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

(2002/C 75 E/13)

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(Submitted by the Commission on 26 November 2001)

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 Commission,

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

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

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

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 use, 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.

(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 Products [1] 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 report 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.

[1] 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).

(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.

(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 Commission [1], 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:

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.'

[1] OJ L 184, 17.7.1999, p. 23.

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 1(a) 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 10(c)'.

(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) 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 30 days following this notification, the information shall be deemed to be accepted;

— the Agency shall coordinate 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 with 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 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.