

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.

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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 B C	2A, 1B, 1C		2A, 1B, 1C	none	
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.