached in accordance with the procedures referred to in Article 32(2).
6. The Agency shall, upon request, inform any person concerned of the final decision.

CHAPTER 3

PHARMACOVIGILANCE

Article 41

For the purpose of this Chapter, Article 77(2) of Directive 2001/82/EEC shall apply.

Article 42

The Agency, acting in close cooperation with the national pharmacovigilance systems established in accordance with Article 73 of Directive 2001/82/EC, shall receive all relevant information about suspected adverse reactions to veterinary medicinal products which have been authorised by the Community in accordance with this Regulation. If necessary the Committee for Veterinary Medicinal Products may, in accordance with Article 27 of this Regulation, formulate opinions on the measures necessary.

These measures may include amendments to the marketing authorisation. They shall be adopted in accordance with the procedures referred to in Article 32(2).

The holder of the marketing authorisation to place the medicinal product on the market and the competent authorities of the Member States shall ensure that all relevant information about suspected adverse reactions to the veterinary medicinal products authorised under this Regulation are brought to the attention of the Agency in accordance with the provisions of this Regulation.

Article 43

The holder of an authorisation to place a veterinary medicinal product on the market granted in accordance with the provisions of this Regulation shall have permanently and continuously at his disposal an appropriately qualified person responsible for pharmacovigilance.

That qualified person shall be resident in the Community and shall be responsible for the following:

- (a) the establishment and maintenance of a system which ensures that information about all suspected adverse reactions which are reported to the personnel of the company and to medical representatives is collected, evaluated and collated so that it may be accessed at a single point within the Community;
- (b) the preparation of the reports referred to in Article 44(3) for the competent authorities of the Member States and the Agency in accordance with the requirements of this Regulation;
- (c) ensuring that any request from the competent authorities 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;
- (d) providing the competent authorities with any other information relevant to the evaluation of the risks and benefits of a veterinary medicinal product, particularly information concerning post-marketing safety studies.

Article 44

1. The holder of the authorisation for placing a veterinary medicinal product on the market shall ensure that all suspected serious adverse reactions, and adverse human reactions, occurring within the Community to a veterinary medicinal product authorised in accordance with the provisions of this Regulation which are brought to his attention by a health-care professional are recorded and reported immediately to the Member States in whose territory the incident occurred, and in no case later than 15 days following the receipt of the information

The holder of the marketing authorisation shall be obliged to record any other suspected serious adverse reactions which meet the notification criteria, in accordance with the guidelines referred to in Article 46, of which he may reasonably be expected to be aware, and to notify immediately the Member States on whose territory the incident occurred and the Agency, no later than 15 days following receipt of the information.

2. The holder of the marketing authorisation for the veterinary medicinal product shall ensure that all suspected serious unexpected adverse reactions, and adverse human reactions, occurring in the territory of a non-member country, are reported immediately to the Member States and the Agency and in no case later than 15 days following the receipt of the information. The arrangements for the reporting of suspected unexpected adverse reactions which are not serious, whether arising in the Community or in a non-member country, shall be adopted in accordance with the procedure referred to in Article 77(2).

Save in exceptional circumstances, these reactions shall be communicated in the form of an electronically transmitted report and in accordance with the guidance referred to in Article 46.

3. In addition, the holder of the authorisation to place a veterinary medicinal product on the market shall be required to maintain detailed records of all suspected adverse reactions occurring within or outside the Community which are reported to him/her by a health-care professional.

Unless other requirements have been laid down as a condition of the granting of the marketing authorisation by the Community, these records shall be submitted, in the form of a updated periodical report on safety, to the Agency and Member States immediately upon request or at least every six months during the first two years following authorisation and once a year for the following two years. Thereafter, the records shall be submitted at three-yearly intervals, or immediately upon request.

These records shall be accompanied by a scientific evaluation.

Article 45

Each Member State shall ensure that all suspected serious adverse reactions, and adverse human reactions, occurring within its territory to a veterinary medicinal product authorised in accordance with the provisions of this Regulation which are brought to its attention are recorded and reported immediately to the Agency and the holder of the authorisation for placing the veterinary medicinal product on the market, and in no case later than 15 days following the receipt of the information.

The Agency shall forward the information to the national pharmacovigilance systems set up in accordance with Article 73 of Directive 2001/82/EC.

Article 46

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

In accordance with this guidance, holders of marketing authorisation shall use the medical terminology accepted at international level for the transmission of adverse reaction reports.

The Agency, in consultation with the Member States and the Commission, shall set up a data-processing network for the rapid transmission of data between the competent Community authorities in the event of an alert relating to faulty manufacture, serious adverse reactions and other pharmacovigilance data regarding veterinary medicinal products authorised in accordance with Article 5 of Directive 2001/82/EC.

Article 47

The Agency shall cooperate with international organisations concerned with veterinary pharmacovigilance.

Article 48

Any amendment necessary to update the provisions of this Chapter to take account of scientific and technical progress shall be adopted in accordance with the procedure referred to in Article 77(2).

TITLE IV

THE EUROPEAN AGENCY FOR THE EVALUATION OF MEDICINAL PRODUCTS RESPONSIBILITIES AND ADMINISTRATIVE STRUCTURE

CHAPTER 1

TASKS OF THE AGENCY

Article 49

A European Agency for the Evaluation of Medicinal Products is hereby established.

The Agency shall be responsible for coordinating the existing scientific resources put at its disposal by the competent authorities of the Member States for the evaluation and supervision of medicinal products.

Article 50

1. The Agency shall comprise:
 - (a) the Committee for Human Medicinal Products, which shall be responsible for preparing the opinion of the Agency on any question relating to the evaluation of medicinal products for human use;

- (b) the Committee for Veterinary Medicinal Products, which shall be responsible for preparing the opinion of the Agency on any question relating to the evaluation of medicinal products for veterinary use;
 - (c) the Committee on Orphan Medicinal Products;
 - [(d) the Committee on Herbal Medicinal Products;]
 - (e) a Secretariat, which shall provide technical and administrative support for the Committees and ensure appropriate coordination between them;
 - (f) an Executive Director, who shall exercise the responsibilities set out in Article 57;
 - (g) a Management Board, which shall exercise the responsibilities set out in Articles 58, 59, and 60;
 - (h) an Advisory Board, the functions of which are laid down in Article 59.
2. The Committees referred to in points (a) to (d) of paragraph 1 may each establish working parties and expert groups. For this purpose they shall adopt, in accordance with their rules of procedure, precise arrangements for delegating certain tasks to these working parties and groups.
 3. The Executive Director, in close consultation with the Committee for Human Medicinal Products and the Committee for Veterinary Medicinal Products, shall set up the administrative structures and procedures allowing the development of advice for companies, as referred to in point (1) of Article 51, particularly regarding the development of new therapies.

Each committee shall establish a standing working party with the sole remit of providing scientific advice to companies.

4. The Committee for Human Medicinal Products and the Committee for Veterinary Medicinal Products may, if they consider it appropriate, seek guidance on important questions of a general scientific or ethical nature.

Article 51

1. The Agency shall 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, and 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.

To this end, the Agency, acting particularly through its Committees, 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 authorisation procedures;

- (b) transmitting on request and making available assessment reports, summaries of product characteristics, labels and package leaflets or inserts for these medicinal products;
- (c) the coordination of the supervision, under practical conditions of use, of medicinal products which have been authorised within the Community and the provision of advice on the measures necessary to ensure the safe and effective use of these products, in particular by evaluation, coordination of the implementation of pharmacovigilance obligations and the monitoring of this implementation;
- (d) assuring the dissemination of information on adverse reactions to medicinal products authorised in the Community, by means of a database permanently accessible to all Member States;
- (e) distributing appropriate pharmacovigilance information to the general public;
- (f) advising on the maximum limits for residues of veterinary medicinal products which may be accepted in foodstuffs of animal origin in accordance with Regulation (EEC) No 2377/90;
- (g) coordinating the verification of compliance with the principles of good manufacturing practice, good laboratory practice and good clinical practice;
- (h) upon request, providing technical and scientific support for steps to improve cooperation between the Community, its Member States, international organisations and non-member countries on scientific and technical issues relating to the evaluation of medicinal products, in particular in the context of discussions organised in the framework of international conferences on harmonisation;
- (i) recording the status of marketing authorisations for medicinal products granted in accordance with Community procedures;
- (j) creating a database on medicinal products, to be accessible to the general public, and giving technical assistance for its maintenance;
- (k) assisting the Community and Member States in the provision of information to health care professionals and the general public about medicinal products evaluated by the Agency;
- (l) advising companies on the conduct of the various tests and trials necessary to demonstrate the quality, safety and efficacy of medicinal products and, in particular, on the observance of good manufacturing practices;
- (m) checking that the conditions laid down in Community legislation on medicinal products and in the marketing authorisations are observed in the case of parallel distribution of medicinal products authorised in accordance with this Regulation;
- (n) drawing up, at the Commission's request, any other scientific opinion concerning the evaluation of medicinal products or the starting materials used in the manufacture of medicinal products.

2. The database provided for in point (j) of paragraph 1 shall include the summaries of product characteristics, the patient or user package leaflet and the information shown on the labelling. The database shall be developed in stages, priority being given to medicinal products authorised under this Regulation and those authorised under Chapters IV (Title III) of Directive 2001/83/EC and Directive 2001/82/EC respectively. The database shall subsequently be extended to include other medicinal products.

Article 52

The Agency may give a scientific opinion, in the context of cooperation with the World Health Organisation, for the assessment of certain medicinal products for human use intended exclusively for the markets of non-member countries. For this purpose, on the recommendation of the World Health Organisation, a request shall be submitted to the Agency, in accordance with the provisions of Article 6. The Committee for Human Medicinal Products shall be responsible for drawing up the Agency's opinion, in accordance with the provisions of Articles 6 to 9. The provisions of Article 10 shall not apply.

Article 53

1. The Agency shall take care to ensure early identification of potential sources of conflict between its scientific opinions and those of other bodies established under Community law carrying out a similar task in relation to issues of common concern.
2. Where the Agency identifies a potential source of conflict, it shall contact the body concerned in order to ensure that any relevant scientific information is shared and to identify the scientific points which are potentially contentious.
3. Where there is a fundamental conflict over scientific points and the body concerned is a Community agency or a scientific committee, the Agency and the body concerned shall work together either to solve the conflict or to submit a joint document to the Commission clarifying the scientific points of conflict.
4. Save as otherwise provided for in this Regulation, in Directive 2001/83/EC or in Directive 2001/82/EC, where there is a fundamental conflict over scientific points and the body concerned is a body in a Member State, the agency and the national body concerned shall work together either to solve the conflict or to prepare a joint document clarifying the scientific points of conflict.

Article 54

1. Each Member State shall appoint, for a three-year term which shall be renewable, one member to the Committee for Human Medicinal Products and one member to the Committee for Veterinary Medicinal Products. Members shall be chosen for their role and experience in the evaluation of medicinal products for human and veterinary use as appropriate and shall maintain relevant contacts with the competent national authorities.

The committees may coopt a maximum of five additional members chosen on the basis of their specific scientific competence. These members shall be appointed for a term of three years which shall be renewable.

The members of each Committee may be accompanied by experts in specific scientific or technical fields.

The Executive Director of the Agency or his/her representative and representatives of the Commission shall be entitled to attend all the meetings of the Committees and working parties convened by the Agency or its committees.

2. In addition to their task of providing objective scientific opinions 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 tasks of the Agency and the work of competent national authorities, including the consultative bodies concerned with the marketing authorisation.
3. The members of the Committees and the experts responsible for evaluating medicinal products shall rely on the scientific assessment and resources available to the national marketing authorisation bodies. Each competent national authority shall monitor the scientific level and independence of the evaluation carried out and facilitate the activities of the Committee members and experts nominated. The Member States shall refrain from giving the Committee members and experts any instruction which is incompatible with their own individual tasks or with the tasks and responsibilities of the Agency.
4. When preparing the opinion, each Committee shall use its best endeavours to reach a scientific consensus. If such a consensus cannot be reached, the opinion shall consist of the position of the majority of members and the divergent positions, with their grounds.
5. Each Committee shall establish its own rules of procedure.

These rules shall in particular lay down the procedures for appointing and replacing the Chairman, the procedures for delegating certain tasks to working parties and the establishment of a procedure for the urgent adoption of opinions, particularly in relation to the provisions on market surveillance and pharmacovigilance laid down in this Regulation.

They shall enter into force after receiving a favourable opinion from the Commission and the Management Board.

Article 55

1. Where, in accordance with the provisions of this Regulation, the Committee for Human Medicinal Products or the Committee for Veterinary Medicinal Products is required to evaluate a medicinal product, it shall appoint one of its members to act as rapporteur for the coordination of the evaluation. The Committee concerned may appoint a second member to act as co-rapporteur.

If there is an appeal against one of its opinions, the Committee concerned shall appoint a different rapporteur and, where necessary, a different co-rapporteur from those appointed for the initial opinion. This appeal procedure may deal only with the points of the opinion initially identified by the applicant and may be based only on the scientific data available at the time the Committee adopted the initial opinion.

2. Member States shall transmit to the Agency the names of national experts with proven experience in the assessment of medicinal products who would be available to serve on working parties or expert groups of the Committee for Human Medicinal Products or the Committee for Veterinary Medicinal Products, together with an indication of their qualifications and specific areas of expertise.

The Agency shall keep an up-to-date list of accredited experts. The list shall include the experts referred to in the first subparagraph and other experts appointed directly by the Agency. The list shall be updated.

3. 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/her employer, shall be remunerated in accordance with a scale of fees to be included in the financial arrangements established by the Management Board.

4. The performance of scientific services for which there are several potential providers may result in a call for an expression of interest, if the scientific and technical context allows, and if it is compatible with the duties of the Agency, in particular the need to provide a high level of public health protection.

The Management Board shall adopt the appropriate procedures on a proposal from the Executive Director.

5. The Agency or any of the committees referred to in points (a) to (d) of Article 50(1) may use the services of experts for the discharge of other specific tasks for which they are responsible.

Article 56

1. The membership of the committees referred to in points (a) to (d) of Article 50(1) shall be made public. When each appointment is published, the professional qualifications of each member shall be specified.
2. Members of the Management Board, members of the Advisory Board, members of the Committees, rapporteurs and experts shall not have financial or other interests in the pharmaceutical industry which could affect their impartiality. They shall undertake to act in the public interest and in an independent manner. All indirect interests which could relate to this industry shall be entered in a register held by the Agency which the public may consult.

Members of the Management Board, members of the Advisory Board, members of the Committees, rapporteurs and experts who participate in meetings or working groups of the Agency shall declare, at each meeting, any specific interests which could be considered to be prejudicial to their independence with respect to the points on the agenda.

Article 57

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/she shall be responsible:
 - (a) for the day-to-day administration of the Agency;
 - (b) for managing all the Agency resources necessary for conducting the activities of the committees referred to in points (a) to (d) of Article 50(1), including making available appropriate scientific and technical support;
 - (c) for ensuring that the time-limits laid down in Community legislation for the adoption of opinions by the Agency are complied with;
 - (d) for ensuring appropriate coordination between the committees referred to in points (a) to (d) of Article 50(1);
 - (e) for the preparation of the statement of revenue and expenditure and the execution of the budget of the Agency;
 - (f) for all staff matters;
 - (g) for requesting the opinion of the Advisory Board on any point concerning the Agency's activities regarding the procedures for authorising medicinal products;
 - (h) for providing the secretariat for the Management Board and the Advisory Board.
3. Each year, the Executive Director shall submit the following to the Management Board for approval, while making a distinction between the Agency's activities concerning medicinal products for human use and those concerning veterinary medicinal products:
 - (a) a draft report covering the activities of the Agency in the previous year, including information about the number of applications evaluated within the Agency, the time taken for completion of the evaluation and the medicinal products authorised, rejected or withdrawn;
 - (b) a draft programme of work for the coming year;
 - (c) the draft annual accounts;
 - (d) the draft forecast budget for the coming year.
4. The Executive Director shall approve all financial expenditure of the Agency.

Article 58

1. The Management Board shall consist of four representatives of the Member States, four representatives of the European Parliament, four representatives of the Commission, and four representatives of patients and industry, appointed by the Commission.

The full members of the Management Board may arrange to be replaced by alternates.

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 majority of two-thirds of its members.
4. 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 European Parliament, the Council, and the Commission.

Article 59

The Advisory Board shall consist of one representative from each of the national authorities competent in the authorisation of human and veterinary medicinal products. The Executive Director or his representative and the representatives of the Commission shall have the right to attend the meetings of the Advisory Board.

The Commission may submit any question concerning Community procedures for the authorisation of medicinal products to the Advisory Board.

The opinions of the Advisory Board shall not be binding in any way.

The Management Board, on the proposal of the Executive Director and following a favourable opinion from the Commission, shall draw up the provisions necessary for the implementation of this Article.

CHAPTER 2

FINANCIAL PROVISIONS

Article 60

1. The revenues of the Agency shall consist of a contribution from the Community and the fees paid by undertakings for obtaining and maintaining a marketing authorisation 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. By 15 February of each year at the latest, the Director shall draw up a preliminary draft budget covering the operational expenditure and the programme of work anticipated for the following financial year, and shall forward this preliminary draft to the Management Board together with an establishment plan.
4. Revenue and expenditure shall be in balance.
5. The Management Board shall adopt the draft budget and forward it to the Commission, which on that basis shall establish the relevant estimates in the preliminary draft general budget of the European Communities, which it shall lay before the Council pursuant to Article 272 of the Treaty.
6. The Management Board shall adopt the Agency's final budget before the beginning of the financial year, adjusting it where necessary to the Community subsidy and the Agency's other resources.
7. The Director shall implement the Agency's budget.
8. Monitoring of the commitment and payment of all the Agency's expenditure and of the establishment and recovery of all the Agency's revenue shall be carried out by the financial controller of the Commission.
9. By 31 March of each year at the latest, the Director shall forward to the Commission, the Management Board and the Court of Auditors the accounts for all the Agency's revenue and expenditure in respect of the preceding financial year. The Court of Auditors shall examine them in accordance with Article 248 of the Treaty.
10. The Management Board, on a recommendation by the European Parliament, shall give a discharge to the Director in respect of the implementation of the budget.
11. After the Court of Auditors has delivered its opinion, the Management Board shall adopt the internal financial provisions specifying, in particular, the detailed rules for establishing and implementing the Agency's budget.

Article 61

The structure and the amount of the fees referred to in Article 60(1) shall be established by the Council acting under the conditions provided for by the Treaty on a proposal from the Commission, following the latter's consultation of organisations representing the interests of the pharmaceutical industry at Community level.

CHAPTER 3

GENERAL PROVISIONS GOVERNING THE AGENCY

Article 62

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 63

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 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 it or 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 rules applying to the staff of the Agency.

Article 64

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

Article 65

The staff of the Agency shall be subject to the rules and regulations applicable to officials and other staff of the European Communities. In respect of its staff, the Agency shall exercise the powers which have been devolved to the appointing authority.

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

Article 66

Members of the Management Board, members of the Advisory Board, members of the Committees referred to in points (a) to (d) of Article 50(1), and experts and officials and other servants of the Agency, shall be required, even after their duties have ceased, not to disclose information of the kind covered by the duty of professional secrecy.

Article 67

The Commission may, in agreement with the Management Board and the relevant Committee, invite representatives of international organisations with interests in the harmonisation of regulations applicable to medicinal products to participate as observers in the work of the Agency. The conditions for participation shall be determined beforehand by the Commission.

Article 68

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 health professions. These contacts may include the participation of observers in certain aspects of the Agency's work, under conditions determined beforehand by the Management Board, in agreement with the Commission.

Article 69

The Management Board shall, in the case of veterinary medicinal products which have limited markets, or in the case of veterinary medicinal products intended for diseases with a regional distribution, adopt the necessary administrative measures to provide help to pharmaceutical companies at the time of submission of their applications. These administrative measures shall include, in particular, the taking over responsibility for some translations by the Agency.

Article 70

To ensure an appropriate level of transparency, the Management Board, on the basis of a proposal by the Executive Director, in agreement with the Commission, shall adopt rules to ensure the availability to the public of regulatory, scientific or technical information concerning the authorisation or supervision of medicinal products which is not of a confidential nature.

TITLE V

GENERAL AND FINAL PROVISIONS

Article 71

1. All decisions to grant, refuse, vary, suspend, withdraw or revoke a marketing authorisation 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.
2. An authorisation to place a medicinal product, governed by this Regulation, on the market shall not be granted, refused, varied, suspended or withdrawn except through the procedures and on the grounds set out in this Regulation.

Article 72

1. Only one authorisation may be granted to a particular applicant for a specific medicinal product.

However for objective verifiable reasons relating to public health or the availability of medicinal products to health professionals and/or patients, the Commission may authorise the same applicant to submit more than one application to the Agency for that medicinal product.
2. As regards medicinal products for human use, the provisions of Article 98(3) of Directive 2001/83/EC apply to medicinal products authorised under this Regulation.
3. Without prejudice to the unique, Community nature of the content of the documents referred to in points (a), (b) and (c) of Article 9(4) and in points (a) to (d) of Article 31(4), this Regulation shall not prohibit the use of two or more commercial designs for a given medicinal product covered by a single authorisation.

Article 73

1. By way of derogation from Article 6 of Directive 2001/83/EC, a medicinal product not authorised for human use belonging to the categories referred to in Article 3(1) and (2) of this Regulation, which is potentially of major interest from the point of view of public health, may be made available to certain patients for compassionate reasons.
2. Before any decision is taken concerning the compassionate use of the medicinal products falling within the categories referred to in Article 3(1) and (2), the manufacturer or the person applying for a marketing authorisation shall notify the Agency.
3. Where a compassionate use is envisaged, the Committee for Human Medicinal Products, after consulting the manufacturer or the applicant, may adopt recommendations on the conditions for use, the conditions for distribution and the patients targeted. The Member States shall take any appropriate measures to ensure that the recommendations may be implemented under the applicable national legislation.
4. The Agency shall keep an up-to-date list of the medicinal products referred to in paragraph 1 made available for compassionate use. Article 22(1) and Article 23 shall apply *mutatis mutandis*.
5. The recommendations referred to in paragraph 3 do not affect the civil or criminal liability of the manufacturer or the applicant for marketing authorisation.
6. No medicinal product administered for compassionate reasons may be the subject of a paid transaction, except in special cases determined beforehand in national legislation.
7. The actual placing on the market of a medicinal product previously administered for compassionate reasons, following the granting of a marketing authorisation or a negative opinion by the Committee for Human Medicinal Products within the meaning of Article 9(2), shall render paragraphs 3 and 6 of this Article invalid.
8. This Article shall be without prejudice to Directive 2001/20/EC of the European Parliament and of the Council¹⁶.

Article 74

1. 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 or the regulations adopted pursuant to it and shall take every measure necessary for their implementation. The penalties shall be effective, proportionate and dissuasive.

¹⁶ OJ L 121, 1.5.2001, p. 34.

Member States shall inform the Commission of these provisions no later than 31 December 2004 of the penalties laid down in accordance with the above subparagraph. They shall send notification of any subsequent alterations as soon as possible.

2. Member States shall inform the Commission immediately of the institution of any litigation concerning the infringement of this Regulation.
3. At the Agency's request, the Commission may impose financial penalties on the holders of marketing authorisations granted under this Regulation if they fail to observe certain obligations laid down in connection with the authorisations. The maximum amounts as well as the conditions and methods for collection of these penalties shall be laid down by the Commission in accordance with the procedure foreseen in Article 77(2).

Article 75

This Regulation shall not affect the competences vested in the European Food Authority created by Regulation (EC) No ... of the Parliament and of the Council¹⁷.

Article 76

At least every ten years, 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 4 of Title III of Directive 2001/83/EC [relating to medicinal products for human use] and in Chapter 4 of Title III of Directive 2001/82/EC [relating to medicinal products for veterinary use].

Article 77

1. The Commission shall be assisted by the Standing Committee on Medicinal Products for Human Use set up by Article 121 of Directive 2001/83/EC and by the Standing Committee on Veterinary Medicinal Products set up by Article 89 of Directive 2001/82/EC.
2. Where reference is made to this paragraph, the regulatory procedure laid down in Article 5 of Decision 1999/468/EC shall apply, in compliance with Article 7 and Article 8 thereof.

The period provided for in Article 5(6) of Decision 1999/468/EC shall be three months.

3. Where reference is made to this paragraph, the advisory procedure laid down in Article 3 of Decision 1999/468/EC shall apply, in compliance with Article 7 and Article 8 thereof.
4. Where reference is made to this paragraph, the management procedure laid down in Article 4 of Decision 1999/468/EC shall apply, in compliance with Article 7 and Article 8 thereof.

¹⁷ OJ L

The period provided for in Article 4(3) of Decision 1999/468/EC shall be one month.

Article 78

Regulation (EEC) No 2309/93/EC is hereby repealed.

References to the repealed Regulation shall be construed as references to this Regulation and shall be read in accordance with the correlation table in Annex II.

Article 79

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

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

Done at Brussels,

For the European Parliament

The President

For the Council

The President

ANNEX I

1. 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.
2. 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.
3. Medicinal products intended for administration to human beings, containing a new active substance which was not included in the composition of any medicinal product for human use authorised in the Community prior to the date of entry into force of this Regulation.
4. Medicinal products intended for veterinary use, containing a new active substance which was not included in the composition of any medicinal product for veterinary use authorised in the Community prior to the date of entry into force of this Regulation.

ANNEX II

Correlation table

Present Regulation	Regulation (EEC) No 2309/93
Article 1	Article 1
Article 2	Article 2
Article 3	Article 3
Article 4	Article 4
Article 5	Article 5
Article 6	Article 6
Article 7	Article 7
Article 8	Article 8
Article 9	Article 9
Article 10	Article 10
Article 11	Article 11
Article 12	Article 12
Article 13	Article 13
Article 14	Article 14
Article 15	Article 15
Article 16	Article 16
Article 17	Article 17
Article 18	Article 18
Article 19	Article 19
Article 20	Article 20
Article 21	Article 21
Article 22	Article 22

Article 23	Article 23
Article 24	Article 24
Article 25	Article 25
Article 26	Article 26
Article 27	Article 27
Article 28	Article 28
Article 29	Article 29
Article 30	Article 30
Article 31	Article 31
Article 32	Article 32
Article 33	Article 33
Article 34	Article 34
Article 35	Article 35
Article 36	Article 36
Article 37	Article 37
Article 38	Article 38
Article 39	Article 39
Article 40	Article 40
Article 41	Article 41
Article 42	Article 42
Article 43	Article 43
Article 44	Article 44
Article 45	Article 45
Article 46	Article 46
Article 47	Article 47
Article 48	Article 48
Article 49	Article 49

Article 50	Article 50
Article 51	Article 51
Article 52	New
Article 53	New
Article 54	Article 52
Article 55	Article 53
Article 56	Article 54
Article 57	Article 55
Article 58	Article 56
Article 59	New
Article 60	Article 57
Article 61	Article 58
Article 62	Article 59
Article 63	Article 60
Article 64	Article 61
Article 65	Article 62
Article 66	Article 63
Article 67	Article 64
Article 68	Article 65
	Article 66 (deleted)
Article 69	New
Article 70	New
Article 71	Articles 67 and 68
Article 72	New
Article 73	New
Article 74	Article 69
	Article 70 (deleted)

Article 75	New
Article 76	Article 71
Article 77	Articles 72 and 73
Article 78	New
Article 79	Article 74
Annex I	Annex (Parts A and B)

FINANCIAL STATEMENT

1. TITLE OF OPERATION

Proposal for a Regulation of the Parliament and of the Council laying down Community procedures for the authorisation and supervision of medicinal products for human and veterinary use and establishing a European Agency for the Evaluation of Medicinal Products

2. BUDGET HEADING(S) INVOLVED

B5-3120 European Agency for the Evaluation of Medicinal Products

3. LEGAL BASIS

Article 95 EC

4. DESCRIPTION OF OPERATION

4.1 General objective

To guarantee a high level of human and animal health protection, in particular through increased market surveillance and a stepping-up of pharmacovigilance procedures.

To increase the number of medicinal products available.

To complete the internal market in pharmaceutical products and to establish a legislative and regulatory framework promoting the competitiveness of the pharmaceutical industry.

To adapt the operation of the Agency and its administrative structure so as to cope with the consequences of the enlargement of the European Union.

4.2 Period covered and arrangements for renewal

Implementation of proposed measures scheduled for 2005, there being no specific target date.

5. CLASSIFICATION OF EXPENDITURE OR REVENUE

5.1 Non-compulsory expenditure

5.2 Non-differentiated appropriations

5.3 Type of revenue involved

Not applicable

6. TYPE OF EXPENDITURE OR REVENUE

Balancing subsidy to the Medicinal Products Agency

7. FINANCIAL IMPACT

7.1 Method of calculating the total cost of the operation (link between individual costs and total cost)

The cost of the operation for the Commission is calculated on the basis of the actual number of meetings of expert committee meetings per year for the type of operations considered for the proposal.

The cost of the operation for the Agency has to be based on the following assumptions:

- an increase in the level of revenue accruing from fees, as a result of greater responsibilities in respect of the evaluation of new categories of medicinal products, including in the event of the current level of these fees being maintained; however, the number of products involved each year and the relationship between cost and the difficulty of carrying out scientific evaluations remain unknown to date;
- an increase in expenditures as a result of the enlargement of the European Union, particularly because of:
 - a greater number of experts having to be convened each budget year, depending on the number of new Member States during each respective year (impossible to estimate as the timetables for accession by candidate countries are not known);
 - higher costs linked to the expansion of telematic networks and databases to accommodate new Member States (impossible to estimate for the same reasons).

On account of the uncertainties mentioned above, it is thus impossible to estimate the cost of the measures for the Agency. In particular, the possible adjustment of the Community subsidy in line with the increased activities of the Agency due to enlargement will have to be taken into account during the general review of Financial Perspectives in this regard.

7.2 Itemised breakdown of cost

Commitment appropriations in EUR million (at current prices)

Breakdown	Year n	n+1	[n+2]	[n+3]	[n+4]	n+ 5 and subsequent financial years	Total
Enlargement-related increase in Agency's activities					Cost to be calculated at time of accession		
Total							

8. FRAUD PREVENTION MEASURES

- Specific checks envisaged

No

9. ELEMENTS OF COST-EFFECTIVENESS ANALYSIS

9.1 Specific and quantified objectives: target population

Not applicable

9.2 Justification of the measure

- Need for a contribution from the Community budget, particularly in view of the subsidiarity principle

Amendment of existing legislation in order to take account of scientific and technical progress, as well as the future enlargement of the European Union

- Choice of ways and means

Amendment of existing legislation on the basis of Article 71 of Council Regulation (EEC) No 2309/93 following an evaluation of the implementation of existing legislation which is the subject of a report by the Commission to the Council and the European Parliament.

- Main factors of uncertainty which could affect the specific results of the operation

The chief factor of uncertainty ties in with the arrangements for enlargement of the European Union, in terms both of the countries concerned and the timetable involved. Another factor of uncertainty relates to the use which the industry will make of the procedures put in place: the number of products concerned per year and the relationship between cost and the difficulty of carrying out scientific evaluations remain unknown to date.

9.3 Monitoring and assessment

- Performance indicators

Number of products authorised in accordance with the procedures, progress of the work on technical harmonisation, timetable for the expansion procedures, database and computer networks to include candidate countries.

- Details and frequency of planned evaluations

Report by the Commission at least once every ten years following the first report, based on this proposal, to be prepared after six years.

- Assessment of the results obtained (where the operation is to be continued or renewed)

The results obtained since 1 January 1995 (data of entry into force of the present system) will be the subject of a report by the Commission to the Council and the European Parliament (adoption by written procedure)

10. ADMINISTRATIVE EXPENDITURE (PART A OF SECTION III OF THE GENERAL BUDGET)

The effective mobilisation of the requisite administrative resources will depend on the Commission's annual decision on how to allocate resources, bearing in mind in particular the additional amounts of money authorised by the budget authority.

10.1 Effect on the number of jobs

Type of job		Staff to be assigned to the operation		of whom		duration
		Permanent jobs	Temporary jobs	by using existing resources in the DG or department concerned	by using supplementary resources	
Officials or temporary agents	A B C	2A, 1B, 1C		2A, 1B, 1C	not applicable	
Other resources						
Total		2A, 1B, 1C		2A, 1B, 1C	not applicable	

Indicate when additional resources should be made available.

10.2 Aggregate cost of additional staffing requirements

(EUR)

	Cost	Method of calculation
Officials	432 000	4 times EUR 108 000 per year
Temporary agents		
Other resources(state budget heading)		
Total	432 000	

The figures represent the total costs of the additional posts for the duration of the operation, where stipulated, or for 12 months if the duration is not stipulated.

10.3 Increase in other operating expenditure involved in operation, in particular costs incurred by committee and expert group meetings

(EUR)

Budget heading(No and title)	Cost	Method of calculation
A0-7031	150 000	Without taking into account figures linked to enlargement (the annual number of experts from candidate countries not being known), the method of calculation is based on a cost of approximately EUR 10 000 per meeting for a number of experts from the 15 Member States.
Total	150 000	15 meetings per year

The amounts must correspond to the total cost of the operation if it is of fixed duration or for 12 months if the duration is not fixed.

IMPACT ASSESSMENT FORM
IMPACT OF THE PROPOSAL ON BUSINESSES, PARTICULARLY ON SMALL
AND MEDIUM-SIZED ENTERPRISES (SMEs)

TITLE OF THE PROPOSAL

Proposal for a Regulation of the European Parliament and of the Council laying down Community procedures for the authorisation and supervision of medicinal products for human and veterinary use and establishing a European Agency for the Evaluation of Medicinal Products

REFERENCE NUMBER OF THE DOCUMENT:

THE PROPOSAL

1. In view of the principle of subsidiarity, why is Community legislation necessary in this field and what are its main objectives?

The proposed legislation introduces new provisions and amends, in a number of respects, the existing legislation relating to the functioning of the centralised and decentralised procedures for approving and suspending the marketing of medicinal products for human and veterinary use.

Pursuant to Article 71 of Regulation (EEC) No 2309/93, the Commission is obliged to report within six years of the entry into force of the Regulation on the experience acquired as a result of the operation of the centralised and decentralised procedures. An audit report prepared on behalf of the Commission¹ has identified the aspects of the authorisation procedures that were operating satisfactorily and those where it was considered that improvement could be achieved.

From a business viewpoint, the proposed measures are intended to:

- increase the level of harmonisation across Member States of the rules governing medicinal products;
- increase the efficiency of operation of the centralised and decentralised procedures;
- thereby improve access and speed of access to the whole of the European market for both innovative and generic medicinal products; and
- allow industry to respond more quickly to the needs of the market.

¹ Evaluation of the operation of Community procedures for the authorisation of medicinal products, CMS Cameron McKenna and Andersen Consulting, October 2000.

The “new systems” for licensing which were introduced in 1995 have contributed to the creation of a single market in pharmaceuticals but, notwithstanding the progress that has been made, there is evidence that the procedures contain shortcomings. The findings of the audit report on the operation of the authorisation procedures show that there is a need to refine, and in some areas make more substantial changes to, the existing regimes. In particular, there is recognition that the centralised procedure is capable of working well and that broadening the scope of the procedure to other products would be beneficial, both in terms of patient access and economies of scale for the companies.

The decentralised procedure was acknowledged as having significant advantages in terms of optionality but any such advantage is tempered to an extent by the failure of the system to operate on the basis of effective mutual recognition involving a significant number of Member States.

The pharmaceutical industry is populated by different types of company and a significant proportion of the industry comprises non-R&D-intensive companies, notably those which focus on their own national markets and those which rely upon the manufacture of generic versions of existing products. The existing regimes do not, at present, fully meet all the needs of these sectors of the industry.

Instituting authorisation procedures that properly protect public health while promoting an innovative profitable pharmaceutical industry is critical for Europe. The pharmaceutical industry is a strategic sector for Europe but there is evidence that over the last decade the industry in Europe is losing competitiveness compared to the USA and that its growth is more erratic than in the US or Japan². The reasons underlying this trend are complex but the ability of companies to compete effectively is influenced, at least in part, by the nature of the regulatory environment.

The forthcoming enlargement of the European Union over the next decade will see the accession of further Member States. In principle, enlargement has the potential to contribute to the overall competitiveness of the European industry, but an important step in realising increased competitiveness is eradication of the shortcomings identified in the existing procedures prior to enlargement.

It is considered appropriate to maintain a balance between the centralised and decentralised authorisation procedures. Both systems have hitherto contributed – though not to the same extent - to the development of a single market in pharmaceuticals and provided a high degree of safety for patients and animals. However, the emergence of new technologies is delivering sophisticated medicinal products which are best suited to centralised approval.

² See "Global competitiveness in Pharmaceuticals", Report prepared for the Enterprise DG of the European Commission by Gambardella A, Orsenigol and Pammolli F., November 2000.

THE IMPACT ON BUSINESSES

2. Who will be affected by the proposal?

- What business sectors?

The measures primarily concern pharmaceutical manufacturers and to a lesser extent wholesalers and distributors of medicinal products.

The pharmaceutical industry in the EU consists of companies with a range of different businesses conducted often with a different geographical focus. The total number of pharmaceutical businesses in the EU is estimated at approximately 3 000³. Large multinational companies dominate the market accounting for approximately 60-65% of the market for pharmaceutical sales. Medium-sized companies (by international standards) make up approximately 30-35% of the market, with small local companies accounting for the balance. In terms of business types, the biotechnology element of the European pharmaceutical industry is still young, but the number of companies is growing with just over 1 000 company units. Generic medicines currently account for around 10% of total pharmaceutical sales in the non-hospital market with penetration highest in Germany, Denmark, UK and the Netherlands⁴. Finally, the veterinary sector accounts for approximately 5% of the value of the human pharmaceutical market⁵. This sector of the market is far more diverse than that relating to medicines for human use, reflecting differences in livestock distribution, methods of production and climate across the EU.

The legislative proposals cover a number of aspects of the regulation of medicinal products and consequently the proposals will impact to some extent upon all pharmaceuticals manufacturers. A number of the proposals will therefore affect all pharmaceutical companies irrespective of the nature of the pharmaceutical business. For example, the provisions relating to the validity of marketing authorisations, compassionate use of medicines, the application of good manufacturing practice to starting materials and pharmacovigilance. A number of the measures are sector-specific or specific to one or other of the authorisation procedures and accordingly the effect of such measures will be more selective. The centralised procedure tends to be used predominantly by large multinational companies and smaller innovation-specialist companies. Accordingly, the proposed changes to the centralised system such as the introduction of conditional authorisations and a fast-track procedure will be relevant for these types of company.

³ The pharmaceutical industry in figures, European Federation of Pharmaceutical Industries Associations, November 2000.

⁴ Generic Medicines: How to ensure their effective contribution to health care, Euro Health Vol 2 No 3, September 1996.

⁵ Fountain R and Thurman D: Animal Health Market to Face Opportunities and Challenges in 98, Feedstuffs Vol. 69 No 48, November 1997.

- What sizes of company (proportion of small and medium-sized enterprises)?

The decentralised (mutual recognition) procedure, although used by the large multinational companies, is also used by a significant proportion of small and medium-sized enterprises (“SMEs”). Accordingly, these companies will be impacted by the proposed amendments to the operation of the decentralised system. The principal sector-specific measures are directed towards manufacturers of products for veterinary use, manufacturers of generic medicines and manufacturers of homeopathic medicines.

- Are there particular geographical regions in the Community where such companies are established?

No, there are no differences.

3. What measures will companies have to take in order to comply with the proposal?

The majority of the proposal measures concern procedural changes and fine-tuning of existing procedures. Accordingly, a number of the measures do not impose direct obligations upon business. The majority of the obligations which are imposed impact at the time of application for a marketing authorisation.

Companies seeking to place a product containing a new chemical entity (“NCE”) on the market will be required to use the centralised authorisation procedure. This will remove, therefore, in respect of some medicinal products, the element of choice which companies currently enjoy when obtaining an authorisation from Member States. It should however, be noted that many products containing an NCE⁶ are already obliged to use the centralised route because they have been developed using biotechnological processes. Moreover, in circumstances where a company has a choice of procedure for a product containing an NCE, most of the companies already opt for the centralised route. It is intended that generic copies of centrally-authorized products may be authorised through either the centralised or the decentralised route. All other medicinal products may do likewise provided they show significant innovation over existing therapies. The broadening in scope of the centralised procedure will bring administrative savings for companies able to benefit from the single-application procedure. Some companies, particularly those in the veterinary sector with NCE-containing products which are relevant to only a limited geographical area of the European market, may be subject to an increase in the overall cost of preparing a centralised application for a marketing authorisation. This is why a derogation has been introduced.

Applicants pursuing an authorisation under the decentralised procedure will be compelled to enter arbitration proceedings if an issue cannot be resolved by the Member States concerned in the case of veterinary medicinal products. Companies may incur some costs in handling arbitration proceedings which they would otherwise avoid by withdrawal of the application. However, any such costs should be outweighed by the fact that companies may be permitted to market a medicinal product which is the subject of arbitration proceedings in the Member States that

⁶ Taken here in broader sense as meaning any new active substance.

have agreed to authorise the product, thus permitting companies to begin to recoup investment costs earlier than at present.

The harmonisation to ten years (plus, for medicines for human use, one year for new therapeutic indications) of the period of data protection afforded to innovator companies will prevent an applicant for a generic (copy) product from making abridged applications in Austria⁷, Denmark, Greece, Finland, Ireland, Luxembourg, Portugal, and Spain on the expiry of six years from the date of first authorisation of the innovator product in the EU. An abridged application is one where the applicant does not present the results of his/her own safety and efficacy testing but relies upon the data underlying the authorisation of the innovator product. However, this restriction is balanced by the fact that companies intending to seek an authorisation for a generic product will be permitted, under a "Bolar-type" provision, to conduct the testing required prior to the expiry of the originator product's period of patent protection.

There is recognition that in some respects the veterinary sector of the pharmaceutical industry has different requirements and faces different issues and the proposal, therefore, seeks to address matters which are a concern in this area of the business. The incremental periods of protection available for data used to extend a marketing authorisation to additional food-producing species, the 13-year period of protection for honey bees and fish, and the introduction of a limited period of data protection for certain MRL data will encourage innovation by providing greater protection for the results of research by delaying somewhat the date at which applicants seeking an authorisation for a generic (copy) product may obtain approval without themselves investing in the research required to obtain and maintain a marketing authorisation. However, consistent with the position for medicines for human use, generic manufacturers will be able to take advantage of a "Bolar-type" provision.

The removal of the requirement for companies to renew marketing authorisations every five years will reduce the cost burden for companies. This amendment is balanced by increased pharmacovigilance reporting requirements; overall, a cost saving is expected for companies, since companies already have established pharmacovigilance systems in place.

4. What economic effects is the proposal likely to have:

- on employment?
- on investment and the creation of new businesses?
- on the competitiveness of businesses?

The proposed package is expected to benefit the pharmaceutical industry in Europe and provide earlier access for patients in the Community to important new medicines.

⁷ Currently in this Member State the period of data protection will not be applied beyond the date of expiry of the patent. This link will cease to exist under the proposed amendment.

The examination in the report by Pammolli *et al*⁸ of the competitive position of the European pharmaceutical business compared with the USA reveals that, in general, the profile of the pharmaceutical industry in Europe is different from that in the USA. The European industry is less specialised in Research and Development activities and has a much larger presence of companies specialising in low value-added activities. The US has developed an industry which is effective not only in the “exploration” of new technologies but also in their “exploitation”. This vertical specialisation enhances innovation – a key driver of competitiveness – by exploiting the advantages of both the small biotechnology firms and the larger multinational firms.

Strengthening the scientific advice procedure within the centralised system will enable companies’ research to be better focused and will reduce the investment risk for small biotechnology companies and thereby provide encouragement for this sector of the industry. In addition, extension of the period of data protection to ten years in all Member States, with an additional year for subsequent clinically-important indications, will encourage innovation by providing a greater opportunity for research-based companies to recoup the costs of their research investment. The Pammolli *et al.* Report⁹ showed that there was too little competition in some Member States, which in turn led to inefficiencies within the industry. Accordingly, the measures to encourage innovation are balanced by those intended to stimulate generic competition - for example, the introduction of a “Bolar-type” provision and the availability of the centralised procedure for generic copies of centrally-authorized products.

A strengthening of innovation and competition within the industry will ultimately promote growth and enhance employment opportunities within the sector. Following the expiry of patent and data protection periods, the proposals aimed at stimulating the prompt approval of generic copies, will provide competition that will exert downward pressure on pricing, thereby helping to facilitate the supply of affordable medicinal products to Member States’ healthcare systems.

The proposal is expected to benefit patients by supplying medicinal products more quickly to the market and, in particular, making available important new treatments at an earlier stage. This will be achieved by a combination of the reduction by half of the length of time available for the consultation of Member States on Commission decisions, the introduction of conditional authorisations and a fast-track procedure, together with a more formalised approach to the availability of medicinal products on a compassionate-use basis. Earlier access to medicines is likely to bring economic benefits by reducing morbidity and mortality and thereby have some influence on national healthcare budgets.

The veterinary sector of the pharmaceutical industry has encountered problems in the availability of medicines for minor species and, following the introduction of the MRL requirement for food-producing animals, for certain therapeutic areas. The increased periods of protection for data used to extend an authorisation for use in additional food-producing species and the increased period for minor species will encourage businesses to exploit their products for use in a broader range of species.

⁸ See note 2.

⁹ See note 2.

This will benefit agricultural producers active in these areas and reduce the hitherto unacceptable level of off-label use.

5. Does the proposal contain measures to take account of the specific situation of small and medium-sized enterprises (reduced or different requirements, etc.)?

The proposal does not contain specific measures for SMEs, but a number of the measures will be particularly beneficial for SMEs. For example, those measures designed to promote innovation, those improving the scientific advice procedure (biotechnology SMEs) and those requiring the introduction of a simplified registration procedure for homeopathic products.

CONSULTATION

6. List the organisations which have been consulted about the proposal and outline their main views.

There has been extensive consultation with interested parties on the operation of the rules governing medicinal products in the European Union and on the amendments which would improve the system. As part of the survey undertaken for the Commission on the operation of the Community procedures, the consultants concerned sought written and oral comments from a broad range of respondents, as follows:

- all holders of a centralised marketing authorisation at the time of the review;
- 159 marketing-authorisation holders (including large multinationals, SMEs, manufacturers of generics and non-prescription and veterinary medicines from different Member States) who had used the decentralised procedure;
- European trade associations representing the interests of human and veterinary medicines including those concerned with NCEs, generics, non-prescription medicines, and homeopathic and herbal medicinal products;
- 15 national consumer organisations and 134 patient associations;
- professional associations responsible for the regulation of doctors, dentists, pharmacists and veterinary practitioners;
- competent authorities responsible for authorising medicinal products;
- chairmen of the Committee for Proprietary Medicinal Products, the Committee for Veterinary Medicinal Products, the Mutual Recognition Facilitation Group and the Veterinary Mutual Recognition Facilitation Group; and
- the ministries responsible for health, social affairs, finance and agriculture.

Many companies were in favour, in principle, of opening up the centralised procedure to other products. There was broad acceptance from businesses of the need to reduce the procedural delays in the Commission decision-making procedure and also for the concept of a formal fast-track procedure.

In relation to the decentralised procedure, although companies were generally satisfied with the performance of the Member States there was dissatisfaction with the limited adherence to the principle of mutual recognition. Many respondents supported the introduction of a dialogue between the Member States prior to the granting of an authorisation in order to encourage greater acceptance of the principles of mutual recognition. Most companies were not in favour of compulsory arbitration in circumstances where Member States were unable to reach agreement, but there was strong support for permitting the marketing of a product pending arbitration in the Member States concerned that felt able to authorise the product.

There was strong support from business for the abolition of the renewal procedure for marketing authorisations.

Finally, there was very strong support for harmonising the periods of data protection, but less consensus on what the harmonised level of protection should be or how it should be applied to products derived from incremental research.

2001/0253 (COD)

Proposal for a

DIRECTIVE OF THE EUROPEAN PARLIAMENT AND OF THE COUNCIL

**amending Directive 2001/83/EC on the Community code relating to medicinal products
for human use**

EXPLANATORY MEMORANDUM

I. GENERAL CONSIDERATIONS

The purpose of the Community provisions concerning the placing on the market of medicinal products for human use is to guarantee a high level of public health protection and to enable the rules of the internal market to operate effectively. No medicinal product may be placed on the market unless its quality, safety and efficacy have been previously demonstrated. These guarantees must be maintained when it is actually placed on the market.

II. JUSTIFICATION

A. Aims

1. On 1 January 1995, new authorisation and monitoring procedures for medicinal products came into force¹ which replaced various procedures based on voluntary cooperation between the competent national authorities. The centralised procedure enables applicants to obtain from the Commission authorisation to place medicinal products on the Community market after evaluation by the European Agency for the Evaluation of Medicinal Products. This procedure is compulsory for biotechnological medicinal products and optional for innovative medicinal products. Where applicants wish to obtain authorisation to place other medicinal products on the market in more than one Member State, the mutual recognition procedure has been compulsory since 1998. This procedure is based on the evaluation carried out by the Member State (the "reference Member State") which granted marketing authorisation, which is normally recognised by the Member States concerned by the same application for authorisation ("concerned Member States"). The European Agency for the Evaluation of Medicinal Products and the competent authorities in the Member States pursue a number of objectives, in particular the pooling of the Member States' potential in terms of scientific expertise in order to guarantee a high degree of public health protection, the free movement of pharmaceutical products, and more rapid access for the people of Europe to medicinal products and in particular to new generations of medicinal products. Now, six years later, these objectives are still valid. However, as a result of international and European developments, scientific progress and the forthcoming advent of new therapies, the existing legislation needs to be adapted and consideration must be given to the main features of future marketing authorisation procedures.

Regulation (EEC) No 2309/93 provided for the possibility of changing these procedures, since its Article 71 states that "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 [*medicinal products for human use*] and in Chapter IV of Directive 81/851/EEC [*veterinary medicinal products*]".

¹ Directives 93/39/EEC, 93/40/EEC, 93/41/EEC and Regulation (EEC) No 2309/93.

On the basis of the provisions of this Article 71, an audit of the procedures and the operation of the Agency was commissioned from Cameron McKenna and Andersen Consulting. The results of this work are being analysed and developed in the "Commission Report on the operation of Community marketing authorisation procedures for medicinal products" (COM....).

2. In the light of the experience acquired between 1995 and 2000 and of the analysis of the comments by the various parties concerned (the competent authorities in the Member States, pharmaceutical companies, associations of the pharmaceutical industry, professional associations of doctors and pharmacists, and associations of patients and consumers), the Commission felt it necessary to adapt certain provisions of Regulation (EEC) No 2309/93. It also appears necessary to adapt in an appropriate manner the general provisions relating to the placing on the market of medicinal products for human use, which have been consolidated in Directive 2001/83/EC of the European Parliament and of the Council on the Community code relating to medicinal products for human use, which is the subject of this proposal for amendment. The word "adaptation" must be particularly stressed in this connection since, although procedural arrangements or other provisions need to be amended or added, neither the general principles nor the basic architecture of the system, as laid down by the original 1993 Regulation establishing the Agency, are disputed. The Commission is aware that, in view of the growth of the battery of therapeutic products available, and of the growing necessity for information and transparency with respect to medicinal products and their use, a number of Member States have developed a system for evaluating the relative efficacy of medicinal products, intended to allow a new medicinal product to be positioned with respect to those already on the market. Accordingly, in its Conclusions of 29 June 2000 on Medicinal Products and Public Health², the Council has underlined the importance of the identification of medicines with significant added therapeutic value. The Commission is of the opinion that this type of assessment should not be undertaken within the marketing authorisation framework, where it is essential to maintain the fundamental criteria of quality, safety and efficacy. Even though it appears that action at a Community level may be useful, the Commission has not, therefore at this stage, made any proposals in this regard. After having conducted large consultations on this issue, the Commission will reflect on the possibility of making a proposal in the appropriate legal context.
3. The necessary adaptation must take account of the experience acquired in the six years during which the procedures have been implemented and of the rapid scientific developments in the pharmaceutical field. These considerations must also be seen in the light of ever-increasing globalisation, in particular between the world's three major pharmaceutical "regions" of Europe, North America and Japan. Scientific globalisation is being accompanied by the globalisation of certain regulatory practices and in particular of the scientific and technical criteria for evaluating medicinal products. The increasingly rapid introduction of new technologies in the field of research and development relating to medicinal products requires an adaptable regulatory environment based on stable, well defined principles which are nevertheless truly international in scope. This "global" dimension of regulatory requirements is surely one of the main new factors to be considered in comparison

² OJ C 218, 31.7.2000, p. 10.

with the early 1990s, when the present Community marketing authorisation system was devised. Any regulatory environment applying to the authorisation of medicinal products can no longer be regarded as modern, effective and lasting if it develops in isolation. The Commission and the Member States are already very actively involved, through their participation in ICH³ and VICH⁴, in the international discussions on technical and scientific requirements in the field of human and veterinary medicinal products. However, it is also very important that the regulatory framework of the Community marketing authorisation system should take due account of this new global environment so that the European Community can play a full part on the international stage alongside its – particularly American and Japanese – partners.

4. There is another new dimension in relation to the 1993 context which now has to be considered: the enlargement of the European Union. As in other areas, the future enlargement obviously raises the question of whether certain procedural arrangements for the regulation of medicinal products are appropriate and particularly whether it will be possible, in a context designed for 15 countries, for 20, 25 or 28 Member States to conduct scientific debates and take decisions effectively.
5. As part of all these regulatory and technical considerations, it will obviously be necessary to bear in mind the primary purpose of developing and subsequently marketing medicinal products: to achieve health benefits for patients. While the centralised authorisation system has proved to be effective for evaluating medicinal products, the effectiveness of the mutual recognition system should be improved, since it concerns to some extent new medicinal products but also medicinal products on which the files go back further or generic medicinal products. Particular account should be taken of generic medicinal products since, in the overall context of health systems, it should be made easier to place them on the market.
6. Any changes in the rules must maintain safety of use for the patient, market surveillance and pharmacovigilance. The analysis of the risk/benefit balance must remain the basis for any administrative decision on a medicinal product, irrespective of the authorisation procedures applied. Although the provisions in force have helped to ensure a high level of safety, it is necessary to improve certain existing arrangements with a view to speeding up action in emergencies and to increasing the effectiveness of the system of pharmacovigilance and market surveillance in order, *inter alia*, to take account of the fact that the market subject to such surveillance will increase in size as a result of the forthcoming enlargement of the European Union.
7. Lastly, the regulations must be adapted in order to take account of the experience acquired during these years of intensive cooperation between the Member States, the European Agency for the Evaluation of Medicinal Products and the Commission.

³ International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use.

⁴ International Cooperation on Harmonisation of Technical Requirements for Registration of Veterinary Pharmaceuticals.

8. In general terms, the pharmaceutical legislation must be revised in the light of the objectives set out in the conclusions of the Commission Report:
- to provide a high level of health protection for the people of Europe and tighter surveillance of the market;
 - to complete the internal market in pharmaceutical products taking account of the implications of globalisation and to establish a regulatory and legislative framework that favours the competitiveness of the European pharmaceuticals industry sector;
 - to meet the challenges of the future enlargement of the European Union;
 - to rationalise and simplify the system as far as possible, thus improving its overall consistency and visibility, and the transparency of procedures and decision-making.

B. Legal basis and procedure

The legal basis of this proposal is Article 95 of the Treaty. This Article, which provides for recourse to the co-decision procedure under Article 251, is the legal basis for achieving the objectives set out in Article 14 of the Treaty, which include the free movement of goods and hence of medicinal products for human use. The prime objective of all rules on the production and distribution of medicinal products must be to safeguard public health, but it must be achieved by means which do not restrict the free movement of medicinal products within the Community. Following the entry into force of the Treaty of Amsterdam, all the legislative provisions adopted by the European Parliament and the Council – except directives adopted on the basis of the executive powers conferred on the Commission and seeking to align the provisions on medicinal products – are adopted on the basis of this Article. This is because the differences between national laws, regulations and administrative provisions on medicinal products result in obstacles to intra-Community trade which directly affect the operation of the internal market. Legislative action by the Community is therefore justified in order to prevent or remove such obstacles.

III. DETAILED CONTENT OF THE PROPOSAL

(For greater ease of consultation, the Articles quoted as references are those of Directive 2001/83/EC as amended by this proposal).

A. Adaptation of definitions, terminology and certain concepts

1. The definition of medicinal product is adapted to take account of new therapies and their particular method of administration (*Articles 1 and 2*) (cellular therapy in particular).
2. In order to bring the text into line with current practice, it is proposed that both in the summary of the product characteristics (*Article 11*) and on the packaging (*Articles 54 and 59*), the name of the medicinal product be followed by the strength and the pharmaceutical form in order to improve the information for patients and practitioners.

3. The criteria for refusing, suspending and withdrawing marketing authorisations have been adapted and harmonised so that the key evaluation criteria of quality, safety and efficacy go hand in hand with the concept of risk/benefit balance, which is the basis of the authorisation and its continued validity (*Articles 26, 116 and 117*).
4. Since the possible duality of certain "borderline" products (medical devices, cosmetics, biocides etc.) has led to differences of interpretation as to the applicable legislation, it is proposed that, when a product fully meets the definition of a medicinal product, but may also meet the definition of other regulated products, the pharmaceutical legislation should apply (*Article 2(2)*).
5. Adaptations are proposed to certain provisions relating to the marketing authorisation application file. These adaptations do not involve any substantive changes to the present provisions but are intended to bring certain legal provisions, the wording of which is sometimes outdated, more into line with current administrative, scientific and technical practices. Furthermore, they take account of the guidelines finalised by the ICH.
6. In order to ensure, as in the case of the centralised procedure, that the procedures are transparent, it is proposed that assessment reports and authorisations accompanied by summaries of the characteristics of the medicinal products authorised under the decentralised or mutual recognition procedure be made available to any interested party (*Article 21*).

B. Generic medicinal products

1. In the case of abridged marketing authorisation procedures, it is proposed that the concept of "essentially similar" medicinal product be abandoned since it actually refers to generic medicinal products. A definition of generic medicinal product is inserted into the text, together with a definition of reference medicinal product in relation to which the generic medicinal product is defined, in order to bring the text into line with the commonly accepted terminology (*Article 10(2)*).
2. Again to bring the text into line with practice, it is proposed that, for the reference medicinal product, the concept of actual placing on the market be abandoned and that only the requirement for it to have a marketing authorisation be retained (*Article 10(1)*). This is necessary in order to make it easier for generic medicinal products to gain access to the market.
3. The administrative protection period for data on the reference medicinal product must be harmonised at ten years (*Article 10(1)*). This period has been chosen in order to stipulate the same period irrespective of the type of marketing authorisation procedure and is the same as the period adopted under the centralised procedure. However, in order to promote research on new therapeutic indications with a significant clinical benefit and bringing an improvement to the quality of life and welfare of the patient, it is proposed that the applicant be granted an extra year of data protection in the case of therapeutic indications which meet the abovementioned conditions and are granted during this ten-year period. It is however necessary to maintain an appropriate balance between such innovations and the need to favour the production of generic medicines. It is therefore foreseen that this extra year will only be granted in the cases where the new indication is authorised during the first eight

years of the ten years data protection period, with the aim of not hindering the emergence of a generic market (*Article 10(1)*).

4. Applicants for a marketing authorisation for a generic medicinal product may carry out the tests necessary for submitting the file before the end of the exclusivity period without this being regarded as an infringement of the rules on the protection of industrial and commercial property (*Article 10(4)*). The purpose of this provision is to prevent a large proportion of the requisite tests being conducted outside the Community, as is currently the case, but without affecting the date on which the generic medicinal products arrive on the market.
5. Lastly, in order to facilitate the harmonisation of existing reference medicinal products, it is proposed that an annual plan for gradual harmonisation be introduced (*Article 30(2)*). This will simplify the procedures for applying for a marketing authorisation for generic versions of these reference medicinal products under the mutual recognition or decentralised procedure.

C. The decentralised procedure and the mutual recognition procedure (*Chapter 4*)

1. The scope of these procedures is linked to that of the centralised procedure. In the proposal to amend Regulation (EEC) No 2309/93, it is proposed that the scope provided for in the original Regulation be maintained on the whole, except for certain amendments rendered necessary by the experience acquired during the past six years and by scientific and technological developments. Since the main amendment proposed is to make the centralised procedure compulsory for all new active substances appearing on the Community market, this means a significant change in the scope of the decentralised or mutual recognition procedure. Any medicinal product not compulsorily subject to the centralised procedure will be covered by the decentralised or mutual recognition procedure, on condition that it is intended for the markets of more than one Member State⁵.

These procedures are thus still optional for other medicinal products which represent a therapeutic innovation and will be the procedure of choice for generic medicinal products. It should be stressed in this connection that the procedures will also be open to generic medicinal products whose reference medicinal product has been authorised under the centralised procedure, since it is proposed that the Member States be given the option of authorising at national level the generic versions of medicinal products authorised by the Community on condition that they maintain the harmonisation achieved at Community level. In particular, the summary of the characteristics of the generic product must comply with that of the medicinal product authorised by the Community.

2. The mutual recognition procedure has been criticised because of difficulties encountered in practice. Under the present system, the Member States must recognise an initial authorisation granted by the reference Member State. It is always more difficult to go back on a scientific decision than to take an initial decision jointly as part of a scientific cooperation procedure. It is also proposed (a) to maintain the general principles of the mutual recognition procedure as laid down in the present rules on medicinal products which have already been granted a marketing

⁵ The national procedure still applies to medicinal products strictly confined to a national market.

authorisation in one of the Member States but whose holder wishes to make the product available to other Member States (*Article 28(1) and (2)*), and (b) to add to it a new decentralised procedure for medicinal products not yet authorised in the Community (*Article 28(1) and (3)*). There would be cooperation between Member States before the decision is taken on the basis of the evaluation conducted by one of them. This procedure is modelled on an existing procedure which has proved its worth, namely the procedure applied to the authorisation of major amendments to an existing authorisation.

3. The introduction of the mutual recognition procedure was facilitated by an informal working group, the "Mutual Recognition Facilitation Group" (MRFG), in which representatives of the Member States meet. Since this group has proved to be effective and the amendment proposed to the procedure involves considerable cooperation between Member States, it is proposed that the group be given formal status and be called a co-ordination group (*Article 27*). Under the new mutual recognition or decentralised procedures, disagreements would be referred to this committee (*Article 29(1) and (2)*) and, if it fails to arrive at a consensus, the matter would be referred to the European Agency for the Evaluation of Medicinal Products (*Article 29(3)*).
4. It is proposed in the case of both Regulation (EEC) No 2309/93 and the mutual recognition or decentralised procedure that the obligation to renew the marketing authorisation every five years be removed (*Article 24(1)*). However, to take account of this removal of the obligation to renew the authorisation every five years, the present proposal stipulates that any marketing authorisation which is not followed within two consecutive years by the actual placing on the market of the medicinal product concerned shall cease to be valid (*Article 24(2) and (3)*). The removal of the obligation of renewal goes hand in hand with a strengthening of the pharmacovigilance and market-surveillance procedures.

D. Referral procedures

The referral procedures come into play if a Member State cannot agree with the assessment report and the summary of product characteristics drawn up by another Member State (*Article 29*), if there is a lack of harmonisation in the decisions taken by the Member States (*Article 30*), or if the interests of the Community are involved (*Article 31*). Although few procedures are referred in this way, such referrals have given rise to very many discussions, particularly regarding interpretation and practical application. In particular in cases where a Member State cannot agree with the evaluation or authorisation by another Member State, it is proposed that referral be made automatic, since experience has shown that, in order to avoid referral, firms systematically withdraw their applications in Member States which are not in favour of granting authorisation. However, it is proposed that in such cases the Member States which are in favour of granting authorisation be allowed to do so on the understanding that, depending on the result of the referral, they may subsequently have to amend it. With regard to referrals on matters of Community interest, and in the light of the experience acquired, it is necessary to provide for an appropriate procedure, particularly in the case of referrals concerning an entire therapeutic class or all medicinal products containing the same active substance (*Article 31*). In both these cases, the number of medicinal products concerned may be very large, and the aim is to ensure that the procedure is effective.

Lastly, in order to make this procedure more effective in terms of deadlines, it is proposed that its overall length be reduced from 90 days to 60 days (*Article 32(1)*).

Following referral procedures, the Commission must take a decision, which must be applied by the Member States (*Articles 33 and 34*). The Commission decision-making process has been the subject of much criticism, in particular on account of its length. As in the case of the decisions which the Commission must take following applications for marketing authorisation under the centralised procedure, this process needs to be reorganised. At present the decision-making procedure is subject to a type III (b) "comitology" procedure⁶. It should be noted first of all that from the outset the Commission has always followed the Agency's opinion on highly scientific matters. Furthermore, the opinions have generally been obtained by written procedure without a formal meeting of the regulatory committee, since this possibility is provided for by the legislation. The rare cases requiring a formal vote during a meeting arose during the system's "running-in" period.

In view of the experience acquired and of the adoption of a new "comitology" Decision by the Council on 28 June 1999 (1999/468/EC)⁷, this decision-making procedure now needs to be re-assessed. It is also proposed that decision-making be subject to a consultation procedure under Decision 1999/468/EEC if the draft submitted by the Commission follows the Agency's scientific opinion or, in all other cases, to a management procedure under this Decision. In both cases, the deadlines are adapted in order to shorten the phase in which the Member States are consulted (*Article 34(2)*).

E. Inspection and surveillance

1. The overall quality of medicinal products is based both on the evaluation of the information submitted as part of the application for marketing authorisation and on the constant monitoring of the quality of the manufactured and marketed medicinal products to establish whether they comply with the data supplied. The monitoring of the quality of the manufacture and control of medicinal products must broadly take account of consumer protection, the completion of the internal market and the international dimension, in particular the agreements with non-member countries on mutual recognition. Quality guarantees are based mainly on a quality-assurance system which includes compliance with good manufacturing practice and on inspections by the competent authorities to ensure that all the legal requirements are complied with. The present Regulation covers medicinal products but is not specifically intended to apply to starting materials. It is therefore proposed that it be extended to cover active substances used as starting materials in the manufacture of medicinal products (*Article 111(1)*). Since the Member States adopt differing approaches, the harmonisation of the application of good manufacturing practice for these substances should be proposed. Detailed guidelines setting out appropriate practical provisions will be adopted. The same applies to the system for inspecting the manufacture of these active substances. Lastly, it is proposed that provision be made for issuing certificates of good manufacturing practice attesting compliance with the relevant requirements.
2. It is also necessary to reinforce the general provisions on inspection of medicinal products, if necessary in conjunction with the European Pharmacopoeia (*Article 111(1) and (5)*), and to increase Community coordination by introducing a Community information register on good manufacturing practice (*Article 111(6) and (7)*) and setting up a Community system of data on manufacturing authorisations

⁶ Within the meaning of Council Decision 87/373/EEC (OJ L 197, 18.7.1987, p. 33).

⁷ OJ L 184, 17.7.1999, p. 23.

(*Article 40(4)*)). It is proposed that the inspection system based on the recognition of inspections carried out by one of the Member States be supplemented by a procedure for settling disagreements between Member States on the results of an inspection (*Article 122*). It is also proposed that the possibility of inspecting pharmacovigilance sites and conducting inspections in non-member countries be added (*Article 111(4)*).

F. Pharmacovigilance

On the basis of the experience acquired, it is necessary to place greater emphasis on the need for a preventive approach with regard to pharmacovigilance. There has been considerable technical progress at both Community and international level. Exchanges of data between the Member States, marketing authorisation holders and the European Agency for the Evaluation of Medicinal Products are increasingly dependent on information technologies. There should be a rapid exchange of the data collected by all the partners. Following the agreement on the MedDRA, the use of this medical terminology, drawn up by ICH and officially launched in 1999, should be made compulsory in the interests of public health and to ensure that notifications of adverse reactions to medicinal products are consistent in a multilingual environment (*Article 106*). It is also important to ensure that the Member States' pharmacovigilance systems are harmonised and consistent so that all medicinal products authorised in the Community can be effectively monitored. In connection with the proposal to abolish the five-yearly renewal requirement, and to increase the efficacy of the system, it is proposed that the deadlines for the compulsory submission of periodic safety update reports be shortened (*Article 104*). It is also proposed that the Commission should, where urgent action is necessary, be able to request the Member States to adopt temporary measures with immediate effect (*Article 107*). Furthermore, it is proposed that the inspections regarding the obligations on marketing authorisation holders be reinforced (*Article 111*). Lastly, it is proposed that the coordination between Member States for the pharmacovigilance of medicinal products subject to the mutual recognition or decentralised procedure be improved (*Article 104(5)*).

G. Homeopathy (Chapter 2)

In order to create an additional stage in the harmonisation of this category of medicinal products, the proposal provides for the introduction of a limited mutual recognition procedure. Furthermore, in order to make it easier to place them on the market, invented names may be used, and it is proposed that the blanket prohibition of public advertising be removed (*Article 100*).

H. Packaging

The rules stipulate that the packaging of medicinal products must contain a package leaflet for patients. The order of the headings which must figure in this package leaflet is compulsory. On the basis of the experience acquired, it is necessary to adapt the rules and to propose an order of headings corresponding to patients' needs and habits (*Article 59*).

I. Information

In view of the spread of new information technologies and of growing consumer demand for information, it is proposed that, on an experimental basis, the possibilities of disseminating information on prescription-only medicinal products be extended. Public advertising is not currently authorised for prescription-only medicinal products. This provision has been interpreted as forbidding also all kind of information to the public, and only advertising and

information addressed to health professionals being possible. It is proposed that there should be public advertising of three classes of medicinal products. This type of information would be subject to the principles of good practice to be adopted by the Commission and to the drafting of a code of conduct by the industry. After five years of operation, an evaluation would be carried out in order to determine what action should be taken (*Article 88(2)*) in the wake of this trial.

IV. ADMINISTRATIVE AND LEGISLATIVE SIMPLIFICATION

The present proposal takes due account of the vast amount of work to consolidate the directives in the field of Community legislation on medicinal products for human use (*31 consolidated texts*). It also introduces provisions to rationalise and speed up the procedures relating to marketing authorisations for medicinal products for human use

V. CONSULTATIONS PRIOR TO THE DRAFTING OF THE PROPOSAL

The Commission has had an audit carried out by an external consultant, as stated in the explanatory memorandum. There have been several consultations, meetings and hearings with all the parties concerned. The Commission has also received numerous reports and discussion papers from these parties, particularly the Member States, patients' associations, European federations of the pharmaceutical industry, pharmacists and distributors. All these documents and their analysis have been taken up in the Commission report to the European Parliament and the Council on the operation of the abovementioned marketing authorisation procedures in the Community (COM).

Proposal for a

DIRECTIVE OF THE EUROPEAN PARLIAMENT AND OF THE COUNCIL

amending Directive 2001/83/EC on the Community code relating to medicinal products for human use

(Text with EEA relevance)

THE EUROPEAN PARLIAMENT AND THE COUNCIL OF THE EUROPEAN UNION,

Having regard to the Treaty establishing the European Community, and in particular Article 95 thereof,

Having regard to the proposal by the Commission¹,

Having regard to the opinion of the Economic and Social Committee²,

Having regard to the opinion of the Committee of the Regions³,

Acting in accordance with the procedure laid down in Article 251 of the Treaty⁴,

Whereas:

- (1) Directive 2001/83/EC of the European Parliament and of the Council of 23 October 2001 on the Community code relating to medicinal products for human use⁵, in the interests of clarity and rationalisation, codifies and combines in a single text the texts of Community legislation on medicinal products for human use.
- (2) Community legislation is a major milestone in the achievement of the objective of the free movement of medicinal products for human use and the elimination of obstacles to trade in such products. However, in the light of the experience acquired, new measures have proved necessary to eliminate the remaining obstacles to free movement.
- (3) It is therefore necessary to align the national laws, regulations and administrative provisions which contain differences with regard to the basic principles in order to promote the operation of the internal market.

¹ OJ C
² OJ C
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- (4) The main purpose of any regulation on the production and distribution of medicinal products for human use should be to safeguard public health. However, this objective should be achieved by means which do not hinder the development of the pharmaceutical industry or trade in medicinal products in the Community.
- (5) Article 71 of Council Regulation (EEC) No 2309/93 of 22 July 1993 laying down Community procedures for the authorisation and supervision of medicinal products for human and veterinary use and establishing a European Agency for the Evaluation of Medicinal Products⁶ provides that, within six years of its entry into force, the Commission is required to publish a general report on the experience acquired as a result of the operation of the marketing authorisation procedures laid down in that Regulation and in other Community legal provisions.
- (6) In the light of the Commission's report⁷ on the experience acquired, it has proved necessary to improve the operation of the marketing authorisation procedures for medicinal products in the Community.
- (7) Particularly as a result of scientific and technical progress, the definitions and scope of Directive 2001/83/EC should be clarified in order to achieve high standards for the quality, safety and efficacy of medicinal products for human use. In order to take account, both of the emergence of new therapies and of the growing number of so-called "borderline" products between the medicinal product sector and other sectors, the definition of "medicinal product" should be modified so as to avoid any doubt as to the applicable legislation, when a product, whilst fully falling within the definition of a medicinal product, may also fall within the definition of other regulated products. Also, taking into account the characteristics of pharmaceutical legislation, provision should be made that such legislation is to apply. It is also worth taking advantage of this opportunity to improve the consistency of the terminology of pharmaceutical legislation.
- (8) Wherever it is proposed to change the scope of the centralised procedure, it should no longer be possible to opt for the mutual-recognition or decentralised procedure in respect of new active substances. On the other hand, with regard to generic medicinal products of which the reference medicinal product has obtained a marketing authorisation under the centralised procedure, applicants seeking marketing authorisation should be able to choose either of the two procedures, on certain conditions. Similarly, the mutual-recognition or decentralised procedure should be available as an option for medicinal products which represent a therapeutic innovation or which are of benefit to Society or to patients.
- (9) The evaluation of the operation of marketing authorisation procedures reveals the need to revise most particularly the mutual recognition procedure in order to improve the opportunities for cooperation between Member States. This cooperation process should be formalised by setting up a coordination group for this procedure and by defining its operation so as to settle disagreements within the framework of a revised decentralised procedure.

⁶ OJ L 214, 21.8.1993, p. 1; Regulation as amended by Commission Regulation (EC) No 649/98 (OJ L 88, 24.3.1998, p. 7).

⁷ COM(2001)...final

- (10) With regard to referrals, the experience acquired reveals the need for an appropriate procedure, particularly in the case of referrals relating to an entire therapeutic class or to all medicinal products containing the same active substance.
- (11) Since generic medicines account for a major part of the market in medicinal products, their access to the Community market should be facilitated in the light of the experience acquired.
- (12) The criteria of quality, safety and efficacy should enable the risk/benefit balance of all medicinal products to be assessed both when they are placed on the market and for the purposes of subsequent monitoring. In this connection, it is necessary to harmonise and adapt the criteria for refusal, suspension and withdrawal of marketing authorisations.
- (13) The validity of marketing authorisations should no longer be limited to five years. On the other hand, market surveillance should be stepped up. In addition, any authorisation which does not lead to the actual placing on the market of a medicinal product should cease to be valid.
- (14) The quality of medicinal products for human use produced or available in the Community should be guaranteed by requiring that the active substances used in their composition comply with the principles of good manufacturing practice in relation to those medicinal products. It has proved necessary to reinforce the Community provisions on inspections and to compile a Community register of the results of those inspections.
- (15) Pharmacovigilance and, more generally, market surveillance and sanctions in the event of failure to comply with the provisions should be stepped up. In the field of pharmacovigilance, account should be taken of the facilities offered by new information technologies to improve exchanges between Member States.
- (16) As part of the proper use of medicinal products, the rules on packaging should be adapted to take account of the experience acquired. On the other hand, information relating to certain medicinal products is authorised under strict conditions in the interests of patients and in order to meet their legitimate needs and expectations. Such information should not be equated with direct advertising or marketing of prescription medicines.
- (17) Since most of the measures necessary for the implementation of this Directive are measures of individual scope, use should be made of the advisory procedure under Article 3 of Council Decision 1999/468/EC of 28 June 1999 laying down the procedures for the exercise of implementing powers conferred on the Commission⁸, or of the management procedure under Article 4 thereof. As regards measures of general scope within the meaning of Article 2 of the Decision, those measures should be adopted by use of the regulatory procedure provided for in Article 5 thereof.
- (18) Directive 2001/83/EC should be amended accordingly,

HAVE ADOPTED THIS DIRECTIVE:

⁸ OJ L 184, 17.7.1999, p. 23.

Article 1

Directive 2001/83/EC is amended as follows:

1. Article 1 is amended as follows:

- (a) Point (1) is deleted.
- (b) Point (2) is replaced by the following:

"(2) Medicinal product:

- (a) Any substance or combination of substances presented as having properties for treating or preventing disease in human beings.
- (b) Any substance or combination of substances which may be used in human beings with a view to making a medical diagnosis or to restoring, correcting or modifying physiological functions."

(c) Point (20) is replaced by the following:

"(20) Name of the medicinal product:

The name, which may be either an invented name not liable to confusion with the common name, or a common or scientific name accompanied by a trade mark or the name of the marketing authorisation holder."

(2) Article 2 is replaced by the following:

"Article 2

- 1. The provisions of this Directive shall apply to medicinal products for human use intended to be placed on the market in Member States and either prepared industrially or manufactured by a method involving an industrial process.
- 2. Whenever a substance or combination of substances falls within the definition of 'medicinal product', the provisions of this Directive shall apply, even in cases where the substance or combination of substances falls also within the scope of other Community legislation."

(3) Article 3 is amended as follows:

(a) Point (3) is replaced by the following:

"(3) Medicinal products intended for research and development trials, but without prejudice to the provisions of Directive 2001/20/EC of the European Parliament and of the Council*;

* OJ L 121, 1.5.2001, p. 34."

(b) Point (6) is replaced by the following:

"(6) Whole blood, plasma or blood cells of human origin, except for plasma which is prepared by a method involving an industrial process."

- (4) Article 5 is replaced by the following:

"Article 5

Without prejudice to Regulation [(EEC) No 2309/93], a Member State may, in accordance with legislation in force and to fulfil special needs, exclude from the provisions of this Directive medicinal products supplied in response to a *bona fide* unsolicited order, formulated in accordance with the specifications of an authorised health care professional and for use by his individual patients under his direct personal responsibility."

- (5) Article 6 is amended as follows:

- (a) In paragraph 1, the following second subparagraph is added:

"The various strengths, pharmaceutical forms, administration routes, presentations and any variation under Article 35 shall be authorised under the first subparagraph and shall be considered as part of the same authorisation."

- (b) The following paragraph 1a is inserted:

"1a The marketing authorisation holder shall be responsible for marketing the medicinal product."

- (6) Article 8(3) is amended as follows:

- (a) Points (b) and (c) are replaced by the following:

"(b) Name of the medicinal product.

(c) Qualitative and quantitative particulars of all the constituents of the medicinal product."

- (b) Points (h), (i) and (j) are replaced by the following:

"(h) Description of the control methods employed by the manufacturer.

(i) Results of:

- pharmaceutical (physico-chemical, biological or microbiological) tests,
- pre-clinical (toxicological and pharmacological) tests,
- clinical trials."

(j) A summary, in accordance with Article 11, of the product characteristics, a mock-up of the outer packaging, containing the details foreseen in Article 54 and of the immediate packaging of the medicinal product, containing the details foreseen in Article 55 together with a package leaflet in accordance with Article 59."

(c) The following point (m) is added:

"(m) A copy of any designation of the medicinal product as an orphan medicinal product under Regulation (EC) No 141/2000 of the European Parliament and of the Council^{*}, accompanied by a copy of the relevant Agency opinion.

^{*} OJ L 18, 22.1.2000, p. 1."

(d) The following third subparagraph is added:

"The documents and information concerning the results of the pharmaceutical and pre-clinical tests and the clinical trials referred to in point (i) of the first subparagraph shall be accompanied by detailed summaries in accordance with the provisions of Article 12."

7. Article 10 is replaced by the following:

"Article 10

1. By way of derogation from point (i) of Article 8(3), and without prejudice to the law relating to the protection of industrial and commercial property, the applicant shall not be required to provide the results of pre-clinical tests or of clinical trials if he/she can demonstrate that the medicinal product has been a generic of a reference medicinal product authorised under Article 6 for not less than ten years in a Member State or in the Community.

The ten-year period referred to in the first subparagraph shall be extended to 11 years if, during the first eight years of those ten years, the marketing authorisation holder obtains an authorisation for one or more new therapeutic indications which, during the scientific evaluation prior to their authorisation, are held to bring a significant clinical benefit in comparison with existing therapies.

2. For the purposes of this Article:

(a) *reference medicinal product* shall mean a medicinal product authorised under Article 6, in accordance with the provisions of Article 8;

(b) *generic medicinal product* shall mean a medicinal product which has the same qualitative and quantitative composition in active principles and the same pharmaceutical form, and whose bioequivalence with the reference medicinal product has been demonstrated by appropriate bioavailability tests. The various immediate-release oral pharmaceutical forms are deemed to be one and the same pharmaceutical form. Bioavailability studies may not be required of the applicant if he/she can demonstrate that the product meets the criteria of Annex I.

3. The first subparagraph of paragraph 1 shall not apply to changes in the active substance(s), therapeutic indications, strength, pharmaceutical form or route of administration vis-à-vis the reference medicinal product, and the results of appropriate pre-clinical tests or clinical trials shall be provided.

4. Conducting the necessary tests and trials with a view to application of paragraphs 1, 2 and 3 to a generic medicinal product shall not be regarded as contrary to patent rights or to complementary protection certificates for those medicinal products."

- (8) The following Articles 10a to 10c are inserted:

"Article 10a

By way of derogation from point (i) of Article 8(3), and without prejudice to the law relating to the protection of industrial and commercial property, the applicant shall not be required to provide the results of pre-clinical tests and clinical trials if he/she can demonstrate that the component(s) of the medicinal product have been of well established medicinal use within the Community for at least the last ten years, with recognised efficacy and an acceptable level of safety in terms of the conditions set out in Annex I. In that event, the test and trial results shall be replaced by appropriate scientific literature.

Article 10b

In the case of new medicinal products containing active substances used in the composition of authorised medicinal products but not hitherto used in combination for therapeutic purposes, the results of pre-clinical tests and clinical trials relating to that combination shall be provided, but it shall not be necessary to provide scientific references relating to each individual active substance.

Article 10c

Following issuance of a marketing authorisation, the authorisation holder may allow use to be made of the pharmaceutical, pre-clinical and clinical documentation contained in the file on the medicinal product, with a view to examining subsequent applications relating to other medicinal products possessing the same qualitative and quantitative composition in terms of active substances and the same pharmaceutical form."

- (9) Article 11 is amended as follows:

- (a) Point (1) is replaced by the following:

"(1) Name of the medicinal product, followed by the strength and the pharmaceutical form;"

- (b) Point (6) is replaced by the following:

"(6) Pharmaceutical particulars:

6.1 excipients,

6.2 shelf life, when necessary after reconstitution of the medicinal product or when the immediate packaging is opened for the first time,

6.3 special precautions for storage,

- 6.4 nature and contents of immediate packaging,
- 6.5 special precautions for disposal of unused medicinal products or waste materials derived from such medicinal products, if appropriate."

(c) The following paragraph (10) is added:

"(10) Classification in accordance with Article 70."

(10) Article 12 is replaced by the following:

"Article 12

1. The applicant shall ensure that, before the detailed summaries referred to in point (j) of Article 8(3) are submitted to the competent authorities, they have been drawn up and signed by experts with the necessary technical or professional qualifications, which should be set out in a brief *curriculum vitae*.
2. Persons having the technical and professional qualifications referred to in paragraph 1 shall justify any use made of scientific literature under Article 10a(1) in accordance with the conditions set out in Annex I.
3. The detailed summaries shall form part of the file which the applicant submits to the competent authorities."

(11) Article 13 is replaced by the following:

"Article 13

1. Member States shall ensure that homeopathic medicinal products manufactured and placed on the market within the Community are registered or authorised in accordance with Articles 14, 15 and 16, except where such medicinal products are covered by a registration or authorisation issued in accordance with national legislation up to 31 December 1993.
2. Member States shall establish a special simplified registration procedure for the homeopathic medicinal products referred to in Article 14."

(12) Article 14 is amended as follows:

(a) In paragraph 1, the following second subparagraph is inserted:

"If new scientific evidence so warrants, the Commission may amend the third indent of the first subparagraph by the procedure referred to in Article 121(2)."

(b) Paragraph 3 is deleted.

(13) In Article 15, the sixth indent is replaced by the following:

"– one or more mock-ups of the outer packaging and the immediate packaging of the medicinal products to be registered,"

(14) Article 16 is amended as follows:

- (a) In paragraph 1, "Articles 8, 10 and 11" is replaced by "Article 8 and Articles 10 to 11".
- (b) In paragraph 2, "toxicological and pharmacological" is replaced by "pre-clinical".

(15) Articles 17 and 18 are replaced by the following:

"Article 17

1. Member States shall take all appropriate measures to ensure that the procedure for granting an authorisation to place a medicinal product on the market is completed within 150 days of the submission of a valid application, including 120 days for drawing up the assessment report and the summary of the product characteristics.

With a view to granting a marketing authorisation in two or more Member States in respect of the same medicinal product, applications shall be submitted in accordance with Articles 27 to 39.

2. Where a Member State notes that another marketing authorisation application for the same medicinal product is being examined in another Member State, the Member State concerned shall decline to assess the application and shall advise the applicant that the procedure set out in Articles 27 to 39 is applicable.

Article 18

Where a Member State is informed in accordance with point (m) of Article 8(3) that another Member State has authorised a medicinal product which is the subject of a marketing authorisation application in the Member State concerned, it shall reject the application unless it has been submitted in compliance with Articles 27 to 39."

(16) Article 19 is amended as follows:

- (a) In the introductory sentence, "Articles 8 and 10(1)" is replaced by "Article 8 and Articles 10 to 10c".
- (b) In point (1), "Articles 8 and 10(1)" is replaced by "Article 8 and Articles 10 to 10c".
- (c) In point (3), "Articles 8(3) and 10(1)" is replaced by "Article 8(3) and Articles 10 to 10c".

(17) In point (b) of Article 20, "in exceptional and justifiable cases" is replaced by "in justifiable cases".

(18) In Article 21, paragraphs 3 and 4 are replaced by the following:

- "3. The competent authorities shall make available to any interested party a copy of the authorisation together with the summary of the product characteristics.

4. The competent authorities shall draw up an assessment report and comments on the file as regards the results of the pharmaceutical and pre-clinical 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.

At the request of any interested party, the competent authorities shall make available the assessment report, together with the reasons for their opinion, after deletion of information of a commercially confidential nature."

- (19) Article 22 is replaced by the following:

"Article 22

In exceptional circumstances, and following consultation with the applicant, an authorisation may be granted subject to certain specific obligations to carry out further studies following the granting of authorisation.

Such authorisations may be granted only for objective and verifiable reasons and shall be based on one of the causes referred to in Part 4(G) of Annex I."

- (20) In Article 23, the following third paragraph is added:

"In order that the risk-benefit balance may be continuously assessed after the issue of a marketing authorisation, any information modifying the content of the file and any new information not appearing in the original file shall be forwarded to the competent authorities."

- (21) Article 24 is replaced by the following:

"Article 24

1. Without prejudice to paragraphs 2 and 3, a marketing authorisation shall be valid indefinitely.
2. Any authorisation which is not followed within two years of its issue by the actual placing on the market of the authorised product in the authorising Member State shall cease to be valid.
3. When an authorised product previously placed on the market in the authorising Member State is no longer actually present on the market for a period of two consecutive years, the authorisation for that product shall cease to be valid."

- (22) Article 26 is replaced by the following:

"Article 26

The marketing authorisation shall be refused if, after verification of the particulars and documents listed in Article 8 and Articles 10 to 10c, it is clear that:

- (a) the risk/benefit balance is not considered to be favourable; or

- (b) its therapeutic efficacy is insufficiently substantiated by the applicant; or
- (c) its qualitative and quantitative composition is not as declared.

Authorisation shall likewise be refused if the particulars and documents submitted in support of the application do not comply with Article 8 and Articles 10 to 10c.”

- (23) The heading of Chapter 4 of Title III is replaced by the following:

"Chapter 4

Mutual recognition procedure and decentralised procedure".

- (24) Articles 27 to 32 are replaced by the following:

"Article 27

1. A coordination group is hereby set up for the examination of any question relating to marketing authorisation of a medicinal product in two or more Member States in accordance with the procedures laid down in this Chapter. The Agency shall provide the secretariat of this coordination group.
2. The coordination group shall be composed of one representative per Member State appointed for a term of three years, which shall be renewable. Members of the coordination group may arrange to be accompanied by experts.
3. The coordination group shall draw up, its own Rules of Procedure, which shall enter into force after a favourable opinion of the Commission.

Article 28

1. With a view towards the grant of a marketing authorisation for a medicinal product in more than one Member State, an applicant shall submit an application based on an identical dossier in these Member States. The dossier shall contain the information and documents referred to in Article 8 and Articles 10 to 11. The documents submitted shall include a list of Member States concerned by the application.

The applicant shall request one Member State to act as “reference Member State” and to prepare an assessment report on the medicinal product according to paragraphs 2 or 3.

Where appropriate, the assessment report shall contain an analysis for the purposes of the second subparagraph of Article 10(1).

2. Where the medicinal product has already received a marketing authorisation at the time of application, the Member States concerned shall recognise the marketing authorisation granted by the reference Member State. To this end, the marketing authorisation holder shall request the reference Member State either to prepare an assessment report on the medicinal product or, if necessary, to update any existing assessment report. The reference Member State shall prepare or update the assessment report within 60 days of

receipt of the application. The assessment report together with the summary of product characteristics shall be sent to the Member States concerned and to the applicant.

3. In cases where the medicinal product has not received a marketing authorisation at the time of application, the applicant shall request the reference Member State to prepare a draft assessment report, a draft summary of product characteristics, and a draft of the labelling and package leaflet. The reference Member State shall prepare these draft documents within 120 days of receipt of a valid application and shall send them to the concerned Member States and to the applicant.
4. Within 90 days of receipt of the documents referred to in paragraphs 2 and 3, the Member States concerned shall approve the assessment report, the summary of product characteristics, and the labelling and package leaflet and shall inform the reference Member State to this effect. The reference Member State shall record the agreement of all parties, close the procedure and inform the applicant accordingly.
5. Each Member State where an application has been submitted in accordance with paragraph 1 shall adopt a decision in conformity with the approved assessment report, the summary of product characteristics and the labelling and package leaflet as approved, within 30 days of acknowledgement of the agreement.

Article 29

1. If, within the period laid down in Article 28(4), a Member State cannot approve the assessment report, the summary of product characteristics, the labelling and the package leaflet on the grounds of serious potential risk to public health, it shall give a detailed exposition of the reasons for its position to the reference Member State, to the other Member States concerned and to the applicant. The points of disagreement shall be forthwith referred to the coordination group..
2. Within the coordination group, all Member States referred to in paragraph 1 shall use their best endeavours to reach agreement on the action to be taken. They shall allow the applicant the opportunity to make his/her point of view known orally or in writing. If, within 60 days of the communication of the elements of disagreement, the Member States reach an agreement, the reference Member State shall record the broad agreement, close the procedure and inform the applicant accordingly. Article 28(5) shall apply.
3. If the Member States fail to reach an agreement within the 60-day period laid down in paragraph 2, the Agency shall be immediately informed, with a view to the application of the procedure under Article 32. The Agency shall be provided with a detailed statement of the matters on which the Member States have been unable to reach agreement and the reasons for their disagreement. A copy shall be forwarded to the applicant.

4. As soon as the applicant is informed that the matter has been referred to the Agency, he/she shall forthwith forward to the Agency a copy of the information and particulars referred to in the first subparagraph of Article 28(1).
5. In the circumstances referred to in paragraph 3, Member States that have approved the assessment report, the draft summary of product characteristics and the labelling and package leaflet of the reference Member State may, at the request of the applicant, authorise the medicinal product without waiting for the outcome of the procedure laid down in Article 32. In that event, the authorisation granted shall be without prejudice to the outcome of that procedure.

Article 30

1. If two or more applications submitted in accordance with Article 8 and Articles 10 to 11 have been made for marketing authorisation for a particular medicinal product, and if Member States have adopted divergent decisions concerning the authorisation of the medicinal product or its suspension or withdrawal, a Member State, the Commission or the applicant or the marketing authorisation holder may refer the matter to the Committee on Human Medicinal Products, hereinafter referred to as “the Committee”, for application of the procedure laid down in Article 32.
2. In order to promote harmonisation of authorisations for medicinal products authorised for not less than ten years in the Community, Member States may, each year, forward to the coordination group a list of medicinal products for which a harmonised summary of product characteristics should be drawn up.

The coordination group shall lay down a list taking into account the proposals from all Member States and shall forward this list to the Commission.

The Commission or a Member State, in agreement with the Agency and taking into account the views of interested parties, may refer these products in accordance with paragraph 1.

Article 31

1. The Member States or the Commission or the applicant or the marketing authorisation holder may, in specific cases where the interests of the Community are involved, refer the matter to the Committee for application of the procedure laid down in Article 32 before any decision is reached on a request for a marketing authorisation or on the suspension or withdrawal of an authorisation, or on any other variation to the terms of a marketing authorisation which appears necessary, in particular to take account of the information collected in accordance with Title IX.

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

The Member States and the applicant or the marketing authorisation holder shall supply the Committee with all available information relating to the matter in question.

2. Where the referral to the Committee concerns a range of medicinal products or a therapeutic class, the Agency may limit the procedure to certain specific parts of the authorisation.

In that event, Article 35 shall apply to those medicinal products only if they were covered by the authorisation procedures referred to in this Chapter."

Article 32

1. When reference is made to the procedure laid down in this Article, the Committee shall consider the matter concerned and shall issue a reasoned opinion within 60 days of the date on which the matter was referred to it.

However, in cases submitted to the Committee in accordance with Articles 30 and 31, this period may be extended by the Committee for a further period of up to 90 days, taking into account the views of the applicants or the marketing authorisation holders concerned.

In an emergency, and on a proposal from its Chairman, the Committee may agree to 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. Before issuing its opinion, the Committee shall provide the applicant or the marketing authorisation holder with an opportunity to present written or oral explanations.

The opinion of the Committee shall be accompanied by a draft summary of product characteristics for the product and a draft text of the labelling and package leaflet.

If necessary, the Committee may call upon any other person to provide information relating to the matter before it.

The Committee may suspend the time-limits referred to in paragraph 1 in order to allow the applicant or the marketing authorisation holder to prepare explanations.

4. The Agency shall forthwith inform the applicant or the marketing authorisation holder where the opinion of the Committee is that:
 - (a) the application does not satisfy the criteria for authorisation; or
 - (b) the summary of the product characteristics proposed by the applicant or the marketing authorisation holder in accordance with Article 11 should be amended; or

- (c) the authorisation should be granted subject to certain conditions, in view of conditions considered essential for the safe and effective use of the medicinal product including pharmacovigilance; or
- (d) a marketing authorisation should be suspended, varied or withdrawn.

Within 15 days of receipt of the opinion, the applicant or the marketing authorisation holder may notify the Agency in writing of his intention to appeal. In that case, he/she shall forward the detailed grounds for appeal to the Agency within 60 days of receipt of the opinion. Within 60 days of receipt of the grounds for appeal, the Committee shall reconsider its opinion according to Article 53(1) of Regulation (EEC) No 2309/93. The conclusions reached on the appeal shall be annexed to the assessment report referred to in paragraph 5 of this Article.

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

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

- (a) a draft summary of the product characteristics, as referred to in Article 11;
- (b) any conditions affecting the authorisation within the meaning of point (c) of paragraph 4;
- (c) the proposed text of the labelling and leaflet."

(25) Article 33 is amended as follows:

- (a) In the second paragraph, "Article 32(5)(a) and (b)" is replaced by "Article 32(5) second indent".
- (b) In the fourth paragraph, the words "or the marketing authorisation holder" are added after the word "applicant".

(26) Article 34 is replaced by the following:

"Article 34

- 1. The Commission shall make a final decision in accordance with the procedure referred to in Article 121(3), where the draft decision is in conformity with the Agency's opinion.

The Commission shall make a final decision in accordance with the procedure referred to in Article 121(4), where the draft decision is not in conformity with the Agency's opinion.

2. The rules of procedure of the Standing Committee established by Article 121(1) shall be adjusted to take account of the tasks incumbent upon it in accordance with this Chapter.

Those adjustments shall entail the following provisions:

- (a) except in cases referred to in the third paragraph of Article 33, the opinion of the Standing Committee shall be given in writing;
- (b) Member States shall be allowed 15 days to forward written observations on the draft decision to the Commission. However, in cases where the decision is of an urgent nature, the Chairman may set a shorter deadline taking into account the degree of urgency involved;
- (c) Member States shall have the option of submitting a written request that the draft Decision be discussed in a plenary meeting of the Standing Committee.

Where, in the opinion of the Commission, the written observations of a Member State raise important new questions of a scientific or technical nature which have not been addressed in the opinion delivered by the Agency, the Chairman shall suspend the procedure and refer the application back to the Agency for further consideration.

The provisions necessary for the implementation of this paragraph shall be adopted by the Commission in accordance with the procedure referred to in Article 121(2).

3. The decision as referred to in paragraph 1 shall be addressed to all Member States and reported for information to the marketing authorisation holder or applicant. The Member States concerned and the reference Member State shall either grant or withdraw marketing authorisation, or vary its terms as necessary to comply with the decision within 30 days following its notification, and they shall refer to it. They shall inform the Commission and the Agency accordingly."

(27) The third subparagraph of Article 35(1) is deleted.

(28) In Article 38, paragraph 2 is replaced by the following:

"2. No later than [date], the Commission shall publish a report on the experience acquired on the basis of the procedures described in this Chapter and shall propose any amendments which may be necessary to improve those procedures."

(29) Article 39 is replaced by the following:

"Article 39

The provisions of Article 29(3), (4) and (5) and of Articles 30 to 34 shall not apply to the homeopathic medicinal products referred to in Article 14.

The provisions of Articles 28 to 34 shall not apply to the homeopathic medicinal products referred to in Article 16(2)."

(30) The following paragraph 4 is added to Article 40:

"4. The Member States shall forward to the Agency a copy of the authorisation referred to in paragraph 1. The Agency shall enter that information on the database."

(31) In Article 46, point (f) is replaced by the following:

"(f) to comply with the principles and guidelines of good manufacturing practice for medicinal products and, in so doing, to use only active substances employed as starting materials which have been manufactured in accordance with the detailed guidelines on good manufacturing practice for starting materials."

(32) A new Article 46a is inserted:

"Article 46a

1. For the purpose of this Directive, manufacture of active substances used as starting materials shall include both total and partial manufacture or import of an active substance used as a starting material as defined in the second part of Section C of Annex I, and the various processes of dividing up, packaging or presentation prior to its incorporation into a medicinal product, including repackaging or re-labelling, such as are carried out by a distributor of starting materials.
2. Any amendments necessary to adapt paragraph 1 to new scientific and technical developments shall be laid down in accordance with the procedure referred to in Article 121(2)."

(33) In Article 47, the following third and fourth paragraphs are added:

"The principles of good manufacturing practice for active substances used as starting materials referred to in point (f) of Article 46 shall be adopted in the form of detailed guidelines.

The Commission shall also publish guidelines on the format and content of the authorisation referred to in Article 40(1), on the reports referred to in Article 111(3) and on the format and content of the certificate of good manufacturing practice referred to in Article 111(5)."

(34) In Article 49(1), "minimum" is deleted.

(35) In Article 50(1), "in the State concerned" is replaced by "within the Community".

(36) In Article 51(1), point (b) is replaced by the following:

"(b) in the case of medicinal products coming from third countries, irrespective of whether the product has been manufactured in the Community, that each production batch has undergone in a Member State a full qualitative analysis, a quantitative analysis of at least all the active constituents and all the other tests or checks necessary to ensure the quality of medicinal products in accordance with the requirements of the marketing authorisation."

(37) Article 54 is amended as follows:

(a) Point (a) is replaced by the following:

"(a) the name of the medicinal product followed by its strength and pharmaceutical form (baby, child or adult as appropriate); the common name shall be included where the product contains only one active substance and if its name is an invented name;"

(b) In point (d), "guidelines" is replaced by "detailed guidance".

(c) Point (f) is replaced by the following:

"(f) a special warning that the medicinal product must be stored out of the reach and sight of children;"

(d) Point (k) is replaced by the following:

"(k) the name and address of the marketing authorisation holder and, where applicable, the name of the representative appointed by the holder to represent him/her;"

(e) Point (n) is replaced by the following:

"(n) in the case of non-prescription medicinal products, instructions for use"

(38) Article 55 is amended as follows:

(a) In paragraph 1, "in Articles 54 and 62" is replaced by "in Article 54";

(b) The first indent of paragraph 2 is replaced by the following:

"– the name of the medicinal product as laid down in point (a) of Article 54,"

(c) The first indent of paragraph 3 is replaced by the following:

"– the name of the medicinal product as laid down in point (a) of Article 54 and, if necessary, the route of administration,"

(39) In Article 57, the following second paragraph is added:

"For medicinal products authorised under the provisions of Regulation [(EEC) No 2309/93], Member States shall, when applying this Article, observe the detailed guidance referred to in Article 65 of this Directive."

(40) Article 59 is replaced by the following:

"Article 59

1. The package leaflet shall be drawn up in accordance with the summary of the product characteristics; it shall include, in the following order:
 - (a) for the identification of the medicinal product:
 - (i) the name of the medicinal product followed by its strength and pharmaceutical form, (baby, child or adult as appropriate). The common name shall be included where the product contains only one active substance and if its name is an invented name;
 - (ii) the pharmaco-therapeutic group or type of activity in terms easily comprehensible for the patient;
 - (b) the therapeutic indications;
 - (c) a list of information which is necessary before taking the medicinal product:
 - (i) contra-indications;
 - (ii) appropriate precautions for use;
 - (iii) forms of interaction with other medicinal products and other forms of interaction (e.g. alcohol, tobacco, foodstuffs) which may affect the action of the medicinal product;
 - (iv) (iv) special warnings;
 - (d) a description of the adverse reactions which may occur under normal use of the medicinal product and, if necessary, the action to be taken in such a case; the patient should be expressly asked to communicate any adverse reaction which is not mentioned in the package leaflet to his doctor or pharmacist;
 - (e) the necessary and usual instructions for proper use, and in particular:
 - (i) the dosage,
 - (ii) the method and, if necessary, route of administration;
 - (iii) the frequency of administration, specifying if necessary the appropriate time at which the medicinal product may or must be administered;and, as appropriate, depending on the nature of the product:
 - (iv) the duration of treatment, where it should be limited;
 - (v) the action to be taken in the case of an overdose (such as symptoms, emergency procedures);

- (vi) what to do when one or more doses have not been taken;
- (vii) indication, if necessary, of the risk of withdrawal effects;
- (f) a reference to the expiry date indicated on the label, with:
 - (i) a warning against using the product after this date;
 - (ii) where appropriate, special storage precautions;
 - (iii) if necessary, a warning against certain visible signs of deterioration;
 - (iv) the full qualitative composition (in active substances and excipients) and the quantitative composition in active substances, using common names, for each presentation of the medicinal product;
 - (v) for each presentation of the product, the pharmaceutical form and content in weight, volume or units of dosage;
 - (vi) the name and address of the marketing authorisation holder and, where applicable, the name of his appointed representatives in the Member States;
- (g) where the medicinal product is authorised according to the procedure provided for in Articles 28 to 39 under different names in the Member States concerned, a list of the names authorised in each Member State;
- (h) the date on which the package leaflet was last revised.

2. The list set out in point (c) of paragraph 1 shall:

- (a) take into account the particular condition of certain categories of users (children, pregnant or breastfeeding women, the elderly, persons with specific pathological conditions);
 - (b) mention, if appropriate, possible effects on the ability to drive vehicles or to operate machinery;
 - (c) list those excipients knowledge of which is important for the safe and effective use of the medicinal product and which are included in the detailed guidance published pursuant to Article 65."
- (41) In Article 61(4), "or as appropriate" is replaced by "and".
- (42) In Article 62, "for health education" is replaced by "for the patient".
- (43) Article 63 is amended as follows:
- (a) The following third subparagraph is added to paragraph 1:

"In the case of certain orphan medicinal products, the particulars listed in Article 54 may, on reasoned request, appear in one of the official languages of the Community."

(b) Paragraph 3 is replaced by the following:

"3. When the product is not intended to be delivered directly to the patient, the competent authorities may grant an exemption to the obligation that certain particulars should appear on the labelling and in the package leaflet and that the leaflet must be in the official language or languages of the Member State where the product is placed on the market."

(44) Article 65 is replaced by the following:

"Article 65

In consultation with the Member States and the parties concerned, the Commission shall draw up and publish detailed guidance concerning in particular:

- (a) the wording of certain special warnings for certain categories of medicinal products;
- (b) the particular information needs relating to self-medication;
- (c) the legibility of particulars on the labelling and package leaflet;
- (d) the methods for the identification and authentication of medicinal products;
- (e) the list of excipients which must feature on the labelling of medicinal products and the way in which these excipients must be indicated;
- (f) harmonised provisions for the implementation of Article 57."

(45) Article 69(1) is amended as follows:

(a) The first indent is replaced by the following:

"– the scientific name of the stock or stocks followed by the degree of dilution, making use of the symbols of the pharmacopoeia used in accordance with Article 1(5); if the homeopathic medicinal product is composed of two or more stocks, the scientific names of the stocks on the labelling may be replaced by an invented name"

(b) The twelfth indent is replaced by the following:

"– a warning advising the user to consult a doctor if the symptoms persist"

(46) Article 70(2) is amended as follows:

(a) Point (a) is replaced by the following:

"(a) medicinal products on medical prescription for renewable or non-renewable delivery;"

(b) Point (c) is replaced by the following:

"(c) medicinal products on "restricted" medical prescription, reserved for use in certain specialised areas."

- (47) Article 74 is replaced by the following:

"Article 74

When new facts are brought to their attention, the competent authorities shall examine and, as appropriate, amend the classification of a medicinal product by applying the criteria listed in Article 71."

- (48) The heading of Title VII is replaced by the following:

"Title VII

Distribution of medicinal products"

- (49) Article 76 is amended as follows:

(a) The existing text becomes paragraph 1.

(b) The following new paragraph 2 is inserted:

"2. In the case of wholesale distribution and storage, medicinal products shall be covered by a marketing authorisation issued pursuant to [Regulation (EEC) No 2309/93] or by the competent authorities of a Member State in accordance with this Directive."

- (50) The second indent of point (e) of Article 80 is replaced by the following:

"– name of the medicinal product,"

- (51) In Article 82 the second indent of the first paragraph is replaced by the following:

"– the name and pharmaceutical form of the medicinal product,"

- (52) Article 84 is replaced by the following:

"Article 84

The Commission shall publish guidelines on good distribution practice. To this end, it shall consult the Committee and the Pharmaceutical Committee established by Council Decision 75/320/EEC*.

* OJ L 147, 9.6.1975, p. 23."

- (53) Article 86 is amended as follows:

(a) In paragraph 1, the introductory phrase is replaced by the following:

"For the purposes of this Title, "advertising of medicinal products" shall include any form of door-to-door information, canvassing activity or inducement designed to promote the prescription, supply, sale, consumption or awareness of the availability of medicinal products; it shall include in particular:"

(b) The fourth indent of the paragraph 2 is replaced by the following:

"– information relating to human health or diseases, provided that there is no reference, even indirect, to medicinal products, and without prejudice to Article 88(2) of this Directive."

(54) Article 88 is replaced by the following:

"Article 88

1. Member States shall prohibit the advertising to the general public of medicinal products which:
 - (a) are available on medical prescription only, in accordance with Title VI;
 - (b) contain substances defined as psychotropic or narcotic by international convention, such as the United Nations Conventions of 1961 and 1971.
2. The communication of information on certain medicinal products is authorised under strict conditions in the interest of patients in order to respond to their legitimate needs. This provision applies to product information appended to the marketing authorisation as well as to additional related information.

By way of derogation from the prohibition in paragraph 1(a), Member States shall authorise the dissemination of information relating to certain medicinal products authorised in the framework of the affections set out below, in order to respond to the expectations expressed by the patients' groups:

This dissemination of information shall be carried out on the following conditions:

- (a) the medicinal product shall be authorised and prescribed for the treatment of any of the following conditions:
 - acquired immune deficiency syndrome;
 - asthma and chronic broncopulmonary disorders;
 - diabetes;
- (b) the information disseminated complies with the principles set out in this Title;
- (c) implementation of this paragraph shall be conditioned by the setting-up of self-regulatory procedures by the pharmaceutical industry at Member State level;
- (d) the information and its dissemination shall be in conformity with the principles of good practice which are adopted, after consultation with interested parties, in conformity with the procedure set out in Article 121(2).

- (e) in order to monitor the implementation of the principles of good practice referred to above:
 - the additional information related to the medicinal products shall be notified to the Agency. If the Agency does not object within thirty days following this notification, the information shall be deemed to be accepted;
 - the Agency shall coordinate of the monitoring of the information on the medicinal products authorised in conformity with this Directive, in particular through the setting-up of a data base;
 - on a yearly basis, the Agency shall prepare a report on the application of these principles of good practice;
- (f) implementation of this paragraph shall be the subject of an evaluation and a detailed report no later than [*date*]. The Commission shall propose any changes required to improve its implementation.

3. Medicinal products may be advertised to the general public which, by virtue of their composition and purpose, are intended and designed for use without the intervention of a medical practitioner for diagnostic purposes or for the prescription or monitoring of treatment, with the advice of the pharmacist, if necessary
4. Member States shall be able to ban, on their territory, advertising to the general public of medicinal products the cost of which may be reimbursed.
5. The prohibition contained in paragraph 1 shall not apply to vaccination campaigns carried out by the industry and approved by the competent authorities of the Member States.
6. The prohibition referred to in paragraph 1 shall apply without prejudice to Article 14 of Directive 89/552/EEC.
7. Member States shall prohibit the direct distribution of medicinal products to the public by the industry for promotional purposes."

(55) Article 89 is amended as follows:

- (a) the first indent of point (b) of paragraph 1 is replaced by the following:
 - "– the name of the medicinal product, as well as the common name if the medicinal product contains only one active substance,"
- (b) paragraph 2 is replaced by the following:
 - "2. Member States may decide that the advertising of a medicinal product to the general public may, by way of derogation from paragraph 1, include only the name of the medicinal product if it is intended solely as a reminder."

(56) Article 90 is amended as follows:

(a) Point (c) is replaced by the following:

"(c) suggests that the subject's state of health can be immediately improved by taking the medicinal product;"

(b) In point (d), "Article 88(4)" is replaced by "Article 88(5)".

(c) Point (l) is deleted.

(57) In Article 91, paragraph 2 is replaced by the following:

"2. Member States may decide that the advertising of a medicinal product to persons qualified to prescribe or supply such products may, notwithstanding paragraph 1, include only the name of the medicinal product, if it is intended solely as a reminder."

(58) Point (d) of Article 96(1) is replaced by the following:

"(d) each sample shall be no larger than the smallest presentation on the market;"

(59) In Article 98, the following paragraph 3 is added:

"3. The Member States shall authorise the co-promotion of a medicinal product by the holder of the marketing authorisation and one or more companies nominated by him/her."

(60) Article 100 is replaced by the following:

"Article 100

Advertising of the homeopathic medicinal products referred to in Article 14(1) shall be subject to the provisions of this Title with the exception of Article 87(1).

However, only the information specified in Article 69(1) may be used in the advertising of such medicinal products."

(61) In Article 101, the second paragraph is replaced by the following:

"The Member States may impose specific requirements on doctors and other health care professionals in respect of the reporting of suspected serious or unexpected adverse reactions."

(62) Article 102 is replaced by the following:

"Article 102

In order to ensure the adoption of appropriate and harmonised regulatory decisions concerning the medicinal products authorised within the Community, having regard to information obtained about adverse reactions to medicinal products under normal conditions of use, the Member States shall operate a pharmacovigilance system. This system shall be used to collect information useful in the surveillance of medicinal products, with particular reference to adverse reactions in human beings, and to evaluate such information scientifically.

Member States shall ensure that suitable information collected within this system is communicated to the other Member States and the Agency. The information shall be recorded in the database referred to in point (j) of the second paragraph of Article 51 of Regulation (EEC) No 2309/93 and shall be permanently accessible to all Member States.

This system shall also take into account any available information on misuse and abuse of medicinal products which may have an impact on the evaluation of their benefits and risks.”

- (63) In Article 103, the introductory phrase of the second paragraph is replaced by the following:

"That qualified person shall reside in the Community and shall be responsible for the following:"

- (64) Articles 104 to 107 are amended as follows:

"Article 104

1. The marketing authorisation holder shall be required to maintain detailed records of all suspected adverse reactions occurring either in the Community or in a third country.

Save in exceptional circumstances, these reactions shall be communicated electronically in the form of a report according to the guidelines referred to in Article 106(1).
2. The marketing authorisation holder shall be required to record all suspected serious adverse reactions which are brought to his attention by a health care professional and to report them immediately to the competent authority of the Member State on whose territory the incident occurred, and in no case later than 15 calendar days following the receipt of the information.
3. The marketing authorisation holder shall be required to record and report all other suspected serious adverse reactions which meet the notification criteria in accordance into the guidelines referred to in Article 106(1), of which he can reasonably be expected to have knowledge, immediately to the competent authority of the Member State in whose territory the incident occurred, and in no case later than 15 calendar days following the receipt of the information.

4. The marketing authorisation holder shall ensure that all suspected serious and unexpected adverse reactions occurring in the territory of a third country are reported immediately in accordance with the guidelines referred to in Article 106(1), so that the Agency and the competent authorities of the Member States where the medicinal product is authorised are informed of them, and in no case later than 15 calendar days following the receipt of the information.
5. By way of derogation from paragraphs 2, 3 and 4, in the case of medicinal products which are covered by Directive 87/22/EEC or which have qualified for the procedures laid down in Articles 28 and 29 of this Directive or which have been the subject of the procedures under Articles 32, 33 and 34 of this Directive, the marketing authorisation holder shall also ensure that all suspected serious adverse reactions occurring in the Community are reported in such a way as to be accessible to the reference Member State or to any competent authority acting as reference Member State. The reference Member State shall assume the responsibility of analysing and monitoring such adverse reactions.
6. Unless other requirements have been laid down as a condition of the granting of authorisation, or subsequently as indicated in the guidelines referred to in Article 106(1), reports of all adverse reactions shall be submitted to the competent authorities in the form of a periodic safety update report, either immediately upon request or periodically as follows: six monthly for the first two years after authorisation, annually for the subsequent two years, and thereafter at three-yearly intervals. The periodic safety update reports shall include a scientific evaluation of the benefits and risks of the medicinal product.
7. Following the granting of a marketing authorisation, the marketing authorisation holder may request the amendment of the periods referred to in paragraph 6 according to the procedure laid down by Commission Regulation (EC) No 541/95*.

* OJ L 55, 11.3.1995, p. 7."

Article 105

1. The Agency, in collaboration with the Member States and the Commission, shall set up a data-processing network to facilitate the exchange of pharmacovigilance information regarding medicinal products marketed in the Community intended to allow all competent authorities to share the information at the same time.
2. Making use of the network referred to in paragraph 1, Member States shall ensure that reports of suspected serious adverse reactions that have taken place on their territory are immediately made available to the Agency and the other Member States, and in any case within 15 days of their notification at the latest

3. The Member States shall ensure that reports of suspected serious adverse reactions that have taken place on their territory are immediately made available to the marketing authorisation holder, and in any case within 15 days of their notification at the latest.

Article 106

1. In order to facilitate the exchange of information on pharmacovigilance within the Community, the Commission, after consulting the Agency, the Member States and interested parties, shall draw up guidelines on the collection, verification and presentation of adverse reaction reports, including technical requirements for electronic exchange of pharmacovigilance information in accordance with internationally agreed formats, and shall publish a reference to an internationally agreed medical terminology.

Acting in accordance with the guidelines, marketing authorisation holders shall use internationally agreed medical terminology for the reporting of adverse reactions.

These guidelines shall be published in Volume 9 of *The Rules governing Medicinal Products in the European Community* and shall take account of international harmonisation work carried out in the field of pharmacovigilance.

2. For the interpretation of the definitions referred to in points (11) to (16) of Article 1 and of the principles outlined in this Title, the marketing authorisation holder and the competent authorities shall follow the guidelines referred to in paragraph 1.

Article 107

1. Where, as a result of the evaluation of pharmacovigilance data, a Member State considers that a marketing authorisation should be suspended, withdrawn or varied in accordance with the guidelines referred to in Article 106(1), it shall forthwith inform the Agency, the other Member States and the marketing authorisation holder.
2. Where urgent action to protect public health is necessary, the Member State concerned may suspend the marketing authorisation of a medicinal product, provided that the Agency, the Commission and the other Member States are informed no later than the following working day.

When the Agency is informed in accordance with paragraph 1 or the first subparagraph of this paragraph, the Committee shall prepare an opinion within a time frame to be determined depending on the urgency of the matter.

Acting on the basis of this opinion, the Commission may request all Member States where the product is being marketed to take temporary measures immediately.

The final measures shall be adopted in accordance with the procedure described in Article 121(3), where the draft decision is in accordance with the Agency's opinion.

The final measures shall be adopted in accordance with the procedure described in Article 121(4), where the draft decision is not in accordance with the Agency's opinion.

(65) Article 111 is amended as follows:

(a) Paragraph 1 is replaced by the following:

"1. The competent authority of the Member State concerned shall ensure, by means of repeated inspections, that the legal requirements governing medicinal products are complied with.

The competent authority may carry out inspections at the premises of manufacturers of active substances used as starting materials, or of the premises of marketing authorisation holders whenever it considers that there are serious grounds for suspecting non-compliance with the principles and guidelines of good management practice referred to in Article 47. These inspections may also be carried out at the request of a Member State, the Commission or the Agency.

In order to verify whether the data submitted in order to obtain a conformity certificate comply with the monographs of the European Pharmacopoeia, the standardisation body of the nomenclatures and the quality norms within the meaning of the Convention relating to the elaboration of the European Pharmacopoeia* (European Directorate for the quality of Medicinal Products) may ask the Commission or the Agency to request such an inspection when the starting material concerned is the subject of a European Pharmacopoeia monograph.

The competent authority of the Member State concerned may carry out inspections of starting material manufacturers at the specific request of the manufacturer himself.

Such inspections shall be carried out by officials representing the competent authority who shall be empowered to:

- (a) inspect the manufacturing or commercial establishments of manufacturers of medicinal products or of active substances used as starting materials, and any laboratories employed by the holder of the manufacturing authorisation to carry out checks pursuant to Article 20;
- (b) take samples;
- (c) examine any documents relating to the object of the inspection, subject to the provisions in force in the Member States on 21 May 1975 placing restrictions on these powers with regard to the descriptions of the method of preparation;

- (d) inspect the premises of marketing authorisation holders or any firms employed by the marketing authorisation holder to perform the activities described in Title IX, and in particular Articles 103 and 104.

* OJ L 158, 25.6.1994, p. 19."

- (b) Paragraph 3 is replaced by the following:

"3. After every inspection as referred to in paragraph 1, the officials representing the competent authority shall report on whether the manufacturer complies with the principles and guidelines of good manufacturing practice laid down in Article 47 or, where appropriate, with the requirements laid down in Articles 101 to 108. The content of such reports shall be communicated to the manufacturer or marketing authorisation holder who has undergone the inspection."

- (c) The following paragraphs 4 to 7 are added:

"4. Without prejudice to any arrangements which may have been concluded between the Community and third countries, a Member State, the Commission or the Agency may require a manufacturer established in a third country to submit to an inspection as referred to in paragraph 1.

5. Within 90 days of an inspection as referred to in paragraph 1, a certificate of good manufacturing practice shall be issued to a manufacturer if the outcome of the inspection shows that the manufacturer complies with the principles and guidelines of good manufacturing practice as provided for by Community legislation.

If inspections are performed as part of the certification procedure for the monographs of the European Pharmacopoeia, a certificate shall be drawn up.

6. Member States shall enter the certificates of good manufacturing practice which they issue in a Community register managed by the Agency on behalf of the Community.

7. If the outcome of the inspection as referred to in paragraph 1 is that the manufacturer does not comply with the principles and guidelines of good manufacturing practice as provided for by Community legislation, the information shall be entered in the Community register as referred to in paragraph 6."

(66) Article 116 is replaced by the following:

"Article 116

The competent authorities shall suspend or revoke an authorisation to place a medicinal product on the market if the view is taken that the product is harmful under normal conditions of use, or that it lacks therapeutic efficacy, or that the risk-benefit balance is not positive under the authorised conditions of use, or that its qualitative and quantitative composition is not as declared. Therapeutic efficacy is lacking when it is concluded that therapeutic results cannot be obtained from the medicinal product.

An authorisation shall also be suspended or revoked where the particulars supporting the application as provided for in Article 8 or Articles 10 to 11 are incorrect or have not been amended in accordance with Article 23, or where the controls referred to in Article 112 have not been carried out."

(67) Article 117(1) is replaced by the following:

"1. Without prejudice to the measures provided for in Article 116, Member States shall take all appropriate steps to ensure that the supply of the medicinal product is prohibited and the medicinal product withdrawn from the market, if the view is taken that:

- (a) the medicinal product is harmful under normal conditions of use; or
- (b) it lacks therapeutic efficacy; or
- (c) the risk-benefit balance is not favourable under the authorised conditions of use; or
- (d) its qualitative and quantitative composition is not as declared; or
- (e) the controls on the medicinal product and/or on the ingredients and the controls at an intermediate stage of the manufacturing process have not been carried out or if some other requirement or obligation relating to the grant of the manufacturing authorisation has not been fulfilled."

(68) Article 119 is replaced by the following:

"Article 119

The provisions of this Title shall apply to homeopathic medicinal products."

(69) Articles 121 and 122 are replaced by the following:

"Article 121

1. The Commission shall be assisted by the Standing Committee on Medicinal Products for Human Use, hereinafter called "the Standing Committee", in the task of adapting to technical progress the directives on the removal of technical barriers to trade in the medicinal products sector. The Standing Committee shall be composed of representatives of the Member States and chaired by a representative of the Commission.
2. Where reference is made to this paragraph, the regulatory procedure laid down in Article 5 of Decision 1999/468/EC shall apply, in compliance with Articles 7 and 8 thereof.

The period provided for in Article 5(6) of Decision 1999/468/EC shall be three months.

3. Where reference is made to this paragraph, the advisory procedure laid down in Article 3 of Decision 1999/468/EC shall apply, in compliance with Articles 7 and 8 thereof.
4. Where reference is made to this paragraph, the management procedure laid down in Article 4 of Decision 1999/468/EC shall apply, in compliance with Articles 7 and 8 thereof.

The period provided for in Article 4(3) of Decision 1999/468/EC shall be one month.

5. The Standing Committee shall adopt its own rules of procedure.

Article 122

1. Member States shall take all appropriate measures to ensure that the competent authorities concerned communicate to each other such information as is appropriate to guarantee that the requirements placed on the authorisations referred to in Article 40, on the certificates referred to in Article 111(5) or on the marketing authorisations are fulfilled.
2. Upon reasoned request, Member States shall forthwith communicate the reports referred to in Article 111(3) to the competent authorities of another Member State.
3. The conclusions reached following an inspection under Article 111(1) which is carried out by the inspectorate of the Member State concerned shall be valid throughout the Community.

However, in exceptional cases, if a Member State has is unable, for reasons relating to public health, to accept the conclusions reached following an inspection under Article 111(1), that Member State shall forthwith inform the Commission and the Agency

When the Commission is informed of these difficulties, it may, after consulting the Member States concerned, ask the inspector who performed the original inspection to perform a new inspection; the inspector may be accompanied by two other inspectors from Member States who are not parties to the disagreement."

Article 2

Member States shall bring into force the laws, regulations and administrative provisions necessary to comply with this Directive no later than [date]. They shall immediately inform the Commission thereof.

When Member States adopt those provisions, they shall contain a reference to this Directive or be accompanied by such a reference on the occasion of their official publication. Member States shall determine how such reference is to be made.

Article 3

This Directive shall enter into force on the twentieth day following that of its publication in the *Official Journal of the European Communities*.

Article 4

This Directive is addressed to the Member States.

Done at Brussels,

For the European Parliament
The President

For the Council
The President

FINANCIAL STATEMENT

1. TITLE OF OPERATION

Proposal for a Directive of the European Parliament and of the Council amending Directive 2001/83/EC on the Community code relating to medicinal products for human use

2. BUDGET HEADING(S) INVOLVED

B5-3260A Industrial competitiveness policy for the EU (administration)

3. LEGAL BASIS

Article 95 EC

4. DESCRIPTION OF OPERATION

4.1 General objective

To guarantee a high level of health protection for the people of Europe, particularly through increased market surveillance and a strengthening of pharmacovigilance procedures.

To complete the internal market in pharmaceutical products and to establish a regulatory and legislative framework that favours the competitiveness of the pharmaceuticals sector in Europe.

To adapt the present measures and propose future measures to meet the challenges of the future enlargement of the European Union.

4.2 Period covered and arrangements for renewal

Measures to be implemented in 2005, with no deadline.

5. CLASSIFICATION OF EXPENDITURE OR REVENUE

5.1 DNO

5.2 CND

5.3 Type of revenue involved

None

6. TYPE OF EXPENDITURE OR REVENUE

– Expenditure on scientific expertise and subsidies

7. FINANCIAL IMPACT

7.1 Method of calculating total cost of operation (relation between individual and total costs)

The total cost of the operation is calculated on the basis of the present number of meetings/meetings of experts per year for the type of operations covered by the proposal.

7.2 Itemised breakdown of cost

Commitment appropriations in EUR million (at current prices)

Breakdown	Year n	n+1	n+2	n+3	N+4	n+5 and subsequent years	Total

7.3 Operational expenditure for studies, experts etc. included in Part B of the budget

Commitment appropriations in EUR million (at current prices)

	Year n	n+1	n+2	n+3	n+4	n+5 and subsequent years	Total
– Studies					0.15	0.15	0.300
– Meetings of experts ¹							0
– Information and publications							0
Total					0.15	0.15	0.30

¹ Expenditure meeting the criteria set out in the Commission Communication of 22.4.1992 (SEC(1992) 769).

7.4 Schedule of commitment and payment appropriations

Commitment appropriations in EUR million

	Year n	n+1	n+2	n+3	n+4	n+5 and subsequent Years	Total
Commitment appropriations					0.15	0.15	0.30
Payment appropriations							
Year n							
n+1							
n+2							
n+3							
n+4					0.15		0.15
n+5 and subsequ. years						0.15	0.15
Total							0.30

8. FRAUD-PREVENTION MEASURES

- Are any specific measures planned?

No

9. ELEMENTS OF COST-EFFECTIVENESS ANALYSIS

9.1 Specific and quantified objectives; target population

None

9.2 Grounds for the operation

- Need for Community financial aid, with particular regard for the principle of subsidiarity

Amendment of existing legislation to take account of scientific and technical progress and of the future enlargement of the EU.

- Choice of ways and means

Amendment of existing legislation on the basis of Article 71 of Council Regulation (EEC) No 2309/93 following the evaluation of the implementation of the present legislation, which is the subject of a report from the Commission to the Council and the European Parliament.

- Main factors of uncertainty which could affect the specific results of the operation

The main factor of uncertainty is the arrangements for the enlargement of the EU in terms of both the countries concerned and the timetable for their accession. Another factor of uncertainty involves the way in which industry will use the procedures introduced, since the number of products concerned per year and the rapport cost/difficulty ratio of the associated scientific evaluations are not yet known.

9.3 Monitoring and evaluation of the operation

- Performance indicators

Number of products authorised under the procedures, progress on technical harmonisation, timetable for extending the procedures to the candidate countries, database and IT networks.

- Details and frequency of planned evaluations

A Commission report at least every ten years following the first report, which was drawn up after six years and is the basis of the present proposal.

- Assessment of the results obtained (where the operation is to be continued or renewed)

The results obtained since 1 January 1995 (when the present system came into force) are the subject of a report from the Commission to the Council and the European Parliament (currently being adopted by written procedure)

10. ADMINISTRATIVE EXPENDITURE (SECTION III, PART A OF THE BUDGET)

Actual mobilisation of the necessary administrative resources will depend on the Commission's annual decision on the allocation of resources, taking into account the number of staff and additional amounts authorised by the budgetary authority.

10.1 Effect on the number of posts

Type of post		Staff to be assigned to managing the operation		Source		Duration
		Permanent posts	Temporary posts	Existing resources in the DG or department concerned	Additional resources	
Officials or temporary staff	A	2A, 1B, 1C		2A, 1B, 1C	none	
	B C					
Other resources						
Total		2A, 1B, 1C		2A, 1B, 1C	none	

If additional resources are required, indicate the pace at which they will have to be made available.

10.2 Overall financial impact of additional human resources

(EUR)

	Amounts	Method of calculation
Officials	432 000	4 x EUR 108 000 per year
Temporary staff		
Other resources (indicate budget heading)		
Total	432 000	

The amounts given must express the total cost of additional posts for the entire duration of the operation, if this duration is predetermined, or for 12 months if it is indefinite.

10.3 Increase in other administrative expenditure as a result of the operation, particularly the cost of meetings of committees and groups of experts

(EUR)

Budget heading	Amounts	Method of calculation
A0-7030	20 000	Without taking account of the data relating to enlargement (since the number of experts per year from the candidate countries is not known), the calculation is based on a cost of approx. EUR 10 000 per meeting for a number of experts from the 15 Member States. 2 meetings per year.
A0-7031	50 000	Idem 5 meetings per year.
A0-7032	20 000	Idem 2 meetings per year.
Total	90 000	

The amounts given must correspond to total expenditure arising from the operation if its duration is predetermined or expenditure for 12 months if it is indefinite.

IMPACT ASSESSMENT FORM¹
**IMPACT OF THE PROPOSAL ON BUSINESSES, PARTICULARLY ON SMALL
AND MEDIUM-SIZED ENTERPRISES (SMEs)**

TITLE OF THE PROPOSAL

Proposal for a Directive of the European Parliament and of the Council amending Directive 2001/83/EC on the Community code relating to medicinal products for human use

REFERENCE NUMBER OF THE DOCUMENT

THE PROPOSAL

1. In view of the principle of subsidiarity, why is Community legislation necessary in this field and what are its main objectives?

The proposed legislation introduces new provisions and amends, in a number of respects, the existing legislation relating to the functioning of the centralised and decentralised procedures for approving and suspending marketing of medicinal products for human and veterinary use.

Pursuant to Article 71 of Regulation (EEC) No 2309/93 the Commission is obliged to report within six years of the entry into force of the Regulation on the experience acquired as a result of the operation of the centralised and decentralised procedures. An audit report prepared on behalf of the Commission² has identified those aspects of the authorisation procedures which were operating satisfactorily and those where it was considered that improvement could be achieved.

From a business viewpoint, the proposed measures are intended to:

- increase the level of harmonisation across Member States of the rules governing medicinal products;
- increase the efficiency of operation of the centralised and decentralised procedures;
- thereby improve access and speed of access to the whole of the European market for both innovative and generic medicinal products; and
- allow industry to respond more quickly to the needs of the market.

¹ Since the two authorisation procedures in use at Community level (centralised – decentralised) are inextricably linked and several parts of the legislation on human medicinal products are identical to that on veterinary medicinal products, it was considered appropriate to draw up a global impact sheet, which gives an overview of the effects which the adoption of the three legislative drafts will have. The same impact sheet is therefore annexed to each of the three texts.

² Evaluation of the operation of Community procedures for the authorisation of medicinal products, CMS Cameron McKenna and Anderson Consulting, October 2000.

The so-called “new systems” for licensing which were introduced in 1995 have contributed to the creation of a single market in pharmaceuticals, but notwithstanding the progress that has been made there is evidence that the procedures contain shortcomings. The findings of the audit report on the operation of the authorisation procedures show that there is a need to refine, and in some areas make more substantial changes, to the existing regimes. In particular, there is recognition that the centralised procedure is capable of working well and that broadening the scope of the procedure to other products would be beneficial, both in terms of patient access and economy of scale for the companies.

The decentralised procedure was acknowledged as having significant advantages in terms of optionality but any such advantage is tempered to an extent by the failure of the system to operate on the basis of effective mutual recognition involving a significant number of Member States.

The pharmaceutical industry is populated by different types of company and a significant proportion of the industry comprises non R&D intensive companies, notably those which focus on their own national markets and those which rely upon the manufacture of generic versions of existing products. The existing regimes do not, at present, fully meet all the needs of these sectors of the industry.

Instituting authorisation procedures that properly protect public health while promoting an innovative profitable pharmaceutical industry is critical for Europe. The pharmaceutical industry is a strategic sector for Europe but there is evidence that over the last decade the European industry is losing competitiveness compared to the USA and that its growth is more erratic than in the US or Japan³. The reasons underlying this trend are complex but the ability of companies to compete effectively is influenced, at least in part, by the nature of the regulatory environment.

The forthcoming enlargement of the European Union over the next decade will see the accession of further Member States. In principle, enlargement has the potential to contribute to the overall competitiveness of the European industry, but an important step in realising increased competitiveness is eradication of the shortcomings identified in the existing procedures prior to enlargement.

It is considered appropriate to maintain a balance between the centralised and decentralised authorisation procedures. Both systems have hitherto contributed – though not to the same extent – to the development of a single market in pharmaceuticals and provided a high degree of safety for patients and animals. However, the emergence of new technologies is delivering sophisticated medicinal products which are best suited to centralised approval.

³ See "Global Competitiveness in Pharmaceuticals", Report prepared for DG Enterprise of the European Commission by Gambardella A, Orsenigol and Pammolli F, November 2000.

THE IMPACT ON BUSINESSES

2. Who will be affected by the proposal?

- What business sectors?

The measures primarily concern pharmaceutical manufacturers and to a lesser extent wholesalers and distributors of medicinal products.

The pharmaceutical industry in the EU consists of companies with a range of different businesses conducted often with a different geographical focus. The total number of pharmaceutical businesses in the EU is estimated at approximately 3000⁴. Large multinational companies dominate the market accounting for approximately 60-65% of the market for pharmaceutical sales. Medium-sized companies (by international standards) make up approximately 30-35% of the market with small local companies accounting for the balance. In terms of business types, the biotechnology element of the European pharmaceutical industry is still young, but the number of companies is growing with just in excess of 1 000 company units. Generic medicines currently account for around 10% of total pharmaceutical sales in the non-hospital market with penetration highest in Germany, Denmark, the UK and the Netherlands⁵. Finally, the veterinary sector accounts for approximately 5% of the value of the human pharmaceutical market⁶. This sector of the market is far more diverse than that relating to medicines for human use, reflecting differences in livestock distribution, methods of production and climate variations across the EU.

The legislative proposals cover a number of aspects of the regulation of medicinal products and consequently the proposals will impact to some extent upon all pharmaceuticals manufacturers. A number of the proposals will therefore affect all pharmaceutical companies irrespective of the nature of the pharmaceutical business. For example, the provisions relating to the validity of marketing authorisations, compassionate use of medicines, the application of good manufacturing practice to starting materials and pharmacovigilance. A number of the measures are sector specific or specific to one or other of the authorisation procedures and accordingly the effect of such measures will be more selective. The centralised procedure tends to be used predominately by large multi-national companies and smaller innovation specialist companies. Accordingly, the proposed changes to the centralised system such as the introduction of conditional authorisations and a fast-track procedure will be relevant for these types of company.

⁴ The pharmaceutical industry in figures, European Federation of Pharmaceutical Industries Associations, 2000 Edition.

⁵ Generic Medicines: How to ensure their effective contribution to healthcare, Euro Health Vol. 2 No 3, September 1996.

⁶ Fountain R and Thurman D Animal Health Market to Face Opportunities and Challenges in 98, Feed Stuffs Vol. 69 No 48, November 1997.

- What sizes of company (proportion of small and medium-sized enterprises)?

The decentralised (mutual recognition) procedure, although used by the large multinational companies, is also used by a significant proportion of small and medium-sized enterprises (“SMEs”). Accordingly, these companies will be impacted by the amendments proposed to the operation of the decentralised system. The principal sector specific measures are directed towards manufacturers of products for veterinary use, manufacturers of generic medicines and manufacturers of homeopathic medicines.

- Are there particular geographical regions in the Community where such companies are established?

No, there are no differences due to the geographic region where the firms concerned are established.

3. What measures will companies have to take in order to comply with the proposal?

The majority of the proposal measures concern procedural changes and fine-tuning of existing procedures. Accordingly, a number of the measures do not impose direct obligations upon business. The majority of the obligations which are imposed impact at the time of application for a marketing authorisation.

Companies seeking to place a product containing a new chemical entity (NCE) on the market will be required to use the centralised authorisation procedure. This will remove, therefore, in respect of some medicinal products, the element of choice which companies presently enjoy to obtain an authorisation from Member States. It should however, be noted that many products containing an NCE⁷ are already obliged to use the centralised route because they are developed using biotechnological processes. Moreover, in circumstances where a company has a choice of procedure for a product containing an NCE, most of the companies already opt for the centralised route. It is envisaged that generic copies of centrally authorised products may be authorised through either the centralised route or the decentralised one. All other medicinal products may do likewise provided they show significant innovation over existing therapies. The broadening in scope of the centralised procedure will bring administrative savings for companies able to benefit from the single application procedure. Some companies, particularly those in the veterinary sector with NCE containing products which are relevant to only a limited geographical area of the European market, may be subject to an increase in the overall cost of preparing a centralised application to market; this is why a derogation has been introduced.

Applicants pursuing an authorisation under the decentralised procedure will be compelled to enter arbitration proceedings if an issue cannot be resolved by the Member States concerned in the case of veterinary medicinal products. Companies may incur some costs in handling arbitration proceedings which they would otherwise avoid by withdrawal of the application. However, any such costs should be outweighed by the fact that companies may be permitted to market a medicinal product which is the subject of arbitration proceedings in those Member States which

⁷ Taken here in a broader sense as meaning any new active substance.

have agreed to authorise the product, thus permitting companies to begin to recoup investment costs earlier than at present.

The harmonisation to ten years (plus, for medicines for human use, one year for new therapeutic indications) of the period of data protection afforded to innovator companies will prevent an applicant for a generic (copy) product from making an abridged applications in Austria⁸, Denmark, Greece, Finland, Ireland, Luxembourg, Portugal, and Spain on the expiry of six years from the date of first authorisation of the innovator product in the EU. An abridged application is one where the applicant does not present the results of his own safety and efficacy testing but relies upon the data underlying the authorisation of the innovator product. However, this restriction is balanced by the fact that companies intending to seek an authorisation for a generic product will be permitted, under a "Bolar" type provision, to conduct testing required prior to expiration of the originator product's period of patent protection.

There is recognition that in some respects the veterinary sector of the pharmaceutical industry has different requirements and faces different issues and the proposal, therefore, seeks to address matters which are a concern in this area of the business. The incremental periods of data protection available for data supporting extensions of a marketing authorisation to additional food producing species, the 13-year period of protection for honey bees and fish and the introduction of a limited period of data protection for certain MRL data will encourage innovation by providing greater protection for the results of research by delaying somewhat the date at which applicants seeking an authorisation for a generic (copy) product, may obtain approval without investing themselves in the research required to obtain and maintain a marketing authorisation. However, consistent with the position for medicines for human use, generic manufacturers will be able to take advantage of a "Bolar" type provision

The removal of the requirement for companies to renew marketing authorisations every five years will reduce the cost burden for companies. This amendment is balanced by increased pharmacovigilance reporting requirements; overall a cost saving is anticipated for companies since companies already have established pharmacovigilance systems in place

4. What economic effects is the proposal likely to have:

- on employment?
- on investment and the creation of new businesses?
- on the competitiveness of businesses?

The proposed package is expected to benefit the pharmaceutical industry in Europe and provide earlier access for patients in the Community to important new medicines.

⁸ Currently in this Member State the period of data protection will not be applied beyond the date of expiry of the patent, this link will cease to exist under the proposed amendments.

The examination in the report by Pammolli *et al*⁹ of the competitive position of the European pharmaceutical business with that in the USA reveals that, in general, the profile of the pharmaceutical industry in Europe is different from that in the USA. The European industry is less specialised in Research and Development activities and has a much larger presence of companies specialised in low value added activities. The US has developed an industry which is effective not only in the "exploration" of new technologies but also in the "exploitation" of such technologies. This vertical specialisation enhances innovation – a key driver of competitiveness – by exploiting the advantages of both the small biotechnology firms and the larger multi-national firms.

Strengthening the scientific advice procedure within the centralised system will enable companies' research to be better focused and will reduce investment risk for small biotechnology companies and, thereby, provide encouragement for this sector of the industry. In addition, extension of the period of data protection to ten years in all Member States with an additional year for subsequent clinically important indications will encourage innovation by providing a greater opportunity for research based companies to recoup the costs of their research investment. The Pammolli *et al* Report¹⁰ showed that there was too little competition in some Member States which in turn led to inefficiencies within the industry. Accordingly, the measures to encourage innovation are balanced by those intended to stimulate generic competition, for example, the introduction of a "Bolar" type provision and the availability of the centralised procedure for generic copies of centrally authorised products.

A strengthening of innovation and competition within the industry will ultimately promote growth and enhance employment opportunities within the sector. Following expiry of patent and data protection periods, the proposals aimed at stimulating the prompt approval of generic copies, will provide competition which will exert downward pressure on pricing, thereby helping to facilitate the delivery of affordable medicinal products to Member States' healthcare systems.

The proposal is expected to benefit patients by delivering medicinal products more quickly to the market and, in particular, making available important new treatments at an earlier stage. This will be achieved by a combination of the reduction by half of the length of time available for Member States' consultation on Commission decisions, the introduction of conditional authorisations and a fast track procedure together with a more formalised approach to the availability of medicinal products on a compassionate use basis. Earlier access to medicines is likely to bring economic benefits by reducing morbidity and mortality and thereby have some influence on national healthcare budgets.

The veterinary sector of the pharmaceutical industry has encountered problems in the availability of medicines for minor species and, following the introduction of the requirement for MRLs for food producing animals, for certain therapeutic areas. The increased periods of data protection for data used to extend an authorisation for use in additional food producing species and the increased period for minor species will encourage businesses to exploit their products for use in a broader range of species.

⁹ See note 3.

¹⁰ See note 3.

This will benefit agricultural producers active in these areas and reduce the hitherto unacceptable level of off-label use.

5. Does the proposal contain measures to take account of the specific situation of small and medium-sized enterprises (reduced or different requirements, etc.)?

The proposal does not contain specific measures for SMEs, but a number of the measures will be particularly beneficial for SMEs. For example, those measures designed to promote innovation, those improving the scientific advice procedure (biotechnology-SMEs) and those requiring the introduction of a simplified registration procedure for homeopathic products.

CONSULTATION

6. List the organisations which have been consulted about the proposal and outline their main views.

There has been extensive consultation with interested parties on the operation of the rules governing medicinal products in the European Union and upon the amendments which would improve the system. As part of the survey undertaken for the Commission on the operation of the Community procedures the consultants concerned sought written and oral comments from a broad range of respondents as follows:

- all holders of a centralised marketing authorisation at the time of the review;
- 159 marketing authorisation holders (including large multi-nationals, SMEs, manufacturers of generics, non prescription and veterinary medicines from different Member States) who had used the decentralised procedure;
- European trade associations representing the interests of human and veterinary medicines including those concerned with NCEs, generics, non-prescription medicines, homeopathic and herbal medicinal products;
- 15 national consumer organisations and 134 patient associations;
- professional associations responsible for the regulation of doctors, dentists, pharmacists and veterinary practitioners;
- competent authorities responsible for authorising medicinal products;
- chairmen of the Committee for Proprietary Medicinal Products, Committee for Veterinary Medicinal Products, Mutual Recognition Facilitation Group and Veterinary Mutual Recognition Facilitation Group; and
- ministries responsible for health, social affairs, finance and agriculture.

Many companies were in favour, in principle, of opening up the centralised procedure to other products. There was broad acceptance from businesses of the need to reduce the procedural delays in the Commission decision making procedure and also for the concept of a formal fast track procedure.

In relation to the decentralised procedure although companies were generally satisfied with the performance of the Member States there was dissatisfaction with the limited adherence to the principle of mutual recognition. Many respondents supported the introduction of a dialogue between the Member States prior to grant of the authorisation in order to encourage greater acceptance of the principles of mutual recognition. Most companies were not in favour of compulsory arbitration in circumstances where Member States were unable to reach agreement, but there was strong support for permitting the marketing of a product pending arbitration in those Member States concerned that felt able to authorise the product.

There was strong support from business for the removal of the renewal procedure for marketing authorisations.

Finally, there was very strong support for harmonisation of the periods of data protection, but less consensus on what the harmonised level of protection should be or how it should be applied to products derived from incremental research.

2001/0254 (COD)

Proposal for a

DIRECTIVE OF THE EUROPEAN PARLIAMENT AND OF THE COUNCIL
amending Directive 2001/82/EC on the Community code relating to veterinary medicinal
products

EXPLANATORY MEMORANDUM

I. GENERAL CONSIDERATIONS

The Community provisions on the marketing of veterinary medicinal products are, for the most part, similar or identical to those concerning products for human medicine. No veterinary medicinal product may be marketed unless its quality, safety and efficacy have been demonstrated, and unless these guarantees are maintained when the product is actually placed on the market.

The veterinary sector nevertheless has a number of specific features.

First, it should be borne in mind that veterinary medicinal products for food-producing animals may be authorised only on terms that guarantee that the food will not be harmful for the consumer. The provisions governing the use of such medicinal products by practitioners and farmers notwithstanding, manufacturers must from the outset provide all the necessary information on residues of these products that may remain in items produced from animals that have been treated.

Second, the availability of certain medicinal products is a growing problem.

Thus, the animals that are to benefit from treatment – particularly farm animals – have a limited economic value, while all the costs of treatment or prevention must be borne by the owner. In addition, certain markets are restricted because of the number of species concerned, the size of the animal populations, the range of disorders, or differences in the regional situations.

II. JUSTIFICATION

A. Aims

1. In the light of experience with the operation of Community marketing procedures for medicinal products and the conclusions of the Commission report to the European Parliament and the Council (COM(2001)...), the Commission saw a need to adapt certain provisions of Regulation (EEC) No 2309/93¹ laying down Community procedures for the authorisation and supervision of medicinal products for human and veterinary use and establishing a European Agency for the Evaluation of Medicinal Products (COM(2001) 404 final, European Parliament and Council Directive 2001/83/EC on the Community code relating to medicinal products for human use², and European Parliament and Council Directive 2001/82/EC on the Community code relating to veterinary medicinal products³. The revision of the latter is the subject of this proposal for amendments.

¹ OJ C
² OJ C
³ OJ C

2. In so far as the general aims and the provisions on the authorisation and use of medicinal products in the Community are comparable in both the human and the animal health sectors – particularly as regards ensuring quality, safety and efficacy – this parallel approach should be maintained as far as possible, as regards both the general terminology and the system for assessing the quality, safety and efficacy of medicinal products as the basis for granting marketing authorisations. This also applies to the constant monitoring of the quality of the medicinal products manufactured by means of a quality-assurance system, a code of good manufacturing practice or inspections, and subsequent monitoring of the safety and efficacy of the products by means of a pharmacovigilance system.

The conclusions of the abovementioned Commission report and the reasons underlying the other proposals for revising pharmaceutical legislation are therefore directly applicable to these proposals for amendments in so far as they do not specifically concern veterinary products.

The recent adoption of the two Community codes relating to medicinal products for human and veterinary use also provides an excellent opportunity for improving and simplifying the general legislative framework and, where appropriate, amplifying or fine-tuning certain provisions on veterinary medicinal products to bring them into line with provisions that already exist for medical products for human use or proposed amendments to those provisions.

3. This proposal also is also intended to take account of the specific problem of the availability of veterinary medicinal products, as envisaged by the Commission in its Communication to the European Parliament and the Council of December 2000⁴. The general aim is to adapt the regulatory framework to the specific features of the animal health sector in order to curtail or reverse the downward trend in the number of veterinary medicinal products available. There is a need, therefore, for a balanced response to the imperatives of animal health and well-being, particularly where food-producing animals are concerned, without prejudice to a high level of protection of the health of the final consumer.
4. Finally, outside the scope of this proposal, the Commission is continuing its reflections on the possibility of developing in parallel a policy analogous to the "orphan drugs for human use" scheme for veterinary medicinal products, by means of a specific legal instrument. The paths to be explored should seek in particular to define indirect incentives to promote the development of new veterinary medicinal products specific to these abandoned market segments (reduced registration fees, technical assistance from the Agency, longer exclusive market rights, and others). Direct incentives could also be considered (financial contributions to R&D, reimbursement of certain investments on granting of marketing authorisation, voluntary co-financing by associations of breeders of the species concerned, etc.) But the Commission considers that if such a proposal should see the light of day, the scope and the ways and means of its application will need to be precisely identified.

⁴ Communication from the Commission to the Council and the European Parliament of 5.12.2000 – Availability of veterinary medicinal products (COM(2000) 806 final).

B. Legal basis and procedure

The legal basis for the proposal is Article 95 and Article 152.4(b) of the Treaty. Article 95, which specifically prescribes use of the co-decision procedure described in Article 251, is the legal basis for achieving the aims set out in Article 14 of the Treaty, which include the free movement of goods – in this case veterinary medicinal products. While taking account of the fact that any regulations on the manufacture and distribution of medicinal products, including veterinary medicinal products, must be fundamentally aimed at safeguarding public health, this aim must be achieved by means that do not impede the manufacture and free movement of medicinal products within Community. Since the Amsterdam Treaty came into force, all legislative provisions adopted by the European Parliament and the Council – except for directives adopted on the basis of executive powers vested in the Commission – and aimed at aligning the provisions on medicinal products have been adopted on the basis of that Article, since the differences between the national legislative, regulatory and administrative provisions on medicinal products tend to hinder intra-Community trade and therefore directly affect the operation of the internal market. The intervention of the Community legislator is therefore justified with a view to preventing or eliminating these obstacles. Furthermore, Article 152.4(b) mentions henceforth explicitly the measures having as direct objective public health protection in the veterinary and phytosanitary sectors. The present proposal contains a number of measures in the veterinary field having as an objective public health protection. The adoption procedure referred to in this Article is the same as the one referred to in Article 95; thus, it is wise to add this Article as a legal basis.

III. DETAILED CONTENTS OF THE PROPOSAL

(To improve readability, the Articles quoted here are those contained in Directive 2001/82/EC as amended by this proposal).

A. Definitions, scope, general terminology

1. It is proposed that use of the term "proprietary medicinal product" [*spécialité pharmaceutique*] be discontinued, since it is no longer used in the legislative provisions and there have been difficulties in defining precisely how it should be interpreted. Use of the term "Ready-made veterinary medicinal product" [*médicament vétérinaire préfabriqué*], defined by reference to "proprietary medicinal product", has therefore also been discontinued (*Article 1*).

It is proposed that the scope of the directive should be clarified and in particular that it should be specified that the granting of a marketing authorisation or any directly associated arrangement is relevant only once a medicinal product has begun to be manufactured industrially (*Article 2(1)*). Nevertheless, it should be made clear that, for reasons of both animal and public health, officinal or magistral veterinary preparations made up in a pharmacy should be subject to the provisions of the directive regarding prescription, dispensing, possession and administration to animals (*Article 3(1)*).

2. The definition of a veterinary medicinal product has been adapted in order to ensure that the directive applies to certain products that must meet the requirements of quality, safety and efficacy. This adaptation only makes it possible not to extend the concept of medicinal product to new types of treatment, such a cell therapy, but also to clarify the status of certain more traditional products, such as those used for

extracorporeal dialysis, even if these products are not at present of comparable importance in both veterinary and human medicine.

3. The additions to the definitions of the terms "adverse reaction", and the inclusion of new definitions (*Article 1*), particularly of "veterinary prescription", "name of medicinal product", "non-proprietary name", "strength", "immediate packaging", "outer packaging", "labelling" or "package leaflet" are in line with the definitions for medicinal products for human use.

The definition "withdrawal period" has also been revised in order to highlight its principal purpose, i.e. protecting the public, when used correctly in a veterinary context (*Article 1*).

4. The possible dual use of certain products – as a pharmaceutical product or veterinary hygiene product, for example – has led to differences in interpretation and the adoption of different regulatory approaches in the various Member States. It is proposed, therefore, that in such circumstances the legislation affording the highest degree of protection for animal and human health, i.e. that covering veterinary medicinal products, should apply in cases of uncertainty (*Article 2(2)*).
5. Finally, this proposed revision provides an opportunity to harmonise and simplify, and to correct certain terminology that is regarded as obsolete or inappropriate for the field. It mainly concerns references to the evaluation criteria – i.e. quality, safety and efficacy – or introducing the idea of weighing benefits against risks, which is central to the system of marketing authorisation for medicinal products.

B. Marketing authorisations: general provisions and procedures

1. The general provisions on applying for a marketing authorisation, assessing applications, granting marketing authorisation, and the respective responsibilities of the competent authorities and the holder of the authorisation do not depend on the type of medicinal product in question – i.e. whether it is for veterinary or human use. The justification and proposed amendments are therefore complementary to those relating to Regulation (EEC) No 2309/93 (COM(2000)...), or similar, if not strictly identical, to those relating to the legislation on medicinal products for human use (COM(2001)...).
2. The same is true of the general provisions on the scope of the authorisation and the responsibility of the holder (*Article 5*), and the additional details on the concept of generics and Community harmonisation (ten years) of the period of administrative protection of data (*Article 13(1), (2) and (3)*), "bibliographical applications" (*Article 13a*), fixed combinations (*Article 13b*), or applications submitted with the consent of the holder (*Article 13c*). The amendments also introduce the possibility of testing a generic before the end of the period of exclusivity without thereby infringing the law on the protection of industrial and commercial property (*Article 13(6)*).
3. Similarly, Chapters 3 and 4 of Title III, on the marketing-authorisation procedure and the mutual-recognition or decentralised authorisation procedures have been adapted in exactly the same way as the corresponding chapters of the Community code relating to medicinal products for human use. Particular attention should be drawn to the proposals concerning the coordination of deadlines for the various procedures

(Articles 21 and 32), authorisation on specific conditions (Article 26), the discontinuation of the five-yearly renewal of the authorisation and the expiry clauses (Article 28), or the transparency of the assessment process (Article 25(3) and (4)). For the decentralised procedure, it is proposed to set up a coordination group on the mutual recognition of veterinary medicinal products, thus formalising an existing process of cooperation between the Member States (Article 31), to clarify operation on the basis of whether or not an authorisation already exists in a Member State (Article 32), and to make the initiation of the arbitration procedure automatic in all cases of dispute between the competent authorities in the Member States (Article 33). The provisions on arbitration have been clarified, particularly with a view to protecting the position of the applicant or the marketing authorisation holder more effectively (Article 36). It is also proposed to speed up certain stages in the procedure for obtaining the opinion of the committee and completing the decision-making process (Article 38), and it is intended to establish a system for the gradual harmonisation of summaries of characteristics of products for veterinary medicinal products that have been authorised by the Member States for more than ten years (Article 34(2)), and to introduce the possibility of the Agency giving an opinion on certain parts of the marketing authorisation if the question at issue concerns more than one product or a therapeutic class (Article 35(2)).

4. It is also proposed to adapt, while taking account of the specific features of veterinary medicinal products, certain provisions regarding the contents of the file accompanying an application for marketing authorisation and the summary of product characteristics (Articles 12, 14, 15). These adaptations will not change the essence of the existing provisions, but will be more concerned with gearing certain provisions with sometimes outdated wording to the administrative, scientific or technical realities of the applications. Thus, the erstwhile "expert reports" will continue to exist, but under the name "detailed and critical summaries", particularly in so far as most of the scientists involved in drafting the reports will be associated to a greater or lesser extent with the applicant. It is also proposed that it should be clearly stated that these summaries form an integral part of the application file. Withdrawal periods are also indicated in the interests of improved protection for the final consumer (Article 14(5.11)).

C. Marketing authorisations: proposals specific to the veterinary sector

1. Obviously, the general principle of authorising the marketing of a veterinary medicinal product before it can be used is not being questioned.

Nevertheless, a number of adjustments have been proposed to permit derogations from the authorisation requirement, either for certain "new" categories of pets, such as dwarf rabbits or ferrets (Article 4(2)), or for the use of a medicinal product on animals subject to compulsory specific health provisions with a view to export to non-member countries or import into the Community. This proposal particularly concerns certain sport animals taking part in international competitions (e.g. horses), or certain valuable productive livestock, which must be vaccinated against infectious diseases that are endemic in certain non-member countries (Article 8(2)). The directive has also been brought into line with other Community provisions in order to enable the Commission to permit the use of immunological veterinary medicinal products without a marketing authorisation in cases of serious epizootic diseases if no suitable medicinal products are available (Article 8(1)). This provision also contributes to improving the consistency of Community measures to combat certain

animal diseases, and particularly concerns alignment with the Commission's proposal for amending Regulation (EEC) No 2309/93 in order to permit authorisation through a centralised procedure for immunological veterinary medicinal products for such diseases. It has also been found necessary to introduce derogations from the need to conduct field trials for these medicinal products (*Article 13d*).

2. If no authorised medicinal product is available for a given species or disorder, it is proposed that the use of other products be made more straightforward. The aim is to help solve the problem of the availability of certain veterinary medicinal products and the intention is to differentiate the provisions regarding pets or animals kept in zoos or circuses (*Article 10*) more clearly from those on food-producing animals (*Article 11*).

In the former case, it is intended to retain the system whereby either another veterinary medicinal product, a medicinal product for human use, or a product prepared extemporaneously must be used in that order of priority ("cascade"). However, this possibility will henceforth be open directly to practitioners on their own direct responsibility. It is also proposed to eliminate all associated administrative formalities – particularly the recording of the use of such products – in so far as such provisions do not affect the level of consumer protection.

In the case of food-producing animals, it is proposed to keep veterinary practice under administrative supervision, thus enabling the Member States to opt for the use of a veterinary medicinal product authorised in another Member State. This provision must be supplemented by *ad hoc* import and inspection measures. The measures aimed at protecting consumers have been retained (withdrawal period, registration of use) and clarified (inclusion of the substance in Annex I, II or III to Regulation (EEC) No 2377/90, existence of maximum residue limits for at least one species).

Regarding horses, given the specific ways in which those are used, it is proposed to allow the use of a substance which does not have any maximal residue limit, under the only condition that the animal in question is excluded from the nutritional chain (*Article 10 (2)*). This implies that many of these are treated in a way comparable to company animals, and this in an unalterable way. The definition of an arbitrary six-month waiting period, provided for in the Commission Decision 2000/68/EC concerning the passport of horses⁵, could only be justified under limited and exceptional circumstances. The Commission considers that such a possibility should not become the general rule in the Community, not only in order to take into consideration the direct protection of European citizens consuming horse meat, but also in order to ensure the general coherence of consumer protection measures within the framework of the use of veterinary medicinal products on all animal species. The *equidae* remain as such food producing species at European level.

3. In addition to the measures concerning the use of products without authorisation for the species or indication concerned, it is also proposed that economic incentives be introduced to encourage the pharmaceutical industry to place veterinary medicinal products on the market without delay.

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The main amendment is a proposal to increase the period of administrative data protection in some cases and hence provide for a more attractive return on investment for an economic operator (*Article 13(4) and (5)*):

- The ten-year protection period would be extended by one year for any extension of the authorisation to another food-producing animal (up to a maximum of three more years for three or more species), provided that such an extension is obtained within three years of the granting of the original authorisation. A measure of this kind would encourage the industry to extend the authorisation of a new medicinal product for a species representing a major economic sector very swiftly to other species representing a smaller market.
- It is also proposed that the period of general protection for medicinal products for bees and fish should be 13 years instead of 10, because of the specific characteristics of these species and the general veterinary treatment procedures that necessitate specific developments on the part of manufacturers.

It is also proposed that the protection should at the same time cover the data contained in the file submitted for the establishment of maximum residue limits as required under Regulation (EEC) No 2377/90 and in the application for authorisation (*Article 13(a)(1) and (2)*), and to strengthen the legal links between the procedures for fixing maximum residue limits and the granting of a marketing authorisation (*Article 6, Article 12(1)*). It is also intended to grant a period of three years of specific protection for a medicinal product containing of substance of which use has been well established in a species for not less than ten years, but for which the marketing authorisation has been obtained for a "new" species by a holder other than the holder of the original authorisation. This protection would, however, be granted only if the new holder had also been the applicant for the establishment of maximum residue limits for the new species and had provided the evidence of the efficacy of the medicinal product in this new species (*Article 13(a)(3)*).

4. In view of the problem of availability of veterinary medicinal products and in particular the difficulties encountered by manufacturers (see the abovementioned Commission report COM (2001)...), it is proposed that the obligations and the division of responsibilities between the applicant for or the marketing authorisation holder for a veterinary medicinal product and the competent authorities in the Member States should be clarified. This mainly concerns the implementation of general checks of the quality of foodstuffs and the residues of chemical substances in connection with the misuse of authorised medicinal products, the use of prohibited substances, or contamination of foodstuffs by pollutants.

Scientific studies to back up a file of maximum residue limits or a file of a marketing authorisation will mean that the applicants will have to develop methods for determining the concentration of active substances and any active metabolites in certain tissues or types of foodstuff of animal origin. Nevertheless, the aims of studies of this kind and the experimental conditions under which they are conducted are not the same as those of the control laboratories responsible for monitoring any residues of chemicals that might be present in foodstuffs in general. Consequently, the control laboratories will as a rule need to develop their own methods.

There is a need to review the provisions on the analytical methods to be used to determine the amounts of residues, particularly as the expression "routine analysis method" has given rise to many questions of interpretation (*Article 12(3)(h), (i), and (j)*). The obligation of the applicant to demonstrate the quality and reliability of the scientific information presented in his/her file and to provide a validated dosage method has not been changed. This provision has even been strengthened by the introduction of the possibility of checking whether the method is satisfactory in the light of the aims of the application (*Article 23(3)*). It is also proposed that the provisions on the monitoring of residues should be strengthened and in particular that the task of the competent authorities should be simplified if specific needs are involved. The marketing authorisation holder should therefore, on request by the competent authorities, supply the reference substances needed for the control. It is also intended that the authorisation-holder should provide the reference laboratory with technical support if it has to use the analytical method described in the authorisation file but encounters practical difficulties (*Article 27(2)*).

5. It is also intended to revise the general provision on total exclusion from human consumption of foodstuffs from animals used for testing medicinal products if maximum residues limits have not been established in accordance with Regulation (EEC) No 2377/90, since this provision is a major obstacle to the development of new medicinal products for food-producing animals. The existing provision impedes the development of a new veterinary medicinal product for several years – even to the point of discouraging pharmaceutical companies from developing innovative medicinal products for major markets.

The example of new medicinal products for dairy cows may serve as an illustration: unless it carries out trials outside the Community, it becomes extremely difficult for a pharmaceutical company and the experts responsible for conducting field trials to find a farmer who will agree to having an animal from his/her herd included in a clinical study of a new veterinary medicinal product if this means that it will not be possible to use the animal for milk production again.

The number of productive livestock used in testing veterinary medicinal products is small compared with the number of animals likely to be treated with a medicinal product outside the authorised use, if only because of the "cascade" provisions described in C.2). Testing of new medicinal products also necessitates close veterinary observation of the animals and major monitoring work on the part of the person responsible for the test. These measures do not compare with the normal conditions of use of an authorised medicinal product in productive livestock. The Commission therefore considers that consumer protection would not be affected in these particular circumstances by abolishing the obligation for the prior establishment of maximum residue limits, since this measure is accompanied by the introduction of a sufficiently long withdrawal period (*Article 95*).

6. It is proposed that the provisions on homeopathic veterinary medicinal products should be adapted to the current situation. Since no use has been made of the possibility for a Member State to refrain from establishing a simplified registration system for homeopathic medicinal products meeting certain criteria, it is proposed that it should be abolished (*Article 16*).

Also, particularly in view of the developments in biological agriculture and the special place of homeopathic medicinal products in that context, it is proposed that the simplified registration system should be extended to veterinary medicinal products intended for food-producing species. This does not, however, affect the provisions on consumer protection (*Article 17(1), Article 18*). It is also proposed, under certain conditions, to authorise the Commission, if appropriate, to adapt the degree of dilution in the light of new scientific knowledge (*Article 17(1)*). It is necessary, therefore, to adapt the provisions on labelling and the package leaflet accompanying homeopathic veterinary medicinal products (*Article 64*).

D. Provisions aimed at improving the monitoring of the quality of medicinal products.

1. Monitoring the general quality of medicinal products depends partly on the system of granting marketing authorisations on the basis of a prior assessment of the information submitted by the applicant, including all pharmaceutical documentation. It also depends on constant subsequent monitoring of the quality of the products manufactured and sold, and their conformity with the specifications laid down in the authorisation.

Quality guarantees are based essentially on a system of quality assurance, including compliance with good manufacturing practice, and monitoring of conformity with all the provisions by the competent authorities – mainly by means of inspections. These general measures are applicable to both medicinal products for human use and veterinary medicinal products.

2. The Commission must therefore pursue the same objectives in the field of veterinary medicinal products and propose similar amendments to those made to the legislation on medicinal products for human use (COM(2000)...). However, account must be taken not only of consumer protection and the completion of the internal market, but also of the international dimension of the pharmaceutical sector (particularly mutual recognition agreements with third countries).
3. The Commission therefore finds it necessary, at this stage, to strengthen the provisions on inspection, in conjunction with the European Pharmacopoeia where appropriate (*Article 80(1) and (4)*), to step up Community coordination by introducing certificates of good manufacturing practice, and to set up a Community register containing the relevant information (*Article 80(5), (6) and (7)*). The latter measure is in a consistent manner supplemented by the establishment of Community system of data on manufacturing authorisations (*Article 44(4)*). All this is also intended to facilitate mutual recognition within the system. It is proposed, however, to introduce a procedure for settling any disputes concerning the outcome of an inspection (*Article 90*). This improvement of Community harmonisation goes hand-in-hand with a total harmonisation of the criteria to be met by the qualified person responsible for the quality of manufacturing (*Articles 53 and 54*).

It is also intended to increase the quality guarantees by extending good manufacturing practice (*Article 50(f)*) to the starting materials used as active substances in veterinary medicinal products. This means that this term must be clearly defined and that there must be procedures for revising the definition in the light of technical progress (*Article 50a*). The practical provisions have been adapted accordingly, both for the adoption of specific detailed guidelines (*Article 51*) and for

the inspection system (*Article 80(1)*). It also appears necessary to clarify the provisions on monitoring the quality of imported products, since even if they had originally been manufactured in the Community, the competent authorities will not be able to ensure that all the specifications, particularly those concerning storage conditions for medicinal products, have been respected outside the Community (*Article 55*).

4. In the field of immunological veterinary medicinal products, the existing legislation stipulates that the Community provisions on quality assurance in connection with manufacturing authorisations, good manufacturing practice and inspections may be supplemented by a system of "official release" of each batch of the product after manufacture, after control by an "official" laboratory designated for this purpose by the competent authorities of the Member State. In these circumstances, the "official batch release" of a batch of vaccine would have to be the subject of mutual recognition.

Since this measure was introduced at Community level (1990), along the lines of long-established practices in some Member States, significant progress has been made in quality and consistency in the manufacturing of vaccines. Furthermore, in view of the number and diversity of immunological products in the veterinary sector, the national laboratories do not necessarily have the means for re-control of the batches that have already been checked by the manufacturers, and only some Member States use the "official release" procedure. Finally, the system of mutual recognition does not operate ideally, mainly because the Member States do not necessarily carry out all the conformity controls provided for in the authorisation file – hence the discrepancies in the Community-level validity of the "official release".

The Commission therefore proposes reviewing this arrangement, partly by restricting the scope for official release of batches to certain types of immunological veterinary medicinal products, i.e. live vaccines or immunological medicinal products for diseases covered by Community measures, which would mean particular responsibility for the competent authorities. It is also proposed to define the obligations on pharmaceutical companies and the competent authorities under these circumstances, particularly as regards the tests that need to be done by official control laboratories (*Article 82*). These proposed amendments are without prejudice to the possibility of requiring copies of any certificates describing the controls conducted by the holder, or to having medicinal products placed on the market controlled by the official laboratory at any time.

E. Labelling and package leaflet

The provisions on labelling of medicinal products and the accompanying package leaflet have not been amended substantially. The terminological improvements in connection with the introduction of the new definitions notwithstanding, it is proposed that certain provisions aimed at improving information for users should be strengthened.

The labelling and the package leaflet must be approved by the competent authorities and conform to the summary of the characteristics of the product (*Article 58(1)*, *Article 61(2)*). The labelling of veterinary medicinal product and the accompanying package leaflet consequently also become important elements in the application for a marketing authorisation and the decision taken by the competent authorities (*Article 25(2)*, *Article 30(e)*, *Article 32(2)*, (3), (4) and (5), *Article 33 (1)*, *Article 36*).

A number of amendments have also been proposed in the general interests of users (*Article 58(1)(e); Article 61(1) and (2)(a) and (b)*) while taking account of certain elements of flexibility, including some for medicinal products that are covered by a centralised marketing authorisation under Regulation (EEC) No 2309/93 (*Article 58(5)*).

It is also proposed that the information on use in food-producing animals – in this case, the withdrawal period (*Article 58(1)(g) and (l)*) should be strengthened. This goes hand-in-hand with a proposal to strengthen the measures relating to the prescription procedures for medicinal products of this kind (*Article 67*). It is proposed that in future all medicinal products for food-producing animals (including, for example, those for which the withdrawal period is nil) should be available only on veterinary prescription.

F. Possession, distribution and dispensing

In addition to the abovementioned provision on the prescribing of medicinal products for food-producing animals, it is proposed that the provisions on emergency recall of medicinal products from the market should be amplified, as the case may be by including wholesale distributors (*Article 65(4)*).

Even if the provisions on the traceability of the distribution circuits for veterinary medicinal products from the manufacturer to the final user have not been amended – indeed they have been strengthened by the fact that the range of prescription-only medicinal products has been extended. It is, however, proposed that retail sale should be simplified for those for which no prescription is required, by abolishing the obligation to keep detailed documentation (*Article 66(2)*).

The special conditions on a possible ban on manufacturing, possessing or selling certain immunological veterinary medicinal products are extended to the marketing authorisation according to a decentralised procedure (*Article 71(2), in conjunction with Article 33(1) second subparagraph*), in order to take account of the proposal for "automatic" initiation of the arbitration procedure.

G. Pharmacovigilance

The pharmacovigilance procedures have been strengthened (*Articles 72-78*) along the lines of the proposals in connection with the centralised procedure and more generally those on medicinal products for human use, particularly in conjunction with the proposal to abolish the five-yearly renewal of the authorisation. It is intended to strengthen the general information network, particularly by electronic means and to increase the frequency with which the periodical safety update reports are to be submitted. One of the aims is to enable the Commission to ask the Member States to take temporary measures with immediate effect, if emergency action is needed.

Proposal for a

DIRECTIVE OF THE EUROPEAN PARLIAMENT AND OF THE COUNCIL

amending Directive 2001/82/EC on the Community code relating to veterinary medicinal products

(Text with EEA relevance)

THE EUROPEAN PARLIAMENT AND THE COUNCIL OF THE EUROPEAN UNION,

Having regard to the Treaty establishing the European Community, and in particular Article 95 and point (b) of Article 152(4) thereof,

Having regard to the proposal of the Commission¹,

Having regard to the opinion of the Economic and Social Committee²,

Having regard to the opinion of the Committee of the Regions³,

Acting in accordance with the procedure referred to in Article 251 of the Treaty⁴,

Whereas:

- (1) Directive 2001/82/EC of the European Parliament and of the Council of 23 October 2001 on the Community code relating to veterinary medicinal products⁵, in the interests of clarity and rationalisation, has codified and combined in a single text the texts of Community legislation on veterinary medicinal products.
- (2) Community legislation constitutes an important stage in the achievement of the objective of free movement of veterinary medicinal products. However, new measures prove necessary in the light of the experience gained, particularly in the Committee for veterinary medicinal products, with a view to eliminating the remaining obstacles to free movement.
- (3) It is therefore necessary to align the national laws, regulations and administrative provisions which contain differences with regard to the basic principles in order to promote the operation of the internal market.

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- (4) Any regulations on the production and distribution of veterinary medicinal products should be essentially aimed at safeguarding public health. The legislation on marketing authorisations for veterinary medicinal products, and the criteria governing the grant of authorisations, are such as to strengthen the protection of public health within the meaning of point (b) of Article 152(4) of the Treaty, as inserted by the Treaty of Amsterdam. That aim should, however, be achieved by means that will not impede the development of the pharmaceuticals industry or trade in medicinal products within the Community.
- (5) Article 71 of Council Regulation (EEC) No 2309/93 of 22 July 1993 laying down Community procedures for the authorisation and supervision of medicinal products for human and veterinary use and establishing a European Agency for the Evaluation of Medicinal Products⁶ provides that, within six years of its entry into force, the Commission is required to publish a general report on the experience acquired as a result of the operation of the marketing authorisation procedures laid down in that Regulation and in other Community legal provisions
- (6) In the light of the Commission's report⁷ on the experience gained, it has proved necessary to improve the operation of the marketing authorisation procedures for medicinal products in the Community.
- (7) Particularly as a result of scientific and technical progress in the field of animal health, the definitions and scope of Directive 2001/82/EC should be clarified in order to ensure a high level of requirements as to the quality, safety and efficacy of veterinary medicinal products. In order to take account, both of the emergence of new therapies and of the growing number of so-called "borderline" products between the medicinal product sector and other sectors, the definition of medicinal product should be modified so as to avoid any doubt as to the applicable legislation when a product, whilst fully falling within the definition of a medicinal product, may also fall within the definition of other regulated products. Also, taking into account the characteristics of the pharmaceutical legislation, it is proposed that such legislation is to apply. It is also worth taking advantage of this opportunity to improve the consistency of the terminology of pharmaceutical legislation.
- (8) The veterinary medicinal products sector has a number of very specific features. Veterinary medicinal products for food-producing animals may be authorised only on conditions that guarantee that the foodstuffs produced will be harmless to consumers as regards any residues of medicinal products.
- (9) The costs of research and development to meet increased requirements as regards the quality, safety and efficacy of veterinary medicinal products are leading to a gradual reduction in the range of products authorised for the species and indications representing smaller market sectors.

⁶ OJ L 214, 24.8.1993, p. 1; Regulation as amended by Commission Regulation (EC) No 649/98 (OJ L 88, 24.3.1998, p. 7).

⁷ COM(2001)...final.

- (10) The provisions of Directive 2001/82/EC also need, therefore, to be adapted to the specific features of the sector, particularly to meet the health and welfare of food-producing animals on terms that guarantee a high level of consumer protection, and in a context that provides adequate economic interest for the veterinary medicinal products industry.
- (11) In certain circumstances, particularly where new types of pets are concerned, the need to obtain a marketing authorisation for a veterinary medicinal product in accordance with Community provisions is clearly unjustified. Moreover, the absence of authorisation to market an immunological product in the Community should not be an obstacle to international movements of certain live animals for which binding health measures have to be taken for this purpose. The provisions on the authorisation or use of such medicinal products to take account of measures to combat certain infectious animal diseases at Community level also need to be adapted.
- (12) An assessment of the operation of the procedures for the granting of market authorisation has revealed the need to revise, in particular, the mutual recognition procedure in order to increase the scope for cooperation between Member States. This cooperation process should be formalised by setting up a coordination group and defining its role in settling disagreements, in the context of a revised decentralised procedure.
- (13) Except in special circumstances, marketing authorisations should be granted for an unlimited period and, in parallel, the procedures for monitoring products actually being marketed should be strengthened.
- (14) In the veterinary sector, if no medicinal product has been authorised for a given species or a given disorder, the use of other existing products should be made a straightforward matter, but without prejudice to consumer health in the case of medicinal products intended for administration to food-producing animals.
- (15) There is also a need to stimulate the interest of the veterinary pharmaceuticals industry in certain market segments in order to encourage the development of new veterinary medicinal products. The period of administrative data-protection vis-à-vis generics needs to be harmonised and extended, subject to certain conditions.
- (16) There is also a need to clarify the obligations of, and division of responsibilities between, the applicant for or marketing authorisation holder of a veterinary medicinal product and the competent authorities in charge of monitoring the quality of foodstuffs, particularly through compliance with the provisions on the use of these medicinal products. In addition, in order to facilitate the testing of new medicinal products while guaranteeing a high level of protection for consumers, sufficiently long withdrawal periods should be laid down for foodstuffs that might be produced by the animals involved in the tests.
- (17) Without prejudice to the provisions aimed at guaranteeing consumer protection, the specific characteristics of homeopathic veterinary medicinal products, and particularly their use in ecological farming, should be taken into account by establishing a simplified procedure for registration on terms defined in advance.

- (18) In order to increase the information available to users and to improve consumer protection in the case of food-producing animals, the provisions on the labelling of veterinary medicinal products and the accompanying package leaflet should also be strengthened. The requirement that a veterinary medicinal product may only be dispensed after a veterinary prescription has been made out should also be extended to all medicinal products for food-producing animals. The administrative procedures for supplying medicinal products for pets should, on the other hand, be simplified.
- (19) The quality of the veterinary medicinal products manufactured or available in the Community should be guaranteed by requiring that the active substances they contain have been produced in accordance with good manufacturing practice. The Community provisions on inspections also need to be strengthened, and a Community register established containing the results of these inspections. The arrangements for the official release of batches of certain immunological medicinal products should be reviewed in order to take account of the improvement of the general system for monitoring the quality of medicinal products and to reflect technical and scientific progress, and also in order to make mutual recognition fully effective.
- (20) The monitoring of the efficacy and safety of the veterinary medicinal products on the market should be improved by stepping up pharmacovigilance measures, particularly where the validity of marketing authorisations is no longer compulsorily limited to five years. The frequency with which the periodical safety update reports are submitted should be increased, there should be an operational network for the exchange of electronic data and, where appropriate, the competent authorities should be enabled to take temporary emergency measures.
- (21) Since most of the measures necessary for the implementation of this Directive are measures of individual scope, use should be made of the advisory procedure provided for in Article 3 of Council Decision 1999/468/EC of 28 June 1999 laying down the procedures for the exercise of implementing powers conferred on the Commission⁸, or of the management procedure under Article 4 thereof. As regards general scope within the meaning of Article 2 of the Decision, those measures should be adopted by use of the regulatory procedure provided for in Article 5 thereof.
- (22) Directive 2001/82/EC should be amended accordingly,

HAVE ADOPTED THIS DIRECTIVE:

Article 1

Directive 2001/82/EC is amended as follows:

- (1) The first citation is replaced by the following:

"Having regard to the Treaty establishing the European Community, and in particular Article 95 and point (b) of Article 152(4) thereof,"

⁸ OJ L 184, 17.7.1999, p. 23.

(2) Article 1 is amended as follows:

(a) Point (1) is deleted.

(b) Point (2) is replaced by the following:

"2. *Veterinary medicinal product*

Any substance or combination of substances

(a) presented for treating or preventing disease in animals.

(b) capable of use in animals with a view to making a medical diagnosis or to restoring, correcting or modifying physiological functions in animals."

(c) Point (3) is deleted.

(d) Points (9) and (10) are replaced by the following:

"9. *Withdrawal period*

Period necessary between the last administration of the veterinary medicinal product to animals, under normal conditions of use and in accordance with good veterinary practice, and the production of foodstuffs from such animals, in order to protect public health, by ensuring *[follow on]* that such foodstuffs do not contain residues in quantities in excess of the maximum residue limits of active substances laid down in Annex I or III to Regulation (EEC) No 2377/90.

10. *Adverse reaction:*

A reaction to a veterinary medical product which is harmful and unintended and which occurs at doses normally used in animals for the prophylaxis, diagnosis or treatment of disease or to restore, correct or modify a physiological function."

(e) The following points (20) to (27) are added:

"(20) *Veterinary prescription*

Any prescription for veterinary medicinal products issued by a professional person qualified to do so.

(21) *Name of veterinary medicinal product*

The name, which may be either an invented name which is not liable to confusion with the common name, or a common or scientific name accompanied by a trade mark or the name of the marketing authorisation holder. .

(22) *Non-proprietary name*

The international name recommended by the World Health Organisation or, failing this, the common name.

(23) *Strength*

The content of active substances, expressed as quantity per unit, per unit volume or per unit weight, depending on how the product is presented.

(24) *Immediate packaging*

The container or any other form of packaging that is in direct contact with the medicinal product.

(25) *Outer packaging*

The packaging into which the immediate packaging is placed.

(26) *Labelling*

The words printed on the outside or immediate packaging.

(27) *Package leaflet*

The leaflet containing information for the user that accompanies the medicinal product."

(3) Articles 2 and 3 are replaced by the following:

"Article 2

1. The provisions of this Directive shall apply to veterinary medicinal products including pre-mixes for medicated feeding stuffs intended to be placed on the market in the Member States and prepared industrially or by a method involving an industrial process.
2. The provisions of this Directive shall apply whenever a substance or composition of substances corresponds to the definition of a medicinal product, even if the substance or composition of substances is also falling within the field of application of other Community legislation.

Article 3

1. This Directive shall not apply to:
 - (a) medicated feedingstuffs as defined in Council Directive 90/167/EEC*.
 - (b) inactivated immunological veterinary medicinal products which are manufactured from pathogens and antigens obtained from an animal or animals from a holding and used for the treatment of that animal or the animals of that holding in the same locality;
 - (c) veterinary medicinal products based on radio-active isotopes;

- (d) any additives covered by Council Directive 70/524/EEC** where they are incorporated in animal feedingstuffs and supplementary animal feedingstuffs in accordance with that Directive.

However, medicated feedingstuffs under point (a) may be prepared only from pre-mixes which have been authorised under this Directive.

- 2. Except for the provisions on possession, prescription, dispensing and administration of veterinary medicinal products, this Directive shall not apply to:
 - (a) any medicinal product prepared in a pharmacy in accordance with a prescription for an individual animal, commonly known as the magistral formula;
 - (b) any medicinal product prepared in a pharmacy in accordance with the prescriptions of a pharmacopoeia and intended to be supplied directly to the end-user, commonly known as the officinal formula.

* OJ L 92, 7.4.1990, p. 42.

** OJ L 270, 14.12.1970, p. 1."

- (4) Article 4(2) is replaced by the following:

"2. Member States may permit exemptions on their territory in respect of veterinary medicinal products intended solely for aquarium fish, ornamental birds, homing pigeons, terrarium animals, small rodents, and ferrets and rabbits kept exclusively as pets from the provisions in Articles 5 to 8, provided that such products do not contain substances the use of which requires veterinary control and that all possible measures have been taken to prevent unauthorised use of the products for other animals."

- (5) Articles 5 and 6 are replaced by the following:

"Article 5

- 1. No veterinary medicinal product may be placed on the market of a Member State unless a marketing authorisation has been issued by the competent authorities of that Member State in accordance with this Directive or a marketing authorisation has been granted in accordance with Regulation (EEC) No 2309/93.

The various strengths, pharmaceutical forms, administration routes, presentations and any amendment under Article 39 must be authorised under the first subparagraph and shall be considered part of the same authorisation.

- 2. The holder of the marketing authorisation shall be responsible for the marketing of the medicinal product.

Article 6

1. In order that a veterinary medicinal product may be the subject of a marketing authorisation for the purpose of administering it to one or more food-producing species, the pharmacologically active substances which it contains must be shown in Annexes I, II or III to Regulation (EEC) No 2377/90.
2. If it is justified by an amendment to the Annexes to Regulation (EEC) No 2377/90, the holder of the marketing authorisation or, where appropriate, the competent authorities shall take all necessary measures for amending or withdrawing the marketing authorisation within 60 days of the date on which the amendment to the Annexes to Regulation (EEC) No 2377/90 was published in the *Official Journal of the European Communities*."

(6) Article 8 is replaced by the following:

"Article 8

In the event of serious epizootic diseases, Member States may provisionally allow the use of immunological veterinary medicinal products without an authorisation for placing on the market, in the absence of a suitable medicinal product and after informing the Commission of the detailed conditions of use.

The Commission may avail itself of the option set out in the first paragraph when explicit provision is made for that option under Community rules concerning certain serious epizootic diseases.

If an animal is being imported from, or exported to, a third country and is thereby subject to specific binding health rules, a Member State may permit the use, for the animal in question, of a immunological veterinary medicinal product that is not covered by a marketing authorisation in the Member State in question but is authorised under the legislation of the third country. Member States shall take all appropriate measures concerning the supervision of the importation and the use of such immunological products."

(7) Articles 10 to 13 are replaced by the following:

"Article 10

1. If there is no authorised medicinal product in a Member State for a condition affecting a species of pet animal or animals kept in zoos or circuses, the veterinarian may, particularly in order to avoid causing unacceptable suffering to the animal concerned, under his/her personal responsibility, treat the animal(s) with:
 - (a) a veterinary medicinal product authorised in the Member State concerned under this Directive or under Regulation (EEC) No 2309/93 for use with another animal species, or for another condition in the same species; or
 - (b) if there is no product as referred to in point (a), a medicinal product authorised for human use in the Member State concerned in accordance with Directive 2001/83/EC of the European Parliament and of the Council* or under Regulation (EEC) No 2309/93; or

- (c) if there is no product as referred to in point (b) and within the limits of the law of the Member State concerned, a veterinary medicinal product prepared extemporaneously by a person authorised to do so under national legislation in accordance with the terms of a veterinary prescription.
2. By way of derogation from Article 11, the provisions of paragraph 1 shall also apply to the treatment by a veterinarian of an animal belonging to the *equidae* family provided that it has been declared, under Commission Decision 93/623/EEC^{**}, as never having been intended for the production of foodstuffs.
 3. By way of derogation from Article 11, and in accordance with the procedure referred to in Article 89(2), the Commission shall establish a list of veterinary medicinal products essential for the treatment of *equidae* and for which the withdrawal period shall be not less than six months according to the control mechanisms laid down in Decision 93/623/EEC^{**}.

* OJ L

** OJ L 298, 3. 12. 1993, p. 45.

Article 11

1. Where there is no authorised medicinal product for a condition affecting a food-producing species, Member States shall, particularly in order to avoid causing unacceptable suffering to the animals concerned, permit the administration by a veterinarian or under his/her direct personal responsibility to an animal or to a small number of animals on a particular holding:
 - (a) of a veterinary medicinal product authorised in the Member State concerned under this Directive or under Regulation (EEC) No 2309/93 for use with another animal species, or for another condition in the same species; or
 - (b) if there is no product as referred to in point (a),
 - (i) either, of a medicinal product authorised for use in the Member State concerned with human beings in accordance with Directive 2001/83/EC or under Regulation (EEC) No 2309/93, or
 - (ii) of a veterinary medicinal product authorised in another Member State in accordance with this Directive for use in the same species for the condition in question or for another condition; or
 - (c) if the product or products as referred to in point (b) is/are not available and within the limits of the law of the Member State concerned, of a veterinary medicinal product prepared extemporaneously by a person authorised to do so under national legislation in accordance with the terms of a veterinary prescription.

2. Paragraph 1 shall apply provided that pharmacologically active substances included in the medicinal product are listed in Annex I, II or III to Regulation (EEC) No 2377/90, and that the veterinarian specifies an appropriate withdrawal period.

Unless the medicinal product used indicates a withdrawal period for the species concerned, the specified withdrawal period shall not be less than:

- (a) 7 days for eggs;
 - (b) 7 days for milk;
 - (c) 28 days for meat from poultry and mammals including fat and offal;
 - (d) 500 degree-days for fish meat.
3. When a veterinarian has recourse to the provisions of paragraphs 1 and 2 of this Article, he/she shall keep adequate records of the date of examination of the animals, details of the owner, the number of animals treated, the diagnosis, the medicinal products prescribed, the doses administered, the duration of treatment and the withdrawal periods recommended, and make these records available for inspection by the competent authorities for a period of at least five years.
 4. Without prejudice to the other provisions of this Directive, Member States shall take all necessary measures concerning the import, distribution and dispensing of and information on the medicinal products which they permit for administration to food-producing animals in accordance with paragraph 1(b)(ii) of this Article.

Article 12

1. For the purposes of obtaining a marketing authorization in respect of a veterinary medicinal product, other than under the procedure established by Regulation (EEC) No 2309/93, an application shall be lodged with the competent authority of the Member State concerned.

In the case of veterinary medical products intended for one or more food-producing species, whose pharmacologically active substances have not yet been included, for the species in question, in Annexes I, II or III to Regulation (EEC) No 2377/90, a marketing authorisation may not be applied for until after a valid application has been made for the establishment of maximum residue limits in accordance with that Regulation. At least six months shall elapse between a valid application for the establishment of maximum residue limits and an application for marketing authorisation.

2. A marketing authorization may only be granted to an applicant established in the Community.
3. The application for marketing authorisation shall include all the administrative information and scientific documentation necessary for demonstrating the quality, safety and efficacy of the veterinary medical product in question. The file shall be submitted in accordance with Annex I and shall contain, in particular, the following information:
 - (a) name or business name and permanent address or registered place of business of the person responsible for placing the product on the market and, if different, of the manufacturer or manufacturers involved and of the sites of manufacture;
 - (b) name of veterinary medicinal product;
 - (c) qualitative and quantitative particulars of all the constituents of the veterinary medicinal product;
 - (d) description of the method of manufacture;
 - (e) therapeutic indications, contra-indications and adverse reactions;
 - (f) dosage for the various species of animal for which the veterinary medicinal product is intended, its pharmaceutical form, method and route of administration and proposed shelf life;
 - (g) if applicable, explanations of the precautionary and safety measures to be taken when the product is stored, when it is administered to animals and when waste therefrom is disposed of, together with an indication of any potential risks the medicinal product might pose to the environment and the health of humans, animals or plants;
 - (h) indication of the withdrawal period in the case of medicinal products intended for food-producing species;
 - (i) description of the testing methods employed by the manufacturer;
 - (j) results of:
 - pharmaceutical (physico-chemical, biological or microbiological) tests;
 - safety tests and residue tests;
 - – pre-clinical and clinical trials;
 - (k) a summary in accordance with Article 14 of the product characteristics, a mock-up of the immediate packaging and the outer packaging of the veterinary medicinal product, together with the package leaflet, in accordance with Articles 58 to 61;

- (l) a document showing that the manufacturer is authorised in his own country to produce veterinary medicinal products;
- (m) copies of any marketing authorization obtained in another Member State or in a third country for the relevant veterinary medicinal product, together with a list of those Member States in which an application for authorization submitted in accordance with this Directive is under examination. Copies of the summary of the product characteristics proposed by the applicant in accordance with Article 14 or approved by the competent authority of the Member State in accordance with Article 25 and copies of the package insert proposed, details of any decision to refuse authorization, whether in the Community or a third country and the reasons for that decision; all this information shall be updated on a regular basis.
- (n) in the case of veterinary medical products intended for one or more food-producing species and containing one or more pharmacologically active substances not yet included, for the species in question, in Annexes I, II or III to Regulation (EEC) No 2377/90 on maximum residue limits of veterinary medicinal products, a document certifying that a valid application for the establishment of maximum residue limits has been submitted to the Agency in accordance with the aforementioned Regulation.

The documents and particulars relating to the results of the tests referred to in point (j) of the first subparagraph shall be accompanied by detailed and critical summaries, drawn up as specified in Article 15.

Article 13

1. By way of derogation from point (j) of the first subparagraph of Article 12(3), and without prejudice to the law relating to the protection of industrial and commercial property, the applicant shall not be required to provide the results of the safety and residue tests or of the pre-clinical and clinical trials if he/she can demonstrate that the medicinal product is a generic of a reference medicinal product authorised within the meaning of Article 5 for not less than ten years in a Member State or the Community.

However, the ten-year period provided for in the first subparagraph is extended to 13 years in the case of veterinary medicinal products for fish or bees.

2. For the purposes of this Article:
 - (a) *reference medicinal product* shall mean a product authorised within the meaning of Article 5 in accordance with the provisions of Article 12;
 - (b) *generic medicinal product* shall mean a medicinal product which has the same qualitative and quantitative composition in terms of active substances, the same pharmaceutical form, and whose bioequivalence with the reference medicinal product has been demonstrated by means of appropriate bioavailability tests. Bioavailability tests may not be required

of the applicant if he/she can demonstrate that the medicinal product meets the criteria set out in Annex I.

3. The first subparagraph of paragraph 1 shall not apply in the event of a change in the active substance or substances, the therapeutic indications, the strength, the pharmaceutical form, the route of administration or the dose vis-à-vis the reference medicinal product, and the results of appropriate safety and residue tests studies and pre-clinical and clinical trials shall be provided.
4. In the case of veterinary medicinal products intended for one or more food-producing species and containing a new active substance that has not been authorised in the Community by [date] the ten-year period provided for in the first subparagraph of paragraph 1 shall be extended by one year for each extension of the marketing authorisation to another food-producing species, if it is authorised within the three years following the granting of the initial marketing authorisation.

The extension of one, two or three years of further data protection also applies to any initial marketing authorisation relative to two, three or four food-producing species, respectively.

This period cannot, however, exceed a total of 13 years, for a marketing authorisation for four or more food-producing species.

The extension of the ten-year period to 11, 12, or 13 years shall be granted only if the marketing authorisation holder had also been at the origin of the maximum residue limits established for the species covered by the authorisation.

5. Conducting the necessary tests and trial with a view to application of paragraphs 1 to 4 to a generic medicinal product shall not be regarded as contrary to patent related rights and to complementary protection certificates for those medicinal products.”

(8) The following Articles 13a to 13d are inserted:

"Article 13a

1. By way of derogation from point (j) of the first subparagraph of Article 12(3), and without prejudice to the law on the protection of industrial and commercial property, the applicant shall not be required to provide the results of the safety and residue tests or of the pre-clinical and clinical trials if he/she can demonstrate that the active substance(s) of the veterinary medicinal product are of well-established veterinary use for not less than ten years in the Community, with recognised efficacy and an acceptable level of safety in accordance with the conditions set out in Annex I. In that event the applicant shall provide appropriate scientific documentation.
2. The assessment report published by the Agency following the evaluation of an application for the establishment of maximum residue limits in accordance with Regulation (EEC) No 2377/90 may be used in an appropriate manner as literature, particularly for the safety tests.

3. If an applicant makes use of scientific literature in order to obtain authorisation for a food-producing species, and submits, in respect of the same medicinal product and with a view to obtaining authorisation for another food-producing species, new residue studies in accordance with Regulation (EEC) No 2377/90, together with further clinical trials, it shall not be permissible for a third party to use such studies or such trials pursuant to Article 13, for a period of three years from the grant of the authorisation for which they were carried out.

Article 13b

1. In the case of new veterinary medicinal products containing active substances used in the composition of authorised veterinary medicinal products but not hitherto used in combination for therapeutic purposes, the results of safety and residue tests and of pre-clinical and clinical trials relating to that combination shall be provided, but it shall not be necessary to provide the documentation relating to each individual active substance.

Article 13c

After marketing authorisation has been granted, the marketing authorisation holder may allow use to be made of the pharmaceutical, safety and residues, pre-clinical and clinical documentation contained in the file for the veterinary medicinal product with a view to examining a subsequent application for a veterinary medicinal product having the same qualitative and quantitative composition in active substances and the same pharmaceutical form..

Article 13d

By way of derogation from point (j) of the first subparagraph of Article 12(3), and in exceptional circumstances with respect to immunological veterinary medicinal products, the applicant shall not be required to provide the results of certain field trials on the target species if these trials cannot be carried out for duly substantiated reasons, in particular on account of other Community provisions."

- (9) Articles 14 and 15 are replaced by the following:

"Article 14

The summary of the product characteristics shall contain the following information:

- (1) Name of the veterinary medicinal product followed by the strength and the pharmaceutical form;
- (2) Qualitative and quantitative composition in terms of the active substances and constituents of the excipient, knowledge of which is essential for proper administration of the medicinal product. The common name or chemical description will be used;
- (3) Pharmaceutical form;
- (4) Pharmacological properties and, in so far as this information is useful for the therapeutic purposes, pharmacokinetic particulars;

- (5) Clinical particulars;
 - 5.1 target species,
 - 5.2 indications for use, specifying the target species,
 - 5.3 contra-indications,
 - 5.4. special warnings for each target species;
 - 5.5 special precautions for use, including special precautions to be taken by the person administering the medicinal product to the animals;
 - 5.6 adverse reactions (frequency and seriousness);
 - 5.7 use during pregnancy, lactation or lay;
 - 5.8 interaction with other medicaments and other forms of interaction;
 - 5.9 amounts to be administered and administration route;
 - 5.10 overdose (symptoms, emergency procedures, antidotes) (if necessary);
 - 5.11 withdrawal periods (expressed in hours or days) for the various foodstuffs, including those for which the withdrawal period is zero.
- (6) Pharmaceutical particulars:
 - 6.1 incompatibilities;
 - 6.2 shelf life, when necessary after reconstitution of the medicinal product or when the immediate packaging is opened for the first time;.
 - 6.3 special precautions for storage,
 - 6.4 nature and composition of immediate packaging;
 - 6.5 special precautions, including those pertaining to the environment, for the disposal of unused medicinal products or waste materials derived from the use of these products, if any.
- (7) Name, or corporate name, and permanent address or registered place of business of the marketing authorisation holder.

Article 15

- 1. Applicants shall ensure that the detailed and critical summaries referred to in the second subparagraph of Article 12(3) are drafted and signed by persons with the requisite technical or professional qualifications, set out in a brief *curriculum vitae*, before being submitted to the competent authorities.
- 2. Persons with the technical or professional qualifications, referred to in paragraph 1, shall justify any use made of the scientific literature referred to in Article 13a(1) in accordance with the conditions set out in Annex I.

3. A brief *curriculum vitae* of the persons referred to in paragraph 1 shall be appended to the detailed critical summaries."

(10) Article 16 is replaced by the following:

"Article 16

1. Member States shall ensure that homeopathic veterinary medicinal products manufactured and marketed within the Community are registered or authorised in accordance with the provisions of Article 17(1) and (2), and Articles 18 and 19.
2. Member States shall establish a simplified registration procedure for the homeopathic veterinary medicinal products referred to in Article 17."

(11) Article 17 is amended as follows:

(a) Paragraph 1 is replaced by the following:

"1. Without prejudice to the provisions of Regulation (EEC) No 2377/90 on the establishment of maximum residue limits of pharmacologically active substances intended for food-producing animals, only homeopathic veterinary medicinal products which satisfy all of the following conditions may be subject to a special, simplified registration procedure:

- (a) they are administered by a route described in the *European Pharmacopoeia* or, in absence thereof, by the pharmacopoeias currently used officially in the Member States;
- (b) no specific therapeutic indication appears on the labelling of the veterinary medicinal product or in any information relating thereto;
- (c) there is a sufficient degree of dilution to guarantee the safety of the medicinal product; in particular, the medicinal product shall not contain either more than one part per 10 000 of the mother tincture or more than 1/100th of the smallest dose used in allopathy with regard to active principles whose presence in an allopathic medicinal product results in the obligation to submit a veterinary prescription.

If it appears justified in the light of new scientific evidence, the Commission may adapt points (b) and (c) of the first subparagraph in accordance with the procedure referred to in Article 89(2).

At the time of registration, Member States shall determine the classification for the dispensing of the medicinal product."

(b) Paragraph 3 is deleted.

(12) Article 18 is amended as follows:

(a) The sixth indent is replaced by the following:

"– one or more mock-ups of the outer packaging and immediate packaging of the medicinal products to be registered,"

(b) The following eighth indent is added:

"– proposed withdrawal period together with all requisite justification."

(13) Article 19 is replaced by the following:

"Article 19

1. Homeopathic veterinary medicinal products other than those referred to in Article 17(1) shall be authorised in accordance with the provisions of Articles 12 to 14.
2. A Member State may introduce or retain on its territory specific rules for the safety tests and pre-clinical and clinical trials of homeopathic veterinary medicinal products intended for pet species and non-food-producing exotic species other than those referred to in Article 17(1), in accordance with the principles and characteristics of homeopathy as practised in that Member State. In this case, the Member State concerned shall notify the Commission of the specific rules in force."

(14) Articles 21, 22 and 23 are replaced by the following:

"Article 21

1. Member States shall take all appropriate measures to ensure that the procedure for granting an authorisation to place a veterinary medicinal product on the market is completed within 150 days of the submission of a valid application, including 120 days for drawing up the assessment report and the summary of product characteristics.

With a view to the grant of a marketing authorisation for a veterinary medicinal product in two or more Member States, applications shall be submitted in accordance with Articles 31 to 43.

2. Where a Member State notes that an application for authorisation of a given veterinary medical product submitted is already being examined in another Member State, the Member State concerned shall decline to assess the application and shall inform the applicant that the procedure described in Articles 31 to 43 applies.

Article 22

Where a Member State is informed, in accordance with point (m) of Article 12(3), that another Member State has authorised a veterinary medicinal product which is the subject of an application for authorisation in the Member State concerned, that Member State shall reject the application unless it has been submitted in compliance with Articles 31 to 43."

Article 23

In order to examine the application submitted pursuant to Articles 12 to 13d, the competent authorities of the Member States:

1. shall check that the documentation submitted in support of the application complies with Articles 12 to 13d and ascertain whether the conditions for the issue of the marketing authorisation have been fulfilled;
2. may submit the medicinal product, its raw materials and if necessary intermediate products or other constituent materials for testing by a State laboratory or by a laboratory designated for that purpose, in order to ensure that the testing methods employed by the manufacturer and described in the application documents, in accordance with point (i) of Article 12(3), are satisfactory;
3. may similarly check, in particular through consultation of a national or Community reference laboratory, that the analytical method used for detecting residues presented by the applicant in accordance with the second subparagraph of Article 12(3) is satisfactory;
4. may, where appropriate, require the applicant to provide further information as regards the items listed in Articles 12 to 13d. Where the competent authorities take this course of action, the time-limits specified in Article 21 shall be suspended until the further data required have been provided. Similarly, these time-limits shall be suspended for any period which the applicant may be given to provide oral or written explanations."

(15) In Article 25, paragraphs 2, 3 and 4 are replaced by the following:

- "2. The competent authorities shall take all necessary measures to ensure that the information concerning the veterinary medicinal product, and in particular the labelling and package leaflet, is in conformity with that approved in the summary of product characteristics when the marketing authorisation is issued or subsequently.
3. The competent authorities shall make available to any interested person a copy of the marketing authorisation together with the summary of product characteristics.

4. The competent authorities shall draw up an assessment report and comments on the dossier as regards the results of the pharmaceutical, safety and residue tests and the pre-clinical and 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 veterinary medicinal product concerned.

At the request of any interested person, the competent authorities shall make available the assessment report and its reasons for the opinion after deleting any information of commercially confidential nature."

(16) Article 26 is amended as follows:

- (a) Paragraph 1 is replaced by the following:

"1. The marketing authorisation may require the holder to indicate on the immediate packaging and/or the outer wrapping and the package leaflet, where the latter is required, other particulars essential for safety or health protection, including any special precautions relating to use and any other warnings resulting from the clinical and pharmacological trials prescribed in point (j) of the first subparagraph of Article 12(3) and in Articles 13 to 13d or from experience gained during the use of the veterinary medicinal product once it has been marketed."

- (b) Paragraph 2 is deleted.

- (c) Paragraph 3 is replaced by the following:

"3. In exceptional circumstances, and following consultation with the applicant, an authorisation may be granted under specific conditions, which shall be reviewed annually. Continuation of the initial authorisation may be linked to the review of these conditions.

Such authorisations may be granted only for objective and verifiable reasons."

(17) Article 27 is amended as follows:

- (a) Paragraphs 2 and 3 are replaced by the following:

"2. The competent authority may require the applicant or the marketing authorisation holder to provide sufficient quantities of the substances to enable controls to be made on the identification of the presence of residues of the veterinary medicinal products in question.

Upon request from the competent authorities, the marketing authorisation holder shall provide his/her technical expertise to facilitate the implementation of the analytical method for detecting residues of the veterinary medicinal products in the national reference laboratory designated under Council Directive 96/23/EC*.

3. In order to allow the continuous evaluation of the relation between the benefits and the risks, the marketing authorisation holder shall also forthwith forward to the competent authorities any new information which might entail the amendment of the contents of the file or of the approved summary of product characteristics. In particular, he/she shall forthwith inform the competent authorities of any prohibition or restriction imposed by the competent authorities of any country in which the veterinary medicinal product is marketed or of any rejection of an application for authorisation submitted in a third country.

* OJ L 125, 23.5.1996, p. 10."

- (c) Paragraph 4 is deleted.
- (d) Paragraph 5 is replaced by the following:

"5. The marketing authorisation holder shall immediately inform the competent authorities, with a view to authorisation, of any alteration which he/she proposes to make to the particulars and documents referred to in Articles 12 to 13d."

- (18) Article 28 is replaced by the following:

"Article 28

1. Without prejudice to paragraphs 2 and 3, the authorisation shall be valid for an unlimited period.
2. Any authorisation that is not followed within two years of its issue by the actual marketing of the authorised veterinary medicinal product in the authorising Member State shall cease to be valid.
3. When an authorised veterinary medicinal product previously placed on the market in the authorising Member State is no longer actually present on the market in that Member State for a period of two consecutive years, the authorisation shall cease to be valid."

- (19) Article 30 is replaced by the following:

"Article 30

The marketing authorisation shall be withheld if the file submitted to the competent authorities does not comply with the provisions of Articles 12 to 13d and Article 15.

The authorisation shall also be withheld if examination of the documents and particulars listed in Articles 12 and 13(1) establishes that:

- (a) the benefit/risk assessment of the veterinary medicinal product is, under the authorised conditions of use, unfavourable; when the application concerns a veterinary medicinal product for zootechnical use, particular regard being had to the benefits for animal health and welfare and to the safety and health benefits for the consumer; or

- (b) the product has no therapeutic effect or the applicant has not provided sufficient proof of such effect as regards the species of animal which is to be treated; or
- (c) its qualitative or quantitative composition is not as stated; or
- (d) the withdrawal period recommended by the applicant is not long enough to ensure that foodstuffs obtained from the treated animal do not contain residues which might constitute a health hazard to the consumer, or is insufficiently substantiated; or
- (e) the labelling or the package leaflet proposed by the applicant does not comply with this Directive;
- (f) the veterinary medicinal product is offered for sale for a use prohibited under other Community provisions.

However, when a Community legislative framework is in the course of being adopted, the competent authority may refuse authorisation for a veterinary medicinal product where such action is necessary for the protection of public health, consumer or animal health.

Authorization shall also be withheld if the application documents submitted to the competent authorities do not comply with Articles 12, 13 (1) and 15."

- (20) The title of Chapter 4 is replaced by the following:

"Chapter 4

Mutual recognition procedure and decentralised procedure"

- (21) Articles 31 to 35 are replaced by the following:

"Article 31

1. A coordination group is set up for the examination of any question relating to marketing authorisation of a veterinary medicinal product in two or more Member States in accordance with the procedures laid down in this Chapter. The Agency shall provide the secretariat for this group.
2. The group shall be composed of one representative per Member State appointed for a renewable period of three years. Members of the group may arrange to be accompanied by experts.
3. The coordination group shall draw up its own rules of procedure, which shall enter into force after a favourable opinion of the Commission.

Article 32

1. With a view towards the grant of a marketing authorisation for a veterinary medicinal product in two or more Member States, the applicant shall submit an application referring to an identical dossier in those Member States. The dossier shall contain all the administrative information and scientific and technical documentation described in Articles 12 to 14. The documents submitted shall include a list of the Member States concerned by the application.

The applicant shall request one Member State to act as reference Member State and to prepare an assessment report in respect of the veterinary medical product according to paragraphs 2 or 3.

Where appropriate, the assessment report shall contain an evaluation for the purposes of Article 13(4) or (5) or Article 13a(3).

2. If the veterinary medicinal product has already received authorisation by the time of application, the Member State(s) concerned shall recognise the marketing authorisation granted by the reference Member State. To this end, the marketing authorisation holder shall request the reference Member State either to prepare an assessment report in respect of the veterinary medicinal product or, if necessary, to update any existing assessment report. The reference Member State shall prepare or update the assessment report within 60 days of receipt of a valid application. The assessment report together with the approved summary of product characteristics, labelling and package leaflet shall be forwarded to the Member State(s) concerned and the applicant.
3. If the veterinary medicinal product has not received authorisation by the time of application, the applicant shall request the reference Member State to prepare a draft assessment report and drafts of the summary of product characteristics, labelling and package leaflet. The reference Member State shall prepare these drafts within 120 days of the receipt of a valid application and shall send them to the concerned Member States and the applicant.
4. Within 90 days of receipt of the documents referred to in paragraphs 2 and 3, the Member States concerned shall approve the assessment report, the summary of product characteristics, the labelling and the package leaflet and inform the reference Member State to this effect.

The reference Member State shall ascertain the agreement, close the procedure and inform the applicant accordingly.

5. Each Member State where an application following paragraph 1 has been submitted shall adopt a decision in conformity with the approved assessment report, summary of product characteristics, labelling and package leaflet within 30 days of acknowledgement of the agreement.

Article 33

1. If a Member State cannot, within the period allowed in Article 32(4), agree with the assessment report, summary of product characteristics, labelling and package leaflet on grounds of a potential serious risk to human or animal health or the environment, a detailed statement of the reasons shall be provided to the reference Member State, the other Member States concerned and the applicant. The points of disagreement shall be referred without delay to the coordination group.

If a Member State to which an application has been submitted invokes the reasons referred to in Article 71(1), it shall no longer be regarded as a Member State concerned by this Chapter.

2. Within the coordination group, all the Member States referred to in Paragraph 1 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 opportunity to make his/her point of view known orally or in writing. If, within 60 days of the communication of the reasons for disagreement to the coordination group the Member States reach an agreement, the reference Member State shall confirm the agreement, close the procedure and inform the applicant accordingly. Article 31(5) shall apply.
3. If within the period of 60 days the Member States fail to reach an agreement, the Agency shall be immediately informed with a view to application of the procedure laid down in Article 36. The Agency shall be provided with a detailed description of the matters on which agreement could not be reached and the reasons for the disagreement. The applicant shall be provided with a copy of this information.
4. As soon as the applicant has been informed that the matter has been referred to the Agency, he/she shall forthwith forward to the Committee a copy of the information and particulars referred to in the first subparagraph of Article 32(1).
5. In the case referred to in paragraph 3, the Member States that have approved the assessment report, summary of product characteristics, labelling and package leaflet of the reference Member State may, on request by the applicant, grant a marketing authorisation for the veterinary medicinal product without waiting for the outcome of the procedure laid down in Article 36. In that case, the authorisation granted shall be without prejudice to the outcome of that procedure.

Article 34

1. If two or more applications submitted in accordance with Articles 12 to 14 have been made for marketing authorisation for a particular veterinary medicinal product and Member States have adopted divergent decisions concerning the authorisation of that veterinary medicinal product, or suspension or withdrawal of authorisation, a Member State, or the Commission, or the marketing-authorisation holder may refer the matter to the Agency for application of the procedure laid down in Article 36.

2. With a view to promoting the harmonisation of veterinary medicinal products authorised for not less than ten years in the Community, and to strengthen the efficiency of the provisions of Article 11, the Member States shall send to the coordination group, no later than [date], a list of veterinary medicinal products for which a harmonised summary of product characteristics should be prepared.

The coordination group shall agree on a list of medicinal products, on the basis of proposals sent by the Member States, and shall forward this list to the Commission.

The medicinal products in this list are subject to the provisions in paragraph 1 following a timetable established in cooperation with the Agency.

The Commission, acting in collaboration with the Agency, and taking into consideration the views of the interested parties, shall agree the final list.

Article 35

1. The Member States or the Commission or the applicant or holder of the marketing authorisation 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 36 before reaching a decision on a request for a marketing authorisation or on the suspension or withdrawal of an authorisation, or on any other variations to the terms of a marketing authorisation which appear necessary, so as to take account in particular of the information collected in accordance with Title VII.

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

The Member State and the applicant or the marketing authorisation holder shall forward to the Committee all available information relating to the matter in question.

2. Where the referral to the Committee concerns a range of medicinal products or a therapeutic class, the Agency may limit the procedure to specific parts of the authorisation.

In that case, Article 39 shall apply to those medicinal products only if they are covered by the marketing authorisation procedure referred to in this Chapter."

(22) Article 36 is amended as follows:

- (a) Paragraph 1 is replaced by the following:

"1. When reference is made to the procedure laid down in this Article, the Committee shall consider the matter concerned and shall issue a reasoned opinion within *sixty* days of the date on which the matter was referred to it.

However, in cases submitted to the Committee in accordance with Articles 34 and 35, this period may be extended by the Committee for a further period of up to 90 days, taking into account the views of the marketing authorisation holders concerned.

In an emergency, and on a proposal from its Chairman, the Committee may agree to a shorter deadline."

(b) Paragraph 3 is replaced by the following:

"3. Before issuing its opinion, the Committee shall provide the applicant or the marketing authorisation holder with an opportunity to present written or oral explanations.

The opinion of the Committee shall include the draft summary of product characteristics and the drafts of the labelling and package leaflet.

If it considers 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 applicant or the marketing authorisation holder to prepare the explanations."

(c) Paragraph 4 is amended as follows:

(i) The introductory wording of the first subparagraph is replaced by the following:

"The Agency shall forthwith inform the applicant or the marketing authorisation holder of the opinion of the Committee if:"

(ii) The second indent of the first subparagraph is replaced by the following:

"– the summary of product characteristics proposed by the applicant or the marketing authorisation holder in accordance with Article 14 should be amended."

(iii) The second subparagraph is replaced by the following:

"Within 15 days of receipt of the opinion, the applicant or the marketing authorisation holder may notify the Agency in writing of his/her intention to appeal. In that case, he/she shall forward the detailed grounds for appeal to the Agency within 60 days of receipt of the opinion. Within 60 days of receipt of the grounds for appeal, the Committee shall reconsider its opinion in accordance with the second subparagraph of Article 53(1) of Regulation (EEC) No 2309/93. The conclusions reached on appeal shall be annexed to the assessment report referred to in paragraph 5."

(d) Paragraph 5 is amended as follows:

(i) The first subparagraph is replaced by the following:

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

(ii) In the second subparagraph, the following point (c) is added:

"(c) the drafts of the labelling and package leaflet"

(23) Article 37 is amended as follows:

(a) The second subparagraph is replaced by the following:

"In the event of a draft decision which envisages the granting of marketing authorisation, the documents referred to in the second subparagraph of Article 36(5), shall be annexed."

(b) The fourth subparagraph is replaced by the following:

"The draft decision shall be forwarded to the Member States and the applicant or marketing authorisation holder."

(24) Article 38 is amended as follows:

(a) Paragraph 1 is replaced by the following:

"1 The Commission shall adopt a final decision in accordance with the procedure referred to in Article 89(3), where the draft decision is in conformity with the Agency's opinion.

2. The Commission shall adopt a final decision in accordance with the procedure referred to in Article 89(4), where the draft decision is not in conformity with the Agency's opinion."

(b) In paragraph 2, the second and third indents are replaced by the following:

"– each Member State shall be allowed at least fifteen days to forward written observations on the draft decision of the Commission. However, if the Decision is urgent, the President may set a shorter deadline in the light of the urgency.

– each Member State may require in writing that the draft decision be discussed by the Standing Committee in plenary session, giving its reasons in detail."

(c) Paragraph 3 is replaced by the following:

"3. A decision as referred to in paragraph 1 shall be addressed to all the Member States and communicated to the marketing authorisation holder or the applicant for information. The concerned Member States and the reference Member State shall either grant or withdraw marketing authorisation, or vary the terms of a marketing authorisation as necessary to comply with the decision within 30 days of its notification and shall refer to it. They shall inform the Commission and the Agency thereof."

(25) In Article 39, the third subparagraph of paragraph 1 is deleted.

(26) In Article 42, paragraph 2 is replaced by the following:

"2. The Commission shall publish, no later than [date], a report on experience gained on the basis of the procedures provided for in this chapter and shall propose any amendments necessary to improve the procedures."

(27) Article 43 is replaced by the following:

"Article 43

The provisions of Article 33(3), (4) and (5) and Articles 34 to 38 shall not apply to the homeopathic veterinary medicinal products referred to in Article 17.

The provisions of Articles 32 to 38 shall not apply to the homeopathic veterinary medicinal products referred to in Article 19(2)."

(28) In Article 44, the following paragraph 4 is added:

"4. The Member State shall forward to the Agency a copy of the manufacturing authorisations referred to in paragraph 1. On the basis of this information the Agency shall compile a database."

(29) In Article 50, point (f) is replaced by the following:

"(f) comply with the principles and the guidelines on good manufacturing practice for medicinal products and use as starting materials only active substances that have been manufactured in accordance with the detailed guidelines on good manufacturing practice for starting materials."

(30) The following Article 50a is inserted:

"Article 50a

1. For the purposes of this Directive, manufacturing active substances for use as starting materials shall include the complete or partial manufacture or the import of an active substance used as a starting material, as defined in Part 2, Section C of Annex I, and the various processes of dividing up, packaging or presentation prior to its incorporation in a veterinary medicinal product, including repackaging or re-labelling, such as carried out by a starting material distributor.

2. Amendments which may be necessary to adapt the provisions of this Article to scientific and technical progress shall be adopted in accordance with the procedure referred to in Article 89(2)."
- (31) In Article 51, the following third and fourth paragraphs are added:
- "The principles and guidelines on good manufacturing practice as regards the manufacturing of active substances for use as starting materials as referred to in Article 50(f) shall be adopted in the form of detailed guidelines.
- The Commission shall also publish guidelines on the form and content of the authorisation referred to in Article 44(1), the reports referred to in Article 80(3) and the form and content of the certificate of good manufacturing practice referred to in Article 80(5)."
- (32) In Article 53, paragraph 1 is replaced by the following:
- "1. Member States shall ensure that the qualified person referred to in Article 52(1) fulfils the conditions of qualification referred to in paragraphs 2 and 3."
- (33) In Article 54, paragraph 1 is replaced by the following:
- "1. A person engaging, in a Member State, in the activities of the person referred to in Article 52(1) on the date on which Directive 81/851/EEC became applicable, without complying with the provisions of Article 53, shall be eligible to continue to engage in those activities in the Community."
- (34) In Article 55, point (b) of paragraph 1 is replaced by the following:
- "(b) in the case of veterinary medicinal products coming from third countries, even if the manufacture has taken place in the Community, each production batch imported has undergone in a Member State a full qualitative analysis, a quantitative analysis of at least all the active substances, and all the other tests or controls necessary to ensure the quality of veterinary medicinal products in accordance with the requirements of the marketing authorisation."
- (35) Article 58 is amended as follows:
- (a) Paragraph 1 is amended as follows:
- (i) The introductory wording is replaced by the following:
- "Except in the case of the medicinal products referred to in Article 17(1), the immediate packaging and outer packaging of veterinary medicinal products shall be approved by the competent authorities. They shall bear the following information, which shall conform with the particulars and documents provided pursuant to Articles 12 to 13d and the summary of product characteristics, and shall appear in legible characters:"

(ii) Points (a) and (b) are replaced by the following:

"(a) the name of the medicinal product, comprising the strength and/or pharmaceutical form, if the medicinal product is available in several strengths and/or pharmaceutical forms;

(b) a statement of the active substances expressed qualitatively and quantitatively per unit or according to the form of administration for a particular volume or weight, using the common names;"

(iii) Point (e) is replaced by the following:

"(e) name or corporate name and permanent address or registered place of business of the marketing authorisation holder and, where appropriate, of the local representative designated by the marketing authorisation holder;"

(iv) Point (g) is replaced by the following:

"(g) the withdrawal period, expressed in hours or days, for veterinary medicinal products to be administered to food-producing species, for all the species concerned and for the various foodstuffs concerned (meat and offal, eggs, milk, honey), including those for which the withdrawal period is nil."

(v) Point (l) is replaced by the following:

"(l) the words "For animal treatment only" or, in the case of the medicinal products referred to in Article 67, the words "For animal treatment only – to be supplied only on veterinary prescription"."

(b) The following paragraph 5 is added:

"5. In the case of medicinal products that have been granted a marketing authorisation under Regulation [(EEC) No 2309/93], Member States may permit or require that the outer packaging bear additional information concerning distribution, possession, sale or any necessary precautions, provided that such information is not in infringement of Community law or the terms of the marketing authorisation, and is not promotional.

This additional information shall appear in a box with a blue border to separate it clearly from the information referred to in paragraph 1."

(36) Article 59 is amended as follows:

(a) The introductory wording of paragraph 1 is replaced by the following:

"As regards ampoules, the particulars listed in the first paragraph of Article 58 (1) shall be given on the outer package. On the immediate packaging, however, only the following particulars shall be necessary:"

(b) Paragraphs 2 and 3 are replaced by the following:

"2. As regards small immediate packaging containing a single dose, other than ampoules, on which it is impossible to give the particulars mentioned in paragraph 1, the requirements of Article 58(1), (2) and (3), shall apply only to the outer package.

3. The particulars mentioned in the third and sixth indents of paragraph 1 shall appear on the outer package and on the immediate packaging of the medicinal products in the language or languages of the country in which they are placed on the market."

(37) Article 60 is replaced by the following:

"Article 60

Where there is no outer package, all the particulars which should feature on such a package pursuant to Articles 58 and 59 shall be shown on the immediate packaging."

(38) Article 61 is amended as follows:

(a) Paragraph 1 is replaced by the following:

"1. The inclusion of a package leaflet in the packaging of veterinary medicinal products shall be obligatory unless all the information required by this Article can be conveyed on the immediate packaging and the outer packaging. Member States shall take all appropriate measures to ensure that the package leaflet relates solely to the veterinary medicinal product with which it is included. The package leaflet shall be worded in terms that are comprehensible to the general public and in the official language or languages of the Member State in which the medicinal product is marketed."

(b) Paragraph 2 is amended as follows:

(i) The introductory wording is replaced by the following:

"The package leaflet shall be approved by the competent authorities. It shall contain at least the following information, which shall conform to the particulars and documents provided pursuant to Articles 12 to 13d and the approved summary of product characteristics:"

(ii) Points (a) and (b) are replaced by the following:

"(a) name or corporate name and permanent address or registered place of business of the marketing-authorisation holder and, where appropriate, of the manufacturer and the local representative designated by the marketing authorisation holder in the Member State;

(b) name of the veterinary medicinal product and its active substances, expressed qualitatively and quantitatively, using, wherever they exist, the international non-proprietary names recommended by the World Health Organisation, and stating the name authorised in each of the Member States whenever the medicinal product has been authorised, under the procedure set out in Articles 31 to 43, under different names in the various Member States concerned."

(c) Paragraph 3 is deleted.

(39) Article 62 is replaced by the following:

"Article 62

Where the provisions of this Title are not observed and a formal notice addressed to the person concerned has been ineffectual, the competent authorities of the Member States may suspend or withdraw marketing authorisation."

(40) In Article 64, paragraph 2 is amended as follows:

(a) The introductory wording is replaced by the following:

"In addition to the clear mention of the words 'homeopathic veterinary medicinal product', the labelling and, where appropriate, package leaflet for the homeopathic veterinary medicinal products referred to in Article 17(1) shall bear the following information and no other information:"

(b) The first indent is replaced by the following:

"– the scientific name of the stock or stocks followed by the degree of dilution, using the symbols of the pharmacopoeia used in accordance with point (8) of Article 1; if the homeopathic veterinary medicinal product is composed of more than one stock, the scientific names of the stocks may be replaced on the labelling by an invented name,"

(41) The title of Title VI is replaced by the following:

**"TITLE VI
POSSESSION, DISTRIBUTION
AND DISPENSING OF VETERINARY MEDICINAL PRODUCTS"**

(42) In Article 65, the following paragraph 3a is inserted:

"3a. The holder of a distribution authorisation shall have an emergency plan guaranteeing the effective implementation of any recall operation ordered by the competent authorities or undertaken in cooperation with the manufacturer of the medicinal product in question or the holder of the marketing authorisation."

(43) Article 66 is amended as follows:

(a) Paragraph 2 is amended as follows:

(i) the introductory wording is replaced by the following:

"Any person permitted under paragraph 1 to sell veterinary medicinal products shall be required to keep detailed records for veterinary medicinal products that may be supplied only on prescription, the following information being recorded in respect of each incoming or outgoing transaction:"

(ii) the third subparagraph is replaced by the following:

"These records shall be available for inspection by the competent authorities for a period of five years."

(b) Paragraphs 3 and 4 are deleted.

(44) Article 67 is amended as follows:

(a) The first paragraph is amended as follows:

(i) the introductory wording is replaced by the following:

"Without prejudice to stricter Community or national rules relating to dispensing veterinary medicinal products and serving to protect human and animal health, a veterinary prescription shall be required for dispensing to the public the following veterinary medicinal products:"

(ii) the following new point (a)* is inserted:

"(a) * veterinary medicinal products for food-producing animals"

(iii) the third indent of point (b) is deleted.

(iv) point (d) is replaced by the following:

"(d) magistral or officinal formulae intended for animals."

(b) The second paragraph is replaced by the following:

"In addition, a prescription shall be required for new veterinary medicinal products containing an active substance which has been authorised for use in a veterinary medicinal product for less than seven years."

(45) The first paragraph of Article 69 is replaced by the following.

"Member States shall ensure that the owners or keepers of food-producing animals can provide proof of purchase, possession and administration of veterinary medicinal products to such animals for a period of five years after slaughter."

(46) The introductory wording of Article 70 is replaced by the following:

"By way of derogation from Article 9 and without prejudice to Article 67, Member States shall ensure that veterinarians providing services in another Member State can take with them and administer to animals small quantities of veterinary medicinal products not exceeding daily requirements other than immunological veterinary medicinal products which are not authorised for use in the Member State in which the services are provided (hereinafter: "host Member State"), providing that the following conditions are satisfied:"

(47) The following subparagraph is added to Article 71(1):

"The Member State may also invoke the provisions of the first subparagraph in order to withhold marketing authorisation according to a decentralised procedure as provided for in Articles 31 to 43."

(48) In Article 72, paragraph 2 is replaced by the following:

"2. The Member States may impose specific requirements on veterinary practitioners and other health care professionals in respect of the reporting of suspected serious or unexpected adverse reactions and human adverse reactions."

(49) Article 73 is amended as follows:

(a) The first paragraph is replaced by the following:

"In order to ensure the adoption of appropriate and harmonised regulatory decisions concerning the veterinary medicinal products authorised within the Community, having regard to information obtained about suspected adverse reactions to veterinary medicinal products under normal conditions of use, the Member States shall administer a veterinary pharmacovigilance system. This system shall be used to collect information useful in the surveillance of veterinary medicinal products, with particular reference to adverse reactions in animals and in human beings related to the use of veterinary medicinal products, and to evaluate such information scientifically."

(b) After the second paragraph, the following paragraph is inserted:

"Member States shall ensure that the information collected within this system is forwarded to the other Member States and the Agency in an appropriate fashion. This information shall be recorded in the database referred to in point (j) of the second paragraph of Article 51 of Regulation (EEC) No 2309/93 and shall be permanently accessible to all Member States."

(50) The introductory wording of the second paragraph of Article 74 is replaced by the following:

"That qualified person shall reside in the Community and shall be responsible for the following:"

(51) Paragraphs 2 to 6 of Article 75 are replaced by the following:

- "2. The marketing authorisation holder shall be required to record all suspected serious adverse reactions and human adverse reactions related to the use of veterinary medicinal products which are brought to his/her attention, and to report them immediately to the competent authority of the Member State on whose territory the incident occurred, and in no case later than 15 calendar days following the receipt of the information.

The marketing authorisation holder shall also be required to record all suspected serious adverse reactions and human adverse reactions related to the use of veterinary medicinal products of which he/she can reasonably be expected to have knowledge, and to report them immediately to the competent authorities of all Member States in which the veterinary medicinal product is authorised, and in no case later than 15 calendar days following the receipt of the information.

Save in exceptional circumstances, any such adverse reactions shall be communicated electronically in the form of a report in accordance with the guidelines referred to in Article 77(1).

3. The marketing authorisation holder shall ensure that any suspected serious and unexpected adverse reactions and human adverse reactions occurring on the territory of a third country are reported immediately in accordance with the guidelines referred to in Article 77(1), so that they are available to the Agency and the competent authorities in the Member State(s) where the veterinary medicinal product is authorised, and in no case later than 15 calendar days following the receipt of the information.
4. By way of derogation from paragraphs 2 and 3, in the case of veterinary medicinal products covered by Directive 87/22/EEC, or having benefited from the authorisation procedures under Articles 31 and 32 or having been the subject of the procedures provided for under Articles 36, 37 and 38 of this Directive, the marketing authorisation holder shall additionally ensure that all suspected serious adverse reactions and human adverse reactions occurring in the Community are reported in such a way so as to be accessible to the reference Member State or a competent authority designated as reference Member State. The reference Member State shall assume responsibility for the analysis and follow up any such adverse reactions.
5. Unless other requirements have been laid down as a condition for the grant of authorisation, records of all adverse reactions shall be submitted to the competent authorities in the form of a periodic safety update report, either immediately upon request or periodically as follows: six monthly for the first two years after authorisation, annually for the subsequent two years, and thereafter at three-yearly intervals. The periodic safety update reports shall include a scientific evaluation of the benefits and risks afforded by the veterinary medicinal product.

6. Following the granting of a marketing authorisation, the holder of such authorisation may request the amendment of the periods referred to in paragraph 5, using the procedure laid down by the Commission Regulation (EC) No 541/95*, if need be.

* OJ L 55, 11.3.1995, p. 7. "

- (52) In Article 76, paragraph 1 is replaced by the following:

"1. The Agency, in collaboration with the Member States and the Commission, shall set up a data-processing network to facilitate the exchange of pharmacovigilance information regarding veterinary medicinal products marketed in the Community."

- (53) In Article 77(1), the second subparagraph is replaced by the following:

"In accordance with those guidelines, the marketing authorisation holder shall use internationally agreed veterinary medical terminology for the transmission of reports on adverse reactions.

The guidelines shall be published by the Commission and shall take account of international harmonisation work achieved in the field of pharmacovigilance."

- (54) Article 78 is amended as follows:

- (a) Paragraph 2 is replaced by the following:

"2. If urgent action is necessary for protecting human or animal health, the Member State concerned may suspend the marketing authorisation of a veterinary medicinal product, provided that the Agency, the Commission and the other Member States are informed on the following working day at the latest."

- (b) The following paragraph 3 is added:

"3. When the Agency is informed in accordance with paragraphs 1 or 2, it shall give its opinion as soon as possible, according to the urgency of the matter.

On the basis of this opinion, the Commission may request all Member States in which the veterinary medicinal is marketed to take temporary measures immediately.

Final measures shall be adopted in accordance with the procedure referred to in Article 89(3), where the draft decision is in conformity with the Agency's opinion.

Final measures shall be adopted in accordance with the procedure referred to in Article 89(4), where the draft decision is not in conformity with the Agency's opinion."

(55) Article 80 is amended as follows:

(a) Paragraph 1 is replaced by the following:

"1. The competent authority of the Member State concerned shall ensure by means of repeated inspection that the legal requirements relating to veterinary medicinal products are complied with.

The competent authority may carry out inspections at the premises of manufacturers of active substances used as starting materials for veterinary medicinal products, and of the premises of the marketing authorisation holder whenever it considers that there are serious grounds for suspecting non-compliance with the provisions of Article 51. Such inspections may also be carried out at the request of another Member State, the Commission or the Agency.

In order to demonstrate that the data submitted with applications for a certificate of compliance comply with the monographs of the European Pharmacopoeia, the body responsible for standardising the nomenclatures and quality norms within the meaning of the Convention relating to the elaboration of a European Pharmacopoeia* (European Directorate for the Quality of Medicines) may ask the Commission or the Agency to request such an inspection when the starting material in question is the subject of a European Pharmacopoeia monograph.

The competent authority of a Member State may carry out an inspection of a starting material manufacturer at the manufacturer's own request.

Such inspections shall be carried out by authorized representatives of the competent authority who shall be empowered to:

- (a) inspect manufacturing or trading establishments and any laboratories entrusted by the holder of the manufacturing authorization, with the task of carrying out control tests pursuant to Article 24;
- (b) take samples;
- (c) examine any documents relating to the object of the inspection, subject to current provisions in the Member States from 9 October 1981 which place restrictions on these powers with regard to the description of the manufacturing method;
- (d) inspect the premises of marketing authorisation holders or any firms performing the activities described in Title VII, and in particular Articles 74 and 75 thereof, on behalf of a marketing authorisation holder.

* OJ L 158, 25.6.1994, p. 19."

(b) Paragraph 3 is replaced by the following:

"3. The officials representing the competent authority shall report after each of the inspections mentioned in paragraph 1 on whether the principles and guidelines on good manufacturing practice referred to in Article 51 or, where appropriate, the requirements set out in Title VII, are being complied with. The inspected manufacturer or market authorisation holder shall be informed of the content of such reports."

(c) The following paragraphs 4 to 7 are added:

"4. Without prejudice to any arrangements which may have been concluded between the Community and a third country, a Member State, the Commission or the Agency may require a manufacturer established in a third country to undergo an inspection as referred to in paragraph 1.

5. Within 90 days after an inspection as referred to in Paragraph 1, a certificate of good manufacturing practice shall be issued to the manufacturer if the inspection established that the manufacturer in question is complying with the principles and guidelines on good manufacturing practice as provided for by Community law.

In the event of an inspection carried out at the request of the European Pharmacopoeia, a certificate of compliance with the monograph shall be issued, if appropriate.

6. Member States shall maintain, for the certificates of good manufacturing practice issued by their competent authorities, a Community register of certificates of good manufacturing practice. This register shall be managed at Community level by the Agency.

7. If an inspection as described in paragraph 1 results in the conclusion that the manufacturer does not comply with good manufacturing practice as provided for under Community law, the competent authority of the Member State shall also include this information in the Community register referred to in paragraph 6."

(56) Article 82 is replaced by the following:

"Article 82

1. Where it is considered necessary for reasons of human or animal health, a Member State may require the holder of a marketing authorisation for a live vaccine, or for a veterinary immunological medicinal product for a disease that is subject to preventive Community measures, to submit samples of batches of the bulk product and/or veterinary medicinal product for control by a national laboratory or a laboratory approved by the Member State before the product is put into circulation.

2. On request by the competent authorities, the marketing authorisation holder shall promptly supply the samples referred to in paragraph 1, together with the reports of the control referred to in Article 81(2).

The competent authority shall inform all the other Member States in which the veterinary medical product is authorised as well as the European Directorate for the Quality of Medicines of its intention to control the batch in question.

In such cases, the competent authorities of another Member State shall not apply the provisions of paragraph 1.

3. After studying the control reports referred to in Article 81(2), the laboratory responsible for the control shall repeat all the tests carried out by the manufacturer on the finished product on the samples provided, in accordance with the relevant provisions shown in the dossier for marketing authorisation.

The list of tests to be repeated by the laboratory responsible for the control shall be restricted to justified tests, providing that all the Member States concerned, and if appropriate the European Directorate for the Quality of Medicines, agree to this.

For immunological veterinary medicinal products authorised under [Regulation (EEC) No 2309/93], the list of tests to be repeated by the control laboratory may be reduced only after agreement by the Agency.

4. The results of the tests shall be recognised by all the Member States concerned.
5. Unless the Commission is informed that a longer period is necessary to conduct the tests, the Member States shall ensure that this control is completed within 60 days of receipt of the samples.

The competent authority shall notify the other Member States concerned, the European Directorate for the Quality of Medicines, the marketing authorisation holder and, if appropriate the manufacturer, the results of the tests within the same period of time.

If a competent authority concludes that a batch of a veterinary medicinal product is not in conformity with the control report of the manufacturer or the specifications provided for in the marketing authorisation, it shall take all the necessary measures vis-à-vis the marketing authorisation holder and the manufacturer, where appropriate, and shall inform accordingly the other Member States in which the veterinary medicinal product is authorised."

(57) Article 83 is amended as follows:

(a) Paragraph 1 is amended as follows:

(i) Point (a) is replaced by the following:

"(a) the benefit/risk assessment of the veterinary medicinal product is, under the authorised conditions of use, unfavourable, particular regard being had to the benefits for animal health and welfare and to the safety and health benefits for the consumer, when the authorisation concerns a veterinary medicinal product for zootechnical use".

(ii) The second subparagraph of point (e) is deleted.

(iii) Point (f) is replaced by the following:

"(f) the information given in the application documents pursuant to Articles 12 to 13d and 27 is incorrect;"

(iv) Point (h) is deleted.

(v) The following second subparagraph is added:

"However, when a Community legislative framework is in the course of being adopted, the competent authority may refuse authorisation for a veterinary medicinal product where such action is necessary for the protection of public health, consumer and animal health."

(b) In paragraph 2, point (a) is replaced by the following:

"(a) the particulars supporting the application, as provided for in Articles 12 to 13d, have not been amended in accordance with Article 27(1) and (5);"

(58) In Article 84, point (a) of paragraph 1 is replaced by the following:

"(a) it is clear that the benefit/risk assessment of the veterinary medicinal product is, under the authorised conditions of use, unfavourable, particular regard being had to the benefits for animal health and welfare and to the safety and health benefits for the consumer, when the application concerns a veterinary medicinal product for zootechnical use."

(59) In Article 89, paragraphs 2 and 3 are replaced by the following:

"2. Where reference is made to this paragraph, the regulatory procedure laid down in Article 5 of Decision 1999/468/EC shall apply, in compliance with Article 7 and Article 8 thereof.

The period provided for in Article 5(6) of Decision 1999/468/EC shall be three months.

3. Where reference is made to this paragraph, the advisory procedure laid down in Article 3 of Decision 1999/468/EC shall apply, in compliance with Articles 7 and 8 thereof.

4. Where reference is made to this paragraph, the management procedure laid down in Article 4 of Decision 1999/468/EC shall apply, in compliance with Articles 7 and 8 thereof.

The period provided for in Article 4(3) of Decision 1999/468/EC shall be one month.

5. The Standing Committee shall adopt its own rules of procedure."

(60) Article 90 is replaced by the following:

"Article 90

Member States shall take all necessary measures to ensure that the competent authorities concerned communicate the appropriate information to each other, particularly regarding compliance with the requirements adopted for the authorisations referred to in Article 44, the certificates referred to in Article 80(5) or for authorisation to place products on the market.

Upon reasoned request, Member States shall forthwith communicate the reports referred to in Article 80(3) to the competent authorities of another Member State.

The conclusions reached following an inspection as referred to in Article 80(1) carried out by the inspectors of the Member State concerned shall be valid for the Community.

However, by way of exception, if a Member State has not been able, for serious reasons of human or animal health, to accept the conclusions of an inspection as referred to in Article 80(1), that Member State shall forthwith inform the Commission and the Agency.

When the Commission is informed of such serious reasons, it may, after consulting the Member States concerned, ask the inspector of the competent supervisory authority to carry out a new inspection; the inspector may be accompanied by two other inspectors from Member States that are not parties to the disagreement."

(61) Article 95 is replaced by the following:

"Article 95

"The Member States shall not permit foodstuffs for human consumption to be taken from test animals unless an appropriate withdrawal period has been established by the competent authorities. The withdrawal period shall be at least as laid down in Article 11(2), including, where appropriate, a safety factor reflecting the nature of the substance being tested."

Article 2

Member States shall bring into force the laws, regulations and administrative provisions necessary to comply with this Directive by [date] at the latest and shall immediately inform the Commission thereof.

When Member States adopt those provisions, they shall contain a reference to this Directive or shall be accompanied by such a reference on the occasion of their official publication. Member States shall determine how such reference is to be made.

Article 3

This Directive shall enter into force on the twentieth day following that of its publication in the *Official Journal of the European Communities*.

Article 4

This Directive is addressed to the Member States.

Done at Brussels,

For the European Parliament
The President

For the Council
The President

FINANCIAL STATEMENT

1. TITLE OF OPERATION

Proposal for a Directive of the European Parliament and of the Council amending Directive 2001/82/EC on the Community code relating to veterinary medicinal products

2. BUDGET HEADING(S) INVOLVED

B5-3260A Industrial competitiveness policy for the EU (administration).

3. LEGAL BASIS

Article 95 EC

4. DESCRIPTION OF OPERATION

4.1 General objective

To guarantee a high level of animal health protection, particularly through increased market surveillance and a strengthening of pharmacovigilance procedures.

To increase the number of medicinal products available.

To complete the internal market in pharmaceutical products and to establish a regulatory and legislative framework that favours the competitiveness of the pharmaceuticals sector in Europe.

To adapt the present measures and propose future measures to meet the challenges of the future enlargement of the European Union.

4.2 Period covered and arrangements for renewal

Measures to be implemented in 2005, with no deadline.

5. CLASSIFICATION OF EXPENDITURE OR REVENUE

5.1 DNO

5.2 CND

5.3 Type of revenue involved

None

6. TYPE OF EXPENDITURE OR REVENUE

Expenditure on scientific expertise and subsidies.

7. FINANCIAL IMPACT

7.1 Method of calculating total cost of operation (relation between individual and total costs)

The total cost of the operation is calculated on the basis of the present number of meetings/meetings of experts per year for the type of operations covered by the proposal.

7.2 Itemised breakdown of cost

Commitment appropriations in EUR million (at current prices)

Breakdown	Year n	n+1	n+2	n+3	n+4	n+5 and subsequent Years	Total

7.3 Operational expenditure for studies, experts etc. included in Part B of the budget

Commitment appropriations in EUR million (at current prices)

	Year n	n+1	n+2	n+3	n+4	N+5 and subsequent Years	Total
– Studies					0.08	0.08	0.16
– Meetings of experts ¹							0
– Information and publications							0
Total					0.08	0.08	0.16

¹ Expenditure meeting the criteria set out in Commission Communication SEC(1992) 769, 22.4.1992.

7.4 Schedule of commitment and payment appropriations

Commitment appropriations in EUR million

	Year n	n+1	n+2	n+3	n+4	n+5 and subsequent Years	Total
Commitment appropriations					0.08	0.08	0.16
Payment appropriations							
Year n							
n+1							
n+2							
n+3							
n+4					0.08		0.08
n+5 and subsequ. Years						0.08	0.08
Total							0.16

8. FRAUD-PREVENTION MEASURES

- Are any specific measures planned?

No

9. ELEMENTS OF COST-EFFECTIVENESS ANALYSIS

9.1 Specific and quantified objectives; target population

None

9.2 Grounds for the operation

- Need for Community financial aid, with particular regard for the principle of subsidiarity

Amendment of existing legislation to take account of scientific and technical progress and of the future enlargement of the EU.

- Choice of ways and means

Amendment of existing legislation on the basis of Article 71 of Council Regulation (EEC) No 2309/93 following the evaluation of the implementation of the present legislation, which is the subject of a report from the Commission to the Council and the European Parliament.

- Main factors of uncertainty which could affect the specific results of the operation

The main factor of uncertainty is the arrangements for the enlargement of the EU in terms of both the countries concerned and the timetable for their accession. Another factor of uncertainty involves the way in which industry will use the procedures introduced, since the number of products concerned per year and the rapport cost/difficulty ratio of the associated scientific evaluations are not yet known.

9.3 Monitoring and evaluation of the operation

- Performance indicators

Number of products authorised under the procedures, progress on technical harmonisation, timetable for extending the procedures to the candidate countries, database and IT networks.

- Details and frequency of planned evaluations

A Commission report at least every ten years following the first report, which was drawn up after six years and is the basis of the present proposal.

- Assessment of the results obtained (where the operation is to be continued or renewed)

The results obtained since 1 January 1995 (when the present system came into force) are the subject of a report from the Commission to the Council and the European Parliament (currently being adopted by written procedure)

10. ADMINISTRATIVE EXPENDITURE (SECTION III, PART A OF THE BUDGET)

Actual mobilisation of the necessary administrative resources will depend on the Commission's annual decision on the allocation of resources, taking into account the number of staff and additional amounts authorised by the budgetary authority.

10.1 Effect on the number of posts

Type of post		Staff to be assigned to managing the operation		Source		Duration
		Permanent posts	Temporary posts	Existing resources in the DG or department concerned	Additional resources	
Officials or temporary staff	A	2A, 1B, 1C		2A, 1B, 1C	None	
	B C					
Other resources						
Total		2A, 1B, 1C		2A, 1B, 1C	None	

If additional resources are required, indicate the pace at which they will have to be made available.

10.2 Overall financial impact of additional human resources

(EUR)

	Amounts	Method of calculation
Officials	432 000	4 x EUR 108 000 per year
Temporary staff		
Other resources (indicate budget heading)		
Total	432 000	

The amounts given must express the total cost of additional posts for the entire duration of the operation, if this duration is predetermined, or for 12 months if it is indefinite.

10.3 Increase in other administrative expenditure as a result of the operation, particularly the cost of meetings of committees and groups of experts

(EUR)

Budget heading	Amounts	Method of calculation
A0-7030	20 000	Without taking account of the data relating to enlargement (since the number of experts per year from the candidate countries is not known), the calculation is based on a cost of approx. EUR 10 000 per meeting for a number of experts from the 15 Member States. 2 meetings per year.
A0-7031	50 000	Idem 5 meetings per year.
A0-7032	20 000	Idem 2 meetings per year.
Total	90 000	

The amounts given must express the total cost of additional posts for the entire duration of the operation, if this duration is predetermined, or for 12 months if it is indefinite.

IMPACT ASSESSMENT FORM¹

IMPACT OF THE PROPOSAL ON BUSINESSES, PARTICULARLY ON SMALL AND MEDIUM-SIZED ENTERPRISES (SMEs)

TITLE OF THE PROPOSAL

Proposal for a Directive of the European Parliament and of the Council amending Directive 2001/82/EC on the Community code relating to veterinary medicinal products

DOCUMENT REFERENCE NUMBER:

THE PROPOSAL

1. Given the principle of subsidiarity, why is there a need for Community legislation in this field and what are the main aims?

The proposed legislation introduces new provisions and amends, in a number of respects, the existing legislation relating to the functioning of the centralised and decentralised procedures for approving and suspending marketing of medicinal products for human and veterinary use.

Pursuant to Article 71 of Regulation (EEC) No 2309/93, the Commission is obliged to report within six years of the entry into force of the Regulation on the experience acquired as a result of the operation of the centralised and decentralised procedures. An audit report prepared on behalf of the Commission² has identified the aspects of the authorisation procedures that were operating satisfactorily and those where it was considered that improvement could be achieved.

From a business viewpoint, the proposed measures are intended to:

- increase the level of harmonisation across Member States of the rules governing medicinal products;
- increase the efficiency of operation of the centralised and decentralised procedures;
- thereby improve access and speed of access to the whole of the European market for both innovative and generic medicinal products, and
- allow industry to respond more quickly to the needs of the market.

¹ Given that the two Community-level authorisation procedures (centralised/decentralised) are inseparably linked and that much of the legislation on medicinal products for human use is parallel to the legislation on veterinary medicinal products, it was thought appropriate to draw up an overall impact assessment summarising the implications of the adoption of the three proposals. The same impact assessment have therefore been included as an annex to each of the three texts.

² Evaluation of the operation of Community procedures for the authorisation of medicinal products, CMS Cameron McKenna and Anderson Consulting, October 2000.

The "new systems" for licensing which were introduced in 1995 have contributed to the creation of a single market in pharmaceuticals but, notwithstanding the progress that has been made, there is evidence that the procedures contain shortcomings. The findings of the audit report on the operation of the authorisation procedures show that there is a need to refine, and in some areas make more substantial changes to, the existing regimes. In particular, there is recognition that the centralised procedure is capable of working well and that broadening the scope of the procedure to other products would be beneficial, both in terms of patient access and economies of scale for the companies.

The decentralised procedure was acknowledged as having significant advantages in terms of optionality but any such advantage is tempered to an extent by the failure of the system to operate on the basis of effective mutual recognition involving a significant number of Member States.

The pharmaceutical industry is populated by different types of company and a significant proportion of the industry comprises non-R&D-intensive companies, notably those which focus on their own national markets and those which rely upon the manufacture of generic versions of existing products. The existing regimes do not, at present, fully meet all the needs of these sectors of the industry.

Instituting authorisation procedures that properly protect public health while promoting an innovative profitable pharmaceutical industry is critical for Europe. The pharmaceutical industry is a strategic sector for Europe but there is evidence that over the last decade the industry in Europe is losing competitiveness compared to the USA and that its growth is more erratic than in the US or Japan³. The reasons underlying this trend are complex but the ability of companies to compete effectively is influenced, at least in part, by the nature of the regulatory environment.

The forthcoming enlargement of the European Union over the next decade will see the accession of further Member States. In principle, enlargement has the potential to contribute to the overall competitiveness of the European industry, but an important step in realising increased competitiveness is eradication of the shortcomings identified in the existing procedures prior to enlargement.

It is considered appropriate to maintain a balance between the centralised and decentralised authorisation procedures. Both systems have hitherto contributed – though not to the same extent – to the development of a single market in pharmaceuticals and provided a high degree of safety for patients and animals. However, the emergence of new technologies is delivering sophisticated medicinal products which are best suited to centralised approval.

³ See "Global Competitiveness in Pharmaceuticals", Report prepared for the Enterprise DG of the European Commission by Gambardella A, Orsenigol and Pammolli F, November 2000.

THE IMPACT ON BUSINESS

2. Who will be affected by the proposal?

- What sectors?

The measures primarily concern pharmaceutical manufacturers and to a lesser extent wholesalers and distributors of medicinal products.

The pharmaceutical industry in the EU consists of companies with a range of different businesses conducted often with a different geographical focus. The total number of pharmaceutical businesses in the EU is estimated at approximately 3 000⁴. Large multinational companies dominate the market accounting for approximately 60-65% of the market for pharmaceutical sales. Medium-sized companies (by international standards) make up approximately 30-35% of the market, with small local companies accounting for the balance. In terms of business types, the biotechnology element of the European pharmaceutical industry is still young, but the number of companies is growing with just in excess of 1 000 company units. Generic medicines currently account for around 10% of total pharmaceutical sales in the non-hospital market with penetration highest in Germany, Denmark, UK and the Netherlands⁵. Finally, the veterinary sector accounts for approximately 5% of the value of the human pharmaceutical market⁶. This sector of the market is far more diverse than that relating to medicines for human use, reflecting differences in livestock distribution, methods of production and climate across the EU.

The legislative proposals cover a number of aspects of the regulation of medicinal products and consequently the proposals will impact to some extent upon all pharmaceuticals manufacturers. A number of the proposals will therefore affect all pharmaceutical companies irrespective of the nature of the pharmaceutical business. For example, the provisions relating to the validity of marketing authorisations, compassionate use of medicines, the application of good manufacturing practice to starting materials and pharmacovigilance. A number of the measures are sector-specific or specific to one or other of the authorisation procedures and accordingly the effect of such measures will be more selective. The centralised procedure tends to be used predominantly by large multinational companies and smaller innovation-specialist companies. Accordingly, the proposed changes to the centralised system such as the introduction of conditional authorisations and a fast-track procedure will be relevant for these types of company.

⁴ The pharmaceutical industry in figures, European Federation of Pharmaceutical Industries Associations, 2000 Edition.

⁵ Generic Medicines: How to ensure their effective contribution to healthcare, Euro Health Vol. 2 No 3, September 1996.

⁶ Fountain R. and Thurman D. Animal Health Market to Face Opportunities and Challenges in 98, Feed Stuffs Vol. 69 No 48, November 1997.

- What sizes of business (proportion of SMEs)?

The decentralised (mutual recognition) procedure, although used by the large multinational companies, is also used by a significant proportion of small and medium-sized enterprises (“SMEs”). Accordingly, these companies will be impacted by the proposed amendments to the operation of the decentralised system. The principal sector-specific measures are directed towards manufacturers of products for veterinary use, manufacturers of generic medicines and manufacturers of homeopathic medicines.

- Are there particular geographical areas of the Community where these businesses are found?

No, there are no differences due to the geographic region where the firms concerned are established.

3. What will business have to do to comply with the proposal?

The majority of the proposal measures concern procedural changes and fine-tuning of existing procedures. Accordingly, a number of the measures do not impose direct obligations upon business. The majority of the obligations which are imposed impact at the time of application for a marketing authorisation.

Companies seeking to place a product containing a new chemical entity (NCE) on the market will be required to use the centralised authorisation procedure. This will remove, therefore, in respect of some medicinal products, the element of choice which companies currently enjoy when obtaining an authorisation from Member States. It should however, be noted that many products containing an NCE⁷ are already obliged to use the centralised route because they have been developed using biotechnological processes. Moreover, in circumstances where a company has a choice of procedure for a product containing an NCE, most of the companies already opt for the centralised route. It is intended that generic copies of centrally-authorized products may be authorised through either the centralised or the decentralised route. All other medicinal products may do likewise provided they show significant innovation over existing therapies. The broadening in scope of the centralised procedure will bring administrative savings for companies able to benefit from the single-application procedure. Some companies, particularly those in the veterinary sector with NCE-containing products which are relevant to only a limited geographical area of the European market, may be subject to an increase in the overall cost of preparing a centralised application for a marketing authorisation. This is why a derogation has been introduced.

Applicants pursuing an authorisation under the decentralised procedure will be compelled to enter arbitration proceedings if an issue cannot be resolved by the Member States concerned in the case of veterinary medicinal products. Companies may incur some costs in handling arbitration proceedings which they would otherwise avoid by withdrawal of the application. However, any such costs should be outweighed by the fact that companies may be permitted to market a medicinal product which is the subject of arbitration proceedings in the Member States that

⁷ Taken here in a broader sense as meaning any new active substance.

have agreed to authorise the product, thus permitting companies to begin to recoup investment costs earlier than at present.

The harmonisation to ten years (plus, for medicines for human use, one year for new therapeutic indications) of the period of data protection afforded to innovator companies will prevent an applicant for a generic (copy) product from making abridged applications in Austria⁸, Denmark, Greece, Finland, Ireland, Luxembourg, Portugal, and Spain on the expiry of six years from the date of first authorisation of the innovator product in the EU. An abridged application is one where the applicant does not present the results of his/her own safety and efficacy testing but relies upon the data underlying the authorisation of the innovator product. However, this restriction is balanced by the fact that companies intending to seek an authorisation for a generic product will be permitted, under a "Bolar-type" provision, to conduct the testing required prior to the expiry of the originator product's period of patent protection.

There is recognition that in some respects the veterinary sector of the pharmaceutical industry has different requirements and faces different issues and the proposal, therefore, seeks to address matters which are a concern in this area of the business. The incremental periods of protection available for data used to extend a marketing authorisation to additional food-producing species, the 13-year period of protection for honey bees and fish, and the introduction of a limited period of data protection for certain MRL data will encourage innovation by providing greater protection for the results of research by delaying somewhat the date at which applicants seeking an authorisation for a generic (copy) product may obtain approval without themselves investing in the research required to obtain and maintain a marketing authorisation. However, consistent with the position for medicines for human use, generic manufacturers will be able to take advantage of a "Bolar-type" provision.

The removal of the requirement for companies to renew marketing authorisations every five years will reduce the cost burden for companies. This amendment is balanced by increased pharmacovigilance reporting requirements; overall, a cost saving is expected for companies, since companies already have established pharmacovigilance systems in place

4. What economic effects is the proposal likely to have:

- on employment?
- on investment and the creation of new businesses?
- on the competitiveness of business?

The proposed package is expected to benefit the pharmaceutical industry in Europe and provide earlier access for patients in the Community to important new medicines.

⁸ Currently in this Member State the period of data protection will not be applied beyond the date of expiry of the patent. This link will cease to exist under the proposed amendments.

The examination in the report by Pammolli *et al*⁹ of the competitive position of the European pharmaceutical business compared with the USA reveals that, in general, the profile of the pharmaceutical industry in Europe is different from that in the USA. The European industry is less specialised in Research and Development activities and has a much larger presence of companies specialising in low-value-added activities. The US has developed an industry which is effective not only in the "exploration" of new technologies but also in their "exploitation". This vertical specialisation enhances innovation – a key driver of competitiveness – by exploiting the advantages of both the small biotechnology firms and the larger multinational firms.

Strengthening the scientific advice procedure within the centralised system will enable companies' research to be better focused and will reduce the investment risk for small biotechnology companies and thereby provide encouragement for this sector of the industry. In addition, extension of the period of data protection to ten years in all Member States, with an additional year for subsequent clinically-important indications, will encourage innovation by providing a greater opportunity for research-based companies to recoup the costs of their research investment. The Pammolli *et al* Report¹⁰ showed that there was too little competition in some Member States, which in turn led to inefficiencies within the industry. Accordingly, the measures to encourage innovation are balanced by those intended to stimulate generic competition – for example, the introduction of a "Bolar-type" provision and the availability of the centralised procedure for generic copies of centrally-authorized products.

A strengthening of innovation and competition within the industry will ultimately promote growth and enhance employment opportunities within the sector. Following the expiry of patent and data protection periods, the proposals aimed at stimulating the prompt approval of generic copies, will provide competition that will exert downward pressure on pricing, thereby helping to facilitate the supply of affordable medicinal products to Member States' healthcare systems.

The proposal is expected to benefit patients by supplying medicinal products more quickly to the market and, in particular, making available important new treatments at an earlier stage. This will be achieved by a combination of the reduction by half of the length of time available for the consultation of Member States on Commission decisions, the introduction of conditional authorisations and a fast-track procedure, together with a more formalised approach to the availability of medicinal products on a compassionate-use basis. Earlier access to medicines is likely to bring economic benefits by reducing morbidity and mortality and thereby have some influence on national healthcare budgets.

The veterinary sector of the pharmaceutical industry has encountered problems in the availability of medicines for minor species and, following the introduction of the MRL requirement for food-producing animals, for certain therapeutic areas. The increased periods of protection for data used to extend an authorisation for use in additional food-producing species and the increased period for minor species will encourage businesses to exploit their products for use in a broader range of species.

⁹ See note 3.

¹⁰ See note 3.

This will benefit agricultural producers active in these areas and reduce the hitherto unacceptable level of off-label use.

5. Does the proposal contain measures to take into account the specific situation of small and medium-sized firms (reduced or different requirements, etc.)?

The proposal does not contain specific measures for SMEs, but a number of the measures will be particularly beneficial for SMEs. For example, those measures designed to promote innovation, those improving the scientific advice procedure (biotechnology SMEs) and those requiring the introduction of a simplified registration procedure for homeopathic products.

CONSULTATION

6. List of organisations that have been consulted on the proposal, and outline of their main views.

There has been extensive consultation with interested parties on the operation of the rules governing medicinal products in the European Union and on the amendments which would improve the system. As part of the survey undertaken for the Commission on the operation of the Community procedures, the consultants concerned sought written and oral comments from a broad range of respondents, as follows:

- all holders of a centralised marketing authorisation at the time of the review;
- 159 marketing-authorisation holders (including large multinationals, SMEs, manufacturers of generics and non-prescription and veterinary medicines from different Member States) who had used the decentralised procedure;
- European trade associations representing the interests of human and veterinary medicines including those concerned with NCEs, generics, non-prescription medicines, and homeopathic and herbal medicinal products;
- 15 national consumer organisations and 134 patient associations;
- professional associations responsible for the regulation of doctors, dentists, pharmacists and veterinary practitioners;
- competent authorities responsible for authorising medicinal products;
- chairmen of the Committee for Proprietary Medicinal Products, the Committee for Veterinary Medicinal Products, the Mutual Recognition Facilitation Group and the Veterinary Mutual Recognition Facilitation Group; and
- the ministries responsible for health, social affairs, finance and agriculture.

Many companies were in favour, in principle, of opening up the centralised procedure to other products. There was broad acceptance from businesses of the need to reduce the procedural delays in the Commission decision-making procedure and also for the concept of a formal fast-track procedure.

In relation to the decentralised procedure, although companies were generally satisfied with the performance of the Member States there was dissatisfaction with the limited adherence to the principle of mutual recognition. Many respondents supported the introduction of a dialogue between the Member States prior to the granting of an authorisation in order to encourage greater acceptance of the principles of mutual recognition. Most companies were not in favour of compulsory arbitration in circumstances where Member States were unable to reach agreement, but there was strong support for permitting the marketing of a product pending arbitration in the Member States concerned that felt able to authorise the product.

There was strong support from business for the abolition of the renewal procedure for marketing authorisations.

Finally, there was very strong support for harmonising the periods of data protection, but less consensus on what the harmonised level of protection should be or how it should be applied to products derived from incremental research.