

DIRECTIVE 2001/83/EC OF THE EUROPEAN PARLIAMENT AND OF THE COUNCIL OF 6 NOVEMBER 2001 ON THE COMMUNITY CODE RELATING TO MEDICINAL PRODUCTS FOR HUMAN USE

Official Journal L – 311, 28/11/2004, p. 67 – 128

as amended by

Directive 2002/98/EC of the European Parliament and of the Council of 27 January 2003 setting standards of quality and safety for the collection, testing, processing, storage and distribution of human blood and blood components and amending Directive 2001/83/EC

Official Journal L – 33, 08/02/2003, p. 30 – 40

Directive 2004/24/EC of the European Parliament and the Council of 31 March 2004 amending, as regards traditional herbal medicinal products, Directive 2001/83/EC on the Community code relating to medicinal products for human use

Official Journal L – 136, 30/04/2004, p. 85 – 90

Directive 2004/27/EC of the European Parliament and the Council of 31 March 2004 amending Directive 2001/83/EC on the Community code relating to medicinal products for human use

Official Journal L – 136, 30/04/2004, p. 34 – 57.

This text does not contain the Annex to Directive 2001/83/EC. The Annex currently in force is laid down in Commission Directive 2003/63/EC of 25 June 2003 amending Directive 2001/83/EC of the European Parliament and of the Council on the Community code relating to medicinal products for human use (*Official Journal L 159, 27/6/2003 p. 46 - 94*).

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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 Treaty establishing the European Community, and in particular Article 152(4)(a) thereof, [legal basis of Directive 2002/98/EC]

Having regard to the proposal from the Commission,

Having regard to the opinion of the Economic and Social Committee¹,

Acting in accordance with the procedure laid down in Article 251 of the Treaty²,

Whereas:

(1) Council Directive 65/65/EEC of 26 January 1965 on the approximation of provisions laid down by law, regulation or administrative action relating to medicinal products³, Council Directive 75/318/EEC of 20 May 1975 on the approximation of the laws of Member States relating to analytical, pharmaco-toxicological and clinical standards and protocols in respect of the testing of proprietary medicinal products⁴, Council Directive 75/319/EEC of 20 May 1975 on the approximation of provisions laid down by law, regulation or administrative action relating to proprietary medicinal products⁵, Council Directive 89/342/EEC of 3 May 1989 extending the scope of Directives 65/65/EEC and 75/319/EEC and laying down additional provisions for immunological medicinal products consisting of vaccines, toxins or serums and allergens⁶, Council Directive 89/343/EEC of 3 May 1989 extending the scope of Directives

65/65/EEC and 75/319/EEC and laying down additional provisions for radiopharmaceuticals⁷, Council Directive 89/381/EEC of 14 June 1989 extending the scope of Directives 65/65/EEC and 75/319/EEC on the approximation of provisions laid down by law, regulation or administrative action relating to medicinal products and laying down special provisions for proprietary medicinal products derived from human blood or human plasma⁸, Council Directive 92/25/EEC of 31 March 1992 on the wholesale distribution of medicinal products for human use⁹, Council Directive 92/26/EEC of 31 March 1992 concerning the classification for the supply of medicinal products for human use¹⁰, Council Directive 92/27/EEC of 31 March 1992 on the labelling of medicinal products for human use and on package leaflets¹¹, Council Directive 92/28/EEC of 31 March 1992 on the advertising of medicinal products for human use¹², Council Directive 92/73/EEC of 22 September 1992 widening the scope of Directives 65/65/EEC and 75/319/EEC on the approximation of provisions laid down by law, regulation or administrative action relating to medicinal products and laying down additional provisions on homeopathic medicinal products¹³ have been frequently and substantially amended. In the interests of clarity and rationality, the said Directives should therefore be codified by assembling them in a single text.

(2) The essential aim of any rules governing the production, distribution and use of medicinal products must be to safeguard public health.

(3) However, this objective must be attained by means which will not hinder the development of the pharmaceutical industry or trade in medicinal products within the Community.

(4) Trade in medicinal products within the Community is hindered by disparities between

¹ OJ C 75, 15.3.2000, p. 11.

² Opinion of the European Parliament of 3 July 2001 (not yet published in the Official Journal) and Council Decision of 27 September 2001.

³ OJ 22, 9.2.1965, p. 369/65. Directive as last amended by Directive 93/39/EEC (OJ L 214, 24.8.1993, p. 22).

⁴ OJ L 147, 9.6.1975, p. 1. Directive as last amended by Commission Directive 1999/83/EC (OJ L 243, 15.9.1999, p. 9).

⁵ OJ L 147, 9.6.1975, p. 13. Directive as last amended by Commission Directive 2000/38/EC (OJ L 139, 10.6.2000, p. 28).

⁶ OJ L 142, 25.5.1989, p. 14.

⁷ OJ L 142, 25.5.1989, p. 16.

⁸ OJ L 181, 28.6.1989, p. 44.

⁹ OJ L 113, 30.4.1992, p. 1.

¹⁰ OJ L 113, 30.4.1992, p. 5.

¹¹ OJ L 113, 30.4.1992, p. 8.

¹² OJ L 113, 30.4.1992, p. 13.

¹³ OJ L 297, 13.10.1992, p. 8.

certain national provisions, in particular between provisions relating to medicinal products (excluding substances or combinations of substances which are foods, animal feeding-stuffs or toilet preparations), and such disparities directly affect the functioning of the internal market.

(5) Such hindrances must accordingly be removed; whereas this entails approximation of the relevant provisions.

(6) In order to reduce the disparities which remain rules should be laid down on the control of medicinal products and the duties incumbent upon the Member States' competent authorities should be specified with a view to ensuring compliance with legal requirements.

(7) The concepts of harmfulness and therapeutic efficacy can only be examined in relation to each other and have only a relative significance depending on the progress of scientific knowledge and the use for which the medicinal product is intended. The particulars and documents which must accompany an application for marketing authorization for a medicinal product demonstrate that potential risks are outweighed by the therapeutic efficacy of the product.

(8) Standards and protocols for the performance of tests and trials on medicinal products are an effective means of control of these products and hence of protecting public health and can facilitate the movement of these products by laying down uniform rules applicable to tests and trials, the compilation of dossiers and the examination of applications.

(9) Experience has shown that it is advisable to stipulate more precisely the cases in which the results of toxicological and pharmacological tests or clinical trials do not have to be provided with a view to obtaining authorization for a medicinal product which is essentially similar to an authorized product, while ensuring that innovative firms are not placed at a disadvantage.

(10) However, there are reasons of public policy for not conducting repetitive tests on humans or animals without over-riding cause.

(11) The adoption of the same standards and protocols by all the Member States will enable the competent authorities to arrive at their decisions on the basis of uniform tests and by reference to uniform criteria and will therefore help to avoid differences in evaluation.

(12) With the exception of those medicinal products which are subject to the centralized Community authorization procedure established by Council Regulation (EEC) No 2309/93 of 22 July 1993 laying down Community procedures for the authorization and supervision of medicinal products for human and veterinary use and establishing a European Agency for the Evaluation of Medicinal Products¹⁴ a marketing authorization for a medicinal product granted by a competent authority in one Member State ought to be recognized by the competent authorities of the other Member States unless there are serious grounds for supposing that the authorization of the medicinal product concerned may present a risk to public health. In the event of a disagreement between Member States about the quality, the safety or the efficacy of a medicinal product, a scientific evaluation of the matter should be undertaken according to a Community standard, leading to a single decision on the area of disagreement binding on the Member States concerned. Whereas this decision should be adopted by a rapid procedure ensuring close cooperation between the Commission and the Member States.

(13) For this purpose, a Committee for Proprietary Medicinal Products should be set up attached to the European Agency for the Evaluation of Medicinal Products established in the abovementioned Regulation (EEC) No 2309/93.

¹⁴ OJ L 214, 24.8.1993, p. 1. Regulation as amended by Commission Regulation (EC) No 649/98 (OJ L 88, 24.3.1998, p. 7).

(14) This Directive represents an important step towards achievement of the objective of the free movement of medicinal products. Further measures may abolish any remaining barriers to the free movement of proprietary medicinal products will be necessary in the light of experience gained, particularly in the abovementioned Committee for Proprietary Medicinal Products.

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

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

(17) It is necessary to adopt specific provisions for immunological medicinal products, homeopathic medicinal products, radiopharmaceuticals, and medicinal products based on human blood or human plasma.

(18) Any rules governing radiopharmaceuticals must take into account the provisions of Council Directive 84/466/Euratom of 3 September 1984 laying down basic measures for the radiation protection of persons undergoing medical examination or treatment¹⁵. Account should also

¹⁵ OJ L 265, 5.10.1984, p. 1. Directive repealed with effect from 13 May 2000 by Directive 97/43/Euratom (OJ L 180, 9.7.1997, p. 22).

be taken of Council Directive 80/836/Euratom of 15 July 1980 amending the Directives laying down the basic safety standards for the health protection of the general public and workers against the dangers of ionizing radiation¹⁶, the objective of which is to prevent the exposure of workers or patients to excessive or unnecessarily high levels of ionizing radiation, and in particular of Article 5c thereof, which requires prior authorization for the addition of radioactive substances to medicinal products as well as for the importation of such medicinal products.

(19) The Community entirely supports the efforts of the Council of Europe to promote voluntary unpaid blood and plasma donation to attain self-sufficiency throughout the Community in the supply of blood products, and to ensure respect for ethical principles in trade in therapeutic substances of human origin.

(20) The rules designed to guarantee the quality, safety and efficacy of medicinal products derived from human blood or human plasma must be applied in the same manner to both public and private establishments, and to blood and plasma imported from third countries.

(21) Having regard to the particular characteristics of these homeopathic medicinal products, such as the very low level of active principles they contain and the difficulty of applying to them the conventional statistical methods relating to clinical trials, it is desirable to provide a special, simplified registration procedure for those homeopathic medicinal products which are placed on the market without therapeutic indications in a pharmaceutical form and dosage which do not present a risk for the patient.

(22) The anthroposophic medicinal products described in an official pharmacopoeia and prepared by a homeopathic method are to be

¹⁶ OJ L 246, 17.9.1980, p. 1. Directive as amended by Directive 84/467/Euratom (OJ L 265, 5.10.1984, p. 4), repealed with effect from 13 May 2000 by Directive 96/29/Euratom (OJ L 314, 4.12.1996, p. 20).

treated, as regards registration and marketing authorization, in the same way as homeopathic medicinal products.

(23) It is desirable in the first instance to provide users of these homeopathic medicinal products with a very clear indication of their homeopathic character and with sufficient guarantees of their quality and safety.

(24) The rules relating to the manufacture, control and inspection of homeopathic medicinal products must be harmonized to permit the circulation throughout the Community of medicinal products which are safe and of good quality.

(25) The usual rules governing the authorization to market medicinal products should be applied to homeopathic medicinal products placed on the market with therapeutic indications or in a form which may present risks which must be balanced against the desired therapeutic effect. In particular, those Member States which have a homeopathic tradition should be able to apply particular rules for the evaluation of the results of tests and trials intended to establish the safety and efficacy of these medicinal products provided that they notify them to the Commission.

(26) In order to facilitate the movement of medicinal products and to prevent the controls carried out in one Member State from being repeated in another, minimum requirements should be laid down for manufacture and imports coming from third countries and for the grant of the authorization relating thereto.

(27) It should be ensured that, in the Member States, the supervision and control of the manufacture of medicinal products is carried out by a person who fulfils minimum conditions of qualification.

(28) Before an authorization to market an immunological medicinal product or derived from human blood or human plasma can be granted, the manufacturer must demonstrate his ability to attain batch-to-batch consistency. Before an authorization to market a medicinal product derived from human blood or human

plasma can be granted, the manufacturer must also demonstrate the absence of specific viral contamination, to the extent that the state of technology permits.

(29) The conditions governing the supply of medicinal products to the public should be harmonized.

(30) In this connection persons moving around within the Community have the right to carry a reasonable quantity of medicinal products lawfully obtained for their personal use. It must also be possible for a person established in one Member State to receive from another Member State a reasonable quantity of medicinal products intended for his personal use.

(31) In addition, by virtue of Regulation (EC) No 2309/93, certain medicinal products are the subject of a Community marketing authorization. In this context, the classification for the supply of medicinal products covered by a Community marketing authorization needs to be established. It is therefore important to set the criteria on the basis of which Community decisions will be taken.

(32) It is therefore appropriate, as an initial step, to harmonize the basic principles applicable to the classification for the supply of medicinal products in the Community or in the Member State concerned, while taking as a starting point the principles already established on this subject by the Council of Europe as well as the work of harmonization completed within the framework of the United Nations, concerning narcotic and psychotropic substances.

(33) The provisions dealing with the classification of medicinal products for the purpose of supply do not infringe the national social security arrangements for reimbursement or payment for medicinal products on prescription.

(34) Many operations involving the wholesale distribution of medicinal products for human use may cover several Member States simultaneously.

(35) It is necessary to exercise control over the entire chain of distribution of medicinal products, from their manufacture or import into the Community through to supply to the public, so as to guarantee that such products are stored, transported and handled in suitable conditions. The requirements which must be adopted for this purpose will considerably facilitate the withdrawal of defective products from the market and allow more effective efforts against counterfeit products.

(36) Any person involved in the wholesale distribution of medicinal products should be in possession of a special authorization. Pharmacists and persons authorized to supply medicinal products to the public, and who confine themselves to this activity, should be exempt from obtaining this authorization. It is however necessary, in order to control the complete chain of distribution of medicinal products, that pharmacists and persons authorized to supply medicinal products to the public keep records showing transactions in products received.

(37) Authorization must be subject to certain essential conditions and it is the responsibility of the Member State concerned to ensure that such conditions are met; whereas each Member State must recognize authorizations granted by other Member States.

(38) Certain Member States impose on wholesalers who supply medicinal products to pharmacists and on persons authorized to supply medicinal products to the public certain public service obligations. Those Member States must be able to continue to impose those obligations on wholesalers established within their territory. They must also be able to impose them on wholesalers in other Member States on condition that they do not impose any obligation more stringent than those which they impose on their own wholesalers and provided that such obligations may be regarded as warranted on grounds of public health protection and are proportionate in relation to the objective of such protection.

(39) Rules should be laid down as to how the labelling and package leaflets are to be presented.

(40) The provisions governing the information supplied to users should provide a high degree of consumer protection, in order that medicinal products may be used correctly on the basis of full and comprehensible information.

(41) The marketing of medicinal products whose labelling and package leaflets comply with this Directive should not be prohibited or impeded on grounds connected with the labelling or package leaflet.

(42) This Directive is without prejudice to the application of measures adopted pursuant to Council Directive 84/450/EEC of 10 September 1984 relating to the approximation of the laws, regulations and administrative provisions of the Member States concerning misleading advertising¹⁷.

(43) All Member States have adopted further specific measures concerning the advertising of medicinal products. There are disparities between these measures. These disparities are likely to have an impact on the functioning of the internal market, since advertising disseminated in one Member State is likely to have effects in other Member States.

(44) Council Directive 89/552/EEC of 3 October 1989 on the coordination of certain provisions laid down by law, regulation or administrative action in Member States concerning the pursuit of television broadcasting activities¹⁸ prohibits the television advertising of medicinal products which are available only on medical prescription in the Member State within whose jurisdiction the television broadcaster is located. This principle should be made of general application by extending it to other media.

¹⁷ OJ L 250, 19.9.1984, p. 17. Directive as amended by Directive 97/55/EC (OJ L 290, 23.10.1997, p. 18).

¹⁸ OJ L 298, 17.10.1989, p. 23. Directive as amended by Directive 97/36/EC (OJ L 202, 30.7.1997, p. 60).

(45) Advertising to the general public, even of non-prescription medicinal products, could affect public health, were it to be excessive and ill-considered. Advertising of medicinal products to the general public, where it is permitted, ought therefore to satisfy certain essential criteria which ought to be defined.

(46) Furthermore, distribution of samples free of charge to the general public for promotional ends must be prohibited.

(47) The advertising of medicinal products to persons qualified to prescribe or supply them contributes to the information available to such persons. Nevertheless, this advertising should be subject to strict conditions and effective monitoring, referring in particular to the work carried out within the framework of the Council of Europe.

(48) Advertising of medicinal products should be subject to effective, adequate monitoring. Reference in this regard should be made to the monitoring mechanisms set up by Directive 84/450/EEC.

(49) Medical sales representatives have an important role in the promotion of medicinal products. Therefore, certain obligations should be imposed upon them, in particular the obligation to supply the person visited with a summary of product characteristics.

(50) Persons qualified to prescribe medicinal products must be able to carry out these functions objectively without being influenced by direct or indirect financial inducements.

(51) It should be possible within certain restrictive conditions to provide samples of medicinal products free of charge to persons qualified to prescribe or supply them so that they can familiarize themselves with new products and acquire experience in dealing with them.

(52) Persons qualified to prescribe or supply medicinal products must have access to a neutral, objective source of information about products available on the market. Whereas it is nevertheless for the Member States to take all

measures necessary to this end, in the light of their own particular situation.

(53) Each undertaking which manufactures or imports medicinal products should set up a mechanism to ensure that all information supplied about a medicinal product conforms with the approved conditions of use.

(54) In order to ensure the continued safety of medicinal products in use, it is necessary to ensure that pharmacovigilance systems in the Community are continually adapted to take account of scientific and technical progress.

(55) It is necessary to take account of changes arising as a result of international harmonisation of definitions, terminology and technological developments in the field of pharmacovigilance.

(56) The increasing use of electronic networks for communication of information on adverse reactions to medicinal products marketed in the Community is intended to allow competent authorities to share the information at the same time.

(57) It is the interest of the Community to ensure that the pharmacovigilance systems for centrally authorised medicinal products and those authorised by other procedures are consistent.

(58) Holders of marketing authorisations should be proactively responsible for on-going pharmacovigilance of the medicinal products they place on the market.

(59) The measures necessary for the implementation of this Directive should be adopted in accordance with Council Decision 1999/468/EC of 28 June 1999 laying down the procedures for the exercise of implementing powers conferred on the Commission¹⁹.

(60) The Commission should be empowered to adopt any necessary changes to Annex I in order to take into account scientific and technical progress.

¹⁹ OJ L 184, 17.7.1999, p. 23.

(61) This Directive should be without prejudice to the obligations of the Member States concerning the time-limits for transposition of the Directives set out in Annex II, Part B.

Whereas of Directive 2002/98/EC:

(3) *The quality, safety, and efficacy requirements of proprietary industrially-prepared medicinal products derived from human blood or plasma were ensured through Directive 2001/83/EC of the European Parliament and of the Council of 6 November 2001 on the Community code relating to medicinal products for human use. The specific exclusion of whole blood, plasma and blood cells of human origin from that Directive, however, has led to a situation whereby their quality and safety, in so far as they are intended for transfusion and not processed as such, are not subject to any binding Community legislation. It is essential, therefore, that whatever the intended purpose, Community provisions should ensure that blood and its components are of comparable quality and safety throughout the blood transfusion chain in all Member States, bearing in mind the freedom of movement of citizens within Community territory. The establishment of high standards of quality and safety, therefore, will help to reassure the public that human blood and blood components which are derived from donations in another Member State nonetheless meet the same requirements as those in their own country.*

(4) *In respect of blood or blood components as a starting material for the manufacture of proprietary medicinal products, Directive 2001/83/EC refers to measures to be taken by Member States to prevent the transmission of infectious diseases, comprising the application of the monographs of the European Pharmacopoeia and the recommendations of the Council of Europe and the World Health Organisation (WHO) as regards in particular the selection and testing of blood and plasma donors. Furthermore, Member States should take measures to promote Community self-sufficiency in human blood or blood components and to encourage voluntary unpaid donations of blood and blood components.*

(5) *In order to ensure that there is an equivalent level of safety and quality of blood components, whatever their intended purpose, technical requirements for the collection and testing of all blood and blood components including starting materials for medicinal products should be established by this Directive. Directive 2001/83/EC should be amended accordingly.*

Whereas of Directive 2004/24/EC:

(1) *Directive 2001/83/EC requires that applications for authorisation to place a medicinal product on the market have to be accompanied by a dossier containing particulars and documents relating in particular to the results of physico-chemical, biological or microbiological tests as well as pharmacological and toxicological tests and clinical trials carried out on the product and thus proving its quality, safety and efficacy.*

(2) *Where the applicant can demonstrate by detailed references to published scientific literature that the constituent or the constituents of the medicinal product has or have a well-established medicinal use with recognised efficacy and an acceptable level of safety within the meaning of Directive 2001/83/EC, he/she should not be required to provide the results of pre-clinical tests or the results of clinical trials.*

(3) *A significant number of medicinal products, despite their long tradition, do not fulfil the requirements of a well-established medicinal use with recognised efficacy and an acceptable level of safety and are not eligible for a marketing authorisation. To maintain these products on the market, the Member States have enacted differing procedures and provisions. The differences that currently exist between the provisions laid down in the Member States may hinder trade in traditional medicinal products within the Community and lead to discrimination and distortion of competition between manufacturers of these products. They may also have an impact on the protection of public health since the necessary guarantees of quality, safety and efficacy are not always provided at present.*

(4) Having regard to the particular characteristics of these medicinal products, especially their long tradition, it is desirable to provide a special, simplified registration procedure for certain traditional medicinal products. However, this simplified procedure should be used only where no marketing authorisation can be obtained pursuant to Directive 2001/83/EC, in particular because of a lack of sufficient scientific literature demonstrating a well-established medicinal use with recognised efficacy and an acceptable level of safety. It should likewise not apply to homeopathic medicinal products eligible for marketing authorisation or for registration under Directive 2001/83/EC.

(5) The long tradition of the medicinal product makes it possible to reduce the need for clinical trials, in so far as the efficacy of the medicinal product is plausible on the basis of long-standing use and experience. Pre-clinical tests do not seem necessary, where the medicinal product on the basis of the information on its traditional use proves not to be harmful in specified conditions of use. However, even a long tradition does not exclude the possibility that there may be concerns with regard to the product's safety, and therefore the competent authorities should be entitled to ask for all data necessary for assessing the safety. The quality aspect of the medicinal product is independent of its traditional use so that no derogation should be made with regard to the necessary physico-chemical, biological and microbiological tests. Products should comply with quality standards in relevant European Pharmacopoeia monographs or those in the pharmacopoeia of a Member State.

(6) The vast majority of medicinal products with a sufficiently long and coherent tradition are based on herbal substances. It therefore seems appropriate to limit the scope of the simplified registration in a first step to traditional herbal medicinal products.

(7) The simplified registration should be acceptable only where the herbal medicinal product may rely on a sufficiently long medicinal use in the Community. Medicinal use outside the

Community should be taken into account only if the medicinal product has been used within the Community for a certain time. Where there is limited evidence of use within the Community, it is necessary to assess carefully the validity and relevance of use outside the Community.

(8) With the objective of further facilitating the registration of certain traditional herbal medicinal products and of further enhancing harmonisation, there should be the possibility of establishing a Community list of herbal substances that fulfil certain criteria, such as having been in medicinal use for a sufficiently long time, and hence are considered not to be harmful under normal conditions of use.

(9) Having regard to the particularities of herbal medicinal products, a Committee for Herbal Medicinal Products should be established within the European Agency for the Evaluation of Medicinal Products (hereinafter 'the Agency') set up by Council Regulation (EEC) No 2309/93²⁰. The Committee should carry out tasks concerning the simplified registration and authorisation of medicinal products as provided for in this Directive. Its tasks should relate in particular to establishing Community herbal monographs relevant for the registration as well as the authorisation of herbal medicinal products. It should be composed of experts in the field of herbal medicinal products.

(10) It is important to ensure full consistency between the new Committee and the Committee for Human Medicinal Products already existing within the Agency.

(11) In order to promote harmonisation, Member States should recognise registrations of traditional herbal medicinal products granted by another Member State based on Community herbal monographs or consisting of substances, preparations or combinations thereof contained in a list to be established. For other products, Member States should take due account of such registrations.

²⁰ OJ L 214, 24.8.1993, p. 1 ; Regulation as last amended by Regulation (EC) No 1647/2003, p. 19.

(12) *This Directive allows non-medicinal herbal products, fulfilling the criteria of food legislation, to be regulated under food legislation in the Community.*

(13) *The Commission should present a report on the application of the chapter on traditional herbal medicinal products to the European Parliament and to the Council including an assessment on the possible extension of traditional-use registration to other categories of medicinal products.*

(14) *It is therefore appropriate to amend Directive 2001/83/EC accordingly.*

Whereas of Directive 2004/27/EC:

(1) *Directive 2001/83/EC of the European Parliament and of the Council of 6 November 2001 on the Community code relating to medicinal products for human use, codified and consolidated in a single text the texts of Community legislation on medicinal products for human use, in the interests of clarity and rationalisation.*

(2) *The Community legislation so far adopted has made a major contribution to the achievement of the objective of the free and safe 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, it has become clear that new measures are 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 while realising a high level of human health protection.*

(4) *The main purpose of any regulation on the manufacture 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 Products²¹ provided that, within six years of its entry into force, the Commission was 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. This definition should specify the type of action that the medicinal product may exert on physiological functions. This enumeration of actions will also make it possible to cover medicinal products such as gene therapy, radiopharmaceutical products as well as certain medicinal products for topical use. Also, in view of the characteristics of pharmaceutical legislation, provision should be made for such*

²¹ OJ L 214, 21.8.1993, p. 1. Regulation repealed by Regulation (EC) No 726/2004 (see p. 1 of this Official Journal).

legislation to apply. With the same objective of clarifying situations, where a given product comes under the definition of a medicinal product but could also fall within the definition of other regulated products, it is necessary, in case of doubt and in order to ensure legal certainty, to state explicitly which provisions have to be complied with. Where a product comes clearly under the definition of other product categories, in particular food, food supplements, medical devices, biocides or cosmetics, this Directive should not apply. It is also appropriate 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 procedure or the decentralised procedure in respect of orphan medicinal products and medicinal products which contain new active substances and for which the therapeutic indication is the treatment of acquired immune deficiency syndrome, cancer, neurodegenerative disorder or diabetes. Four years after the date of entry into force of Regulation (EC) No 726/2004, it should no longer be possible to opt for the mutual-recognition procedure or the decentralised procedure in respect of medicinal products which contain new active substances and for which the therapeutic indication is the treatment of auto-immune diseases and other immune dysfunctions and viral diseases.

(9) On the other hand, in the case of generic medicinal products of which the reference medicinal product has been granted 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.

(10) In order to increase availability of medicinal products, in particular on smaller markets, it should, in cases where an applicant does not apply for an authorisation for a

medicinal product in the context of the mutual-recognition procedure in a given Member State, be possible for that Member State, for justified public health reasons, to authorise the placing on the market of the medicinal product.

(11) Evaluation of the operation of marketing authorisation procedures has revealed the need to revise, in particular, 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.

(12) 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.

(13) There is a need to provide for the ethical requirements of Directive 2001/20/EC of the European Parliament and the Council of 4 April 2001 on the approximation of the laws, regulations and administrative provisions of the Member States relating to the implementation of good clinical practice in the conduct of clinical trials on medicinal products for human use²² to apply to all medicinal products authorised within the Community. In particular, with respect to clinical trials conducted outside the Community on medicinal products destined to be authorised within the Community, it should be verified, at the time of the evaluation of the application for authorisation, that these trials were conducted in accordance with the principles of good clinical practice and the ethical requirements equivalent to the provisions of that Directive.

(14) 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. Furthermore, the period for protection

²² OJ L 121, 1.5.2001, p. 34.

of data relating to pre-clinical tests and clinical trials should be harmonised.

(15) Biological medicinal products similar to a reference medicinal product do not usually meet all the conditions to be considered as a generic medicinal product mainly due to manufacturing process characteristics, raw materials used, molecular characteristics and therapeutic modes of action. When a biological medicinal product does not meet all the conditions to be considered as a generic medicinal product, the results of appropriate tests should be provided in order to fulfil the requirements related to safety (pre-clinical tests) or to efficacy (clinical tests) or to both.

(16) 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 at any other time the competent authority deems this appropriate. In this connection, it is necessary to harmonise and adapt the criteria for refusal, suspension and revocation of marketing authorisations.

(17) A marketing authorisation should be renewed once five years after the granting of the marketing authorisation. Thereafter, the marketing authorisation should normally be of unlimited validity. Furthermore, any authorisation not used for three consecutive years, that is to say one which has not led to the placing on the market of a medicinal product in the Member States concerned during that period, should be considered invalid, in order, in particular, to avoid the administrative burden of maintaining such authorisations. However, exemptions from this rule should be granted when these are justified on public health grounds.

(18) The environmental impact should be assessed and, on a case-by-case basis, specific arrangements to limit it should be envisaged. In any event this impact should not constitute a criterion for refusal of a marketing authorisation.

(19) The quality of medicinal products for human use manufactured 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.

(20) 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.

(21) As part of the proper use of medicinal products, the rules on packaging should be adapted to take account of the experience acquired.

(22) The measures necessary for the implementation of this Directive should be adopted in accordance with Council Decision 1999/468/EC of 28 June 1999 laying down the procedures for the exercise of implementing powers conferred on the Commission²³.

(23) Directive 2001/83/EC should be amended accordingly,

HAVE ADOPTED THIS DIRECTIVE:

TITLE 1

DEFINITIONS

Article 1

For the purposes of this Directive, the following terms shall bear the following meanings:

1. (point deleted)

²³ OJ L 184, 17.7.1999, p. 23.

2. Medicinal product:

(a) Any substance or combination of substances presented as having properties for treating or preventing disease in human beings; or

(b) Any substance or combination of substances which may be used in or administered to human beings either with a view to restoring, correcting or modifying physiological functions by exerting a pharmacological, immunological or metabolic action, or to making a medical diagnosis.

3. Substance:

Any matter irrespective of origin which may be:

- human, e.g.
human blood and human blood products;
- animal, e.g.
micro-organisms, whole animals, parts of organs, animal secretions, toxins, extracts, blood products;
- vegetable, e.g.
micro-organisms, plants, parts of plants, vegetable secretions, extracts;
- chemical, e.g.
elements, naturally occurring chemical materials and chemical products obtained by chemical change or synthesis.

4. Immunological medicinal product:

Any medicinal product consisting of vaccines, toxins, serums or allergen products:

(a) vaccines, toxins and serums shall cover in particular:

(i) agents used to produce active immunity, such as cholera vaccine, BCG, polio vaccines, smallpox vaccine;

(ii) agents used to diagnose the state of immunity, including in particular

tuberculin and tuberculin PPD, toxins for the Schick and Dick Tests, brucellin;

(iii) agents used to produce passive immunity, such as diphtheria antitoxin, anti-smallpox globulin, antilymphocytic globulin;

(b) 'allergen product' shall mean any medicinal product which is intended to identify or induce a specific acquired alteration in the immunological response to an allergizing agent.

5. Homeopathic medicinal product:

Any medicinal product prepared from substances called homeopathic stocks in accordance with a homeopathic manufacturing procedure described by the European Pharmacopoeia or, in the absence thereof, by the pharmacopoeias currently used officially in the Member States. A homeopathic medicinal product may contain a number of principles.

6. Radiopharmaceutical:

Any medicinal product which, when ready for use, contains one or more radionuclides (radioactive isotopes) included for a medicinal purpose.

7. Radionuclide generator:

Any system incorporating a fixed parent radionuclide from which is produced a daughter radionuclide which is to be obtained by elution or by any other method and used in a radiopharmaceutical.

8. Kit

Any preparation to be reconstituted or combined with radionuclides in the final radiopharmaceutical, usually prior to its administration.

9. *Radionuclide precursor:*

Any other radionuclide produced for the radiolabelling of another substance prior to administration.

10. *Medicinal products derived from human blood or human plasma:*

Medicinal products based on blood constituents which are prepared industrially by public or private establishments, such medicinal products including, in particular, albumin, coagulating factors and immunoglobulins of human origin.

11. *Adverse reaction:*

A response to a medicinal product which is noxious and unintended and which occurs at doses normally used in man for the prophylaxis, diagnosis or therapy of disease or for the restoration, correction or modification of physiological function.

12. *Serious adverse reaction:*

An adverse reaction which results in death, is life-threatening, requires inpatient hospitalisation or prolongation of existing hospitalisation, results in persistent or significant disability or incapacity, or is a congenital anomaly/birth defect.

13. *Unexpected adverse reaction:*

An adverse reaction, the nature, severity or outcome of which is not consistent with the summary of product characteristics.

14. *Periodic safety update reports:*

The periodical reports containing the records referred to in Article 104.

15. *Post-authorisation safety study:*

A pharmacoepidemiological study or a clinical trial carried out in accordance with the terms of the marketing authorisation, conducted with the aim of identifying or quantifying a safety hazard relating to an authorised medicinal product.

16. *Abuse of medicinal products:*

Persistent or sporadic, intentional excessive use of medicinal products which is accompanied by harmful physical or psychological effects.

17. *Wholesale distribution of medicinal products:*

All activities consisting of procuring, holding, supplying or exporting medicinal products, apart from supplying medicinal products to the public. Such activities are carried out with manufacturers or their depositories, importers, other wholesale distributors or with pharmacists and persons authorized or entitled to supply medicinal products to the public in the Member State concerned.

18. *Public service obligation:*

The obligation placed on wholesalers to guarantee permanently an adequate range of medicinal products to meet the requirements of a specific geographical area and to deliver the supplies requested within a very short time over the whole of the area in question.

18a. *Representative of the marketing authorisation holder:*

The person, commonly known as local representative, designated by the marketing authorisation holder to represent him in the Member State concerned.

19. *Medicinal Prescription:*

Any medicinal prescription issued by a professional person qualified to do so.

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.

21. *Common name:*

The international non-proprietary name recommended by the World Health Organization, or, if one does not exist, the usual common name.

22. *Strength of the medicinal product:*

The content of the active substances expressed quantitatively per dosage unit, per unit of volume or weight according to the dosage form.

23. *Immediate packaging:*

The container or other form of packaging immediately in contact with the medicinal product.

24. *Outer packaging:*

The packaging into which is placed the immediate packaging.

25. *Labelling:*

Information on the immediate or outer packaging.

26. *Package leaflet:*

A leaflet containing information for the user which accompanies the medicinal product.

27. *Agency:*

The European Medicines Agency established by Regulation (EC) No 726/2004²⁴.

28. *Risks related to use of the medicinal product:*

- any risk relating to the quality, safety or efficacy of the medicinal product as regards patients' health or public health;
- any risk of undesirable effects on the environment.

28a. *Risk-benefit balance:*

An evaluation of the positive therapeutic effects of the medicinal product in relation to the risks as defined in point 28, first indent.

29. *Traditional herbal medicinal product:*

A herbal medicinal product that fulfils the conditions laid down in Article 16a(1).

30. *Herbal medicinal product:*

Any medicinal product, exclusively containing as active ingredients one or more herbal substances or one or more herbal preparations, or one or more such herbal substances in combination with one or more such herbal preparations.

31. *Herbal substances:*

All mainly whole, fragmented or cut plants, plant parts, algae, fungi, lichen in an unprocessed, usually dried, form, but sometimes fresh. Certain exudates that have not been subjected to a specific treatment are also considered to be herbal substances. Herbal substances are precisely defined by the plant part used and the botanical name according to the binomial system (genus, species, variety and author).

32. *Herbal preparations:*

Preparations obtained by subjecting herbal substances to treatments such as extraction, distillation, expression, fractionation, purification, concentration or fermentation. These include comminuted or powdered herbal substances, tinctures, extracts, essential oils, expressed juices and processed exudates.

TITLE II

SCOPE

Article 2

1. This Directive shall apply to medicinal products for human use intended to be placed on

²⁴ OJ L 136, 30.4.2004, p. 1.

the market in Member States and either prepared industrially or manufactured by a method involving an industrial process.

2. In cases of doubt, where, taking into account all its characteristics, a product may fall within the definition of a “medicinal product” and within the definition of a product covered by other Community legislation the provisions of this Directive shall apply.

3. Notwithstanding paragraph 1 and Article 3(4), Title IV of this Directive shall apply to medicinal products intended only for export and to intermediate products.

Article 3

This Directive shall not apply to:

1. Any medicinal product prepared in a pharmacy in accordance with a medical prescription for an individual patient (commonly known as the magistral formula).

2. Any medicinal product which is prepared in a pharmacy in accordance with the prescriptions of a pharmacopoeia and is intended to be supplied directly to the patients served by the pharmacy in question (commonly known as the officinal formula).

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 of 4 April 2001 on the approximation of the laws, regulations and administrative provisions of the Member States relating to the implementation of good clinical practice in the conduct of clinical trials on medicinal products for human use²⁵.

4. Intermediate products intended for further processing by an authorized manufacturer.

5. Any radionuclides in the form of sealed sources.

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

Article 4

1. Nothing in this Directive shall in any way derogate from the Community rules for the radiation protection of persons undergoing medical examination or treatment, or from the Community rules laying down the basic safety standards for the health protection of the general public and workers against the dangers of ionizing radiation.

2. This Directive shall be without prejudice to Council Decision 86/346/EEC of 25 June 1986 accepting on behalf of the Community the European Agreement on the Exchange of Therapeutic Substances of Human Origin²⁶.

3. The provisions of this Directive shall not affect the powers of the Member States' authorities either as regards the setting of prices for medicinal products or their inclusion in the scope of national health insurance schemes, on the basis of health, economic and social conditions.

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

Article 5

1. 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 an individual patient under his direct personal responsibility.

²⁵ OJ L 121, 1.5.2001, p. 34.

²⁶ OJ L 207, 30.7.1986, p. 1.

2. Member States may temporarily authorise the distribution of an unauthorised medicinal product in response to the suspected or confirmed spread of pathogenic agents, toxins, chemical agents or nuclear radiation any of which could cause harm.

3. Without prejudice to paragraph 1, Member States shall lay down provisions in order to ensure that marketing authorisation holders, manufacturers and health professionals are not subject to civil or administrative liability for any consequences resulting from the use of a medicinal product otherwise than for the authorised indications or from the use of an unauthorised medicinal product, when such use is recommended or required by a competent authority in response to the suspected or confirmed spread of pathogenic agents, toxins, chemical agents or nuclear radiation any of which could cause harm. Such provisions shall apply whether or not national or Community authorisation has been granted.

4. Liability for defective products, as provided for by Council Directive 85/374/EEC of 25 July 1985 on the approximation of the laws, regulations and administrative provisions of the Member States, concerning liability for defective products²⁷, shall not be affected by paragraph 3.

TITLE III

PLACING ON THE MARKET

CHAPTER I

Marketing authorisation

Article 6

1. No medicinal product may be placed on the market of a Member State unless a marketing authorization has been issued by the competent authorities of that Member State in accordance

²⁷ OJ L 210, 7.8.1985, p. 29. Directive as last amended by Directive 1999/34/EC of the European Parliament and of the Council (OJ L 141, 4.6.1999, p. 20).

with this Directive or an authorization has been granted in accordance with Regulation (EEC) No 2309/93.

When a medicinal product has been granted an initial marketing authorisation in accordance with the first subparagraph, any additional strengths, pharmaceutical forms, administration routes, presentations, as well as any variations and extensions shall also be granted an authorisation in accordance with the first subparagraph or be included in the initial marketing authorisation. All these marketing authorisations shall be considered as belonging to the same global marketing authorisation, in particular for the purpose of the application of Article 10(1).

1a. The marketing authorisation holder shall be responsible for marketing the medicinal product. The designation of a representative shall not relieve the marketing authorisation holder of his legal responsibility.

2. The authorisation referred to in paragraph 1 shall also be required for radionuclide generators, kits, radionuclide precursor radiopharmaceuticals and industrially prepared radiopharmaceuticals.

Article 7

A marketing authorization shall not be required for a radiopharmaceutical prepared at the time of use by a person or by an establishment authorized, according to national legislation, to use such medicinal products in an approved health care establishment exclusively from authorized radionuclide generators, kits or radionuclide precursors in accordance with the manufacturer's instructions.

Article 8

1. In order to obtain an authorization to place a medicinal product on the market regardless of the procedure established by Regulation (EEC) No 2309/93, an application shall be made to the competent authority of the Member State concerned.

2. A marketing authorization may only be granted to an applicant established in the Community.

3. The application shall be accompanied by the following particulars and documents, submitted in accordance with Annex I:

(a) Name or corporate name and permanent address of the applicant and, where applicable, of the manufacturer.

(b) Name of the medicinal product.

(c) Qualitative and quantitative particulars of all the constituents of the medicinal product, including the reference to its international non-proprietary name (INN) recommended by the WHO, where an INN for the medicinal product exists, or a reference to the relevant chemical name.

(ca) Evaluation of the potential environmental risks posed by the medicinal product. This impact shall be assessed and, on a case-by-case basis, specific arrangements to limit it shall be envisaged.

(d) Description of the manufacturing method.

(e) Therapeutic indications, contra-indications and adverse reactions.

(f) Posology, pharmaceutical form, method and route of administration and expected shelf life.

(g) Reasons for any precautionary and safety measures to be taken for the storage of the medicinal product, its administration to patients and for the disposal of waste products, together with an indication of potential risks presented by the medicinal product for the environment.

(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.

(ia) A detailed description of the pharmacovigilance and, where appropriate, of the risk-management system which the applicant will introduce.

(ib) A statement to the effect that clinical trials carried out outside the European Union meets the ethical requirements of Directive 2001/20/EC.

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

(k) A document showing that the manufacturer is authorised in his own country to produce medicinal products.

(l) Copies of any authorisation obtained in another Member State or in a third country to place the medicinal product on the market, together with a list of those Member States in which an application for authorisation submitted in accordance with this Directive is under examination. Copies of the summary of the product characteristics proposed by the applicant in accordance with Article 11 or approved by the competent authorities of the Member State in accordance with Article 21. Copies of the package leaflet proposed in accordance with Article 59 or

approved by the competent authorities of the Member State in accordance with Article 61. Details of any decision to refuse authorization, whether in the Community or in a third country, and the reasons for such a decision.

This information shall be updated on a regular basis.

(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 of 16 December 1999 on orphan medicinal products²⁸, accompanied by a copy of the relevant Agency opinion.

(n) Proof that the applicant has the services of a qualified person responsible for pharmacovigilance and has the necessary means for the notification of any adverse reaction suspected of occurring either in the Community or in a third country.

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 Article 12.

Article 9

In addition to the requirements set out in Articles 8 and 10(1), an application for authorization to market a radionuclide generator shall also contain the following information and particulars:

- a general description of the system together with a detailed description of the components of the system which may affect the composition or quality of the daughter nucleid preparation,

- qualitative and quantitative particulars of the eluate or the sublimate.

²⁸ OJ L 18, 22.1.2000, p. 1.

Article 10

1. By way of derogation from Article 8(3)(i), 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 of clinical trials if he can demonstrate that the medicinal product is a generic of a reference medicinal product which is or has been authorised under Article 6 for not less than eight years in a Member State or in the Community.

A generic medicinal product authorised pursuant to this provision shall not be placed on the market until ten years have elapsed from the initial authorisation of the reference product.

The first subparagraph shall also apply if the reference medicinal product was not authorised in the Member State in which the application for the generic medicinal product is submitted. In this case, the applicant shall indicate in the application form the name of the Member State in which the reference medicinal product is or has been authorised. At the request of the competent authority of the Member State in which the application is submitted, the competent authority of the other Member State shall transmit within a period of one month, a confirmation that the reference medicinal product is or has been authorised together with the full composition of the reference product and if necessary other relevant documentation.

The ten-year period referred to in the second subparagraph shall be extended to a maximum of eleven 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 substances and the same pharmaceutical form as the reference medicinal product, and whose bioequivalence with the reference medicinal product has been demonstrated by appropriate bioavailability studies. The different salts, esters, ethers, isomers, mixtures of isomers, complexes or derivatives of an active substance shall be considered to be the same active substance, unless they differ significantly in properties with regard to safety and/or efficacy. In such cases, additional information providing proof of the safety and/or efficacy of the various salts, esters, or derivatives of an authorised active substance must be supplied by the applicant. The various immediate-release oral pharmaceutical forms shall be considered to be one and the same pharmaceutical form. Bioavailability studies need not be required of the applicant if he can demonstrate that the generic medicinal product meets the relevant criteria as defined in the appropriate detailed guidelines.

3. In cases where the medicinal product does not fall within the definition of a generic medicinal product as provided in paragraph 2(b) or where the bioequivalence cannot be demonstrated through bioavailability studies or in case of changes in the active substance(s), therapeutic indications, strength, pharmaceutical form or route of administration, vis-à-vis the reference medicinal product, the results of the appropriate pre-clinical tests or clinical trials shall be provided.

4. Where a biological medicinal product which is similar to a reference biological product does not meet the conditions in the definition of generic medicinal products, owing to, in particular, differences relating to raw materials or differences in manufacturing processes of the biological medicinal product and the reference biological medicinal product, the results of appropriate pre-clinical tests or clinical trials relating to these conditions must be provided. The type and quantity of supplementary data to be provided must comply with the relevant criteria stated in the Annex and the related

detailed guidelines. The results of other tests and trials from the reference medicinal product's dossier shall not be provided.

5. In addition to the provisions laid down in paragraph 1, where an application is made for a new indication for a well-established substance, a non-cumulative period of one year of data exclusivity shall be granted, provided that significant pre-clinical or clinical studies were carried out in relation to the new indication.

6. Conducting the necessary studies and trials with a view to the application of paragraphs 1, 2, 3 and 4 and the consequential practical requirements shall not be regarded as contrary to patent rights or to supplementary protection certificates for medicinal products.

Article 10a

By way of derogation from Article 8(3)(i), 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 clinical trials if he can demonstrate that the active substances of the medicinal product have been in well-established medicinal use within the Community for at least ten years, with recognised efficacy and an acceptable level of safety in terms of the conditions set out in the Annex. In that event, the test and trial results shall be replaced by appropriate scientific literature.

Article 10b

In the case of 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 new pre-clinical tests or new clinical trials relating to that combination shall be provided in accordance with Article 8(3)(i), but it shall not be necessary to provide scientific references relating to each individual active substance.

Article 10c

Following the granting 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.

Article 11

The summary of the product characteristics shall contain, in the order indicated below, the following information:

1. name of the medicinal product followed by the strength and the pharmaceutical form.
2. qualitative and quantitative composition in terms of the active substances and constituents of the excipient, knowledge of which is essential for proper administration of the medicinal product. The usual common name or chemical description shall be used.
3. pharmaceutical form.
4. clinical particulars:
 - 4.1. therapeutic indications,
 - 4.2. posology and method of administration for adults and, where necessary for children,
 - 4.3. contra-indications,
 - 4.4. special warnings and precautions for use and, in the case of immunological medicinal products, any special precautions to be taken by persons handling such products and administering them to patients, together with any precautions to be taken by the patient,

- 4.5. interaction with other medicinal products and other forms of interactions,
- 4.6. use during pregnancy and lactation,
- 4.7. effects on ability to drive and to use machines,
- 4.8. undesirable effects,
- 4.9. overdose (symptoms, emergency procedures, antidotes).

5. pharmacological properties:

- 5.1. pharmacodynamic properties,
- 5.2. pharmacokinetic properties,
- 5.3. preclinical safety data.

6. pharmaceutical particulars:

- 6.1. list of excipients,
- 6.2. major incompatibilities,
- 6.3. shelf life, when necessary after reconstitution of the medicinal product or when the immediate packaging is opened for the first time,
- 6.4. special precautions for storage,
- 6.5. nature and contents of container,
- 6.6. special precautions for disposal of a used medicinal product or waste materials derived from such medicinal product, if appropriate.

7. marketing authorisation holder.

8. marketing authorisation number(s).

9. date of the first authorisation or renewal of the authorisation.

10. date of revision of the text.

11. for radiopharmaceuticals, full details of internal radiation dosimetry.

12. for radiopharmaceuticals, additional detailed instructions for extemporaneous preparation and quality control of such preparation and, where appropriate, maximum storage time during which any intermediate preparation such as an eluate or the ready-to-use pharmaceutical will conform with its specifications.

For authorisations under Article 10, those parts of the summary of product characteristics of the reference medicinal product referring to indications or dosage forms which were still covered by patent law at the time when a generic medicine was marketed need not be included.

Article 12

1. The applicant shall ensure that, before the detailed summaries referred to in the last subparagraph 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 shall 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 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.

CHAPTER 2

Specific provisions applicable to homeopathic medicinal products

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 granted in accordance with national legislation on or before 31 December 1993. In case of registrations, Article 28 and Article 29(1) to (3) shall apply.

2. Member States shall establish a special simplified registration procedure for the homeopathic medicinal products referred to in Article 14.

Article 14

1. Only homeopathic medicinal products which satisfy all of the following conditions may be subject to a special, simplified registration procedure:

- they are administered orally or externally,

- no specific therapeutic indication appears on the labelling of the medicinal product or in any information relating thereto,

- there is a sufficient degree of dilution to guarantee the safety of the medicinal product; in particular, the medicinal product may not contain either more than one part per 10 000 of the mother tincture or more than 1/100th of the smallest dose used in allopathy with regard to active substances whose presence in an allopathic medicinal product results in the obligation to submit a doctor's prescription.

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).

At the time of registration, Member States shall determine the classification for the dispensing of the medicinal product.

2. The criteria and rules of procedure provided for in Article 4(4), Article 17(1) and Articles 22 to 26, 112, 116 and 125 shall apply by analogy to the special, simplified registration procedure for homeopathic medicinal products, with the exception of the proof of therapeutic efficacy.

Article 15

An application for special, simplified registration may cover a series of medicinal products derived from the same homeopathic stock or stocks. The following documents shall be included with the application in order to demonstrate, in particular, the pharmaceutical quality and the batch-to-batch homogeneity of the products concerned:

- scientific name or other name given in a pharmacopoeia of the homeopathic stock or stocks, together with a statement of the various routes of administration, pharmaceutical forms and degree of dilution to be registered,
- dossier describing how the homeopathic stock or stocks is/are obtained and controlled, and justifying its/their homeopathic use, on the basis of an adequate bibliography,
- manufacturing and control file for each pharmaceutical form and a description of the method of dilution and potentization,
- manufacturing authorization for the medicinal product concerned,
- copies of any registrations or authorizations obtained for the same medicinal product in other Member States,
- one or more mock-ups of the outer packaging and the immediate packaging of the medicinal products to be registered,
- data concerning the stability of the medicinal product.

Article 16

1. Homeopathic medicinal products other than those referred to in Article 14(1) shall be authorized and labelled in accordance with Articles 8, 10, 10a, 10b, 10c and 11.

2. A Member State may introduce or retain in its territory specific rules for the pre-clinical tests and clinical trials of homeopathic medicinal products other than those referred to in Article 14(1) in accordance with the principles and

characteristics of homeopathy as practised in that Member State.

In this case, the Member State concerned shall notify the Commission of the specific rules in force.

3. Title IX shall apply to homeopathic medicinal products, with the exception of those referred to in Article 14(1).

CHAPTER 2a

Specific provisions applicable to traditional herbal medicinal products

Article 16a

1. A simplified registration procedure (hereinafter “traditional- use registration”) is hereby established for herbal medicinal products which fulfil all of the following criteria:

- (a) they have indications exclusively appropriate to traditional herbal medicinal products which, by virtue of their composition and purpose, are intended and designed for use without the supervision of a medical practitioner for diagnostic purposes or for prescription or monitoring of treatment;
- (b) they are exclusively for administration in accordance with a specified strength and posology;
- (c) they are an oral, external and/or inhalation preparation;
- (d) the period of traditional use as laid down in Article 16c(1)(c) has elapsed;
- (e) the data on the traditional use of the medicinal product are sufficient; in particular the product proves not to be harmful in the specified conditions of use and the pharmacological effects or efficacy of the medicinal product are plausible on the basis of long-standing use and experience.

2. Notwithstanding Article 1(30), the presence in the herbal medicinal product of vitamins or minerals for the safety of which there is well-documented evidence shall not prevent the product from being eligible for registration in accordance with paragraph 1, provided that the action of the vitamins or minerals is ancillary to that of the herbal active ingredients regarding the specified claimed indication(s).

3. However, in cases where the competent authorities judge that a traditional herbal medicinal product fulfils the criteria for authorisation in accordance with Article 6 or registration pursuant to Article 14, the provisions of this chapter shall not apply.

Article 16b

1. The applicant and registration holder shall be established in the Community.

2. In order to obtain traditional-use registration, the applicant shall submit an application to the competent authority of the Member State concerned.

Article 16c

1. The application shall be accompanied by:

(a) the particulars and documents:

(i) referred to in Article 8(3)(a) to (h), (j) and (k);

(ii) the results of the pharmaceutical tests referred to in the second indent of Article 8(3)(i);

(iii) the summary of product characteristics, without the data specified in Article 11(4);

(iv) in case of combinations, as referred to in Article 1(30) or Article 16a(2), the information referred to in Article 16a(1)(e) relating to the combination as such; if the individual active ingredients are not sufficiently known, the data shall

also relate to the individual active ingredients;

(b) any authorisation or registration obtained by the applicant in another Member State, or in a third country, to place the medicinal product on the market, and details of any decision to refuse to grant an authorisation or registration, whether in the Community or a third country, and the reasons for any such decision;

(c) bibliographical or expert evidence to the effect that the medicinal product in question, or a corresponding product has been in medicinal use throughout a period of at least 30 years preceding the date of the application, including at least 15 years within the Community. At the request of the Member State where the application for traditional-use registration has been submitted, the Committee for Herbal Medicinal Products shall draw up an opinion on the adequacy of the evidence of the long-standing use of the product, or of the corresponding product. The Member State shall submit relevant documentation supporting the referral;

(d) a bibliographic review of safety data together with an expert report, and where required by the competent authority, upon additional request, data necessary for assessing the safety of the medicinal product.

Annex I shall apply by analogy to the particulars and documents specified in point (a).

2. A corresponding product, as referred to in paragraph 1(c), is characterised by having the same active ingredients, irrespective of the excipients used, the same or similar intended purpose, equivalent strength and posology and the same or similar route of administration as the medicinal product applied for.

3. The requirement to show medicinal use throughout the period of 30 years, referred to in paragraph 1(c), is satisfied even where the marketing of the product has not been based on a specific authorisation. It is likewise satisfied if the number or quantity of ingredients of the

medicinal product has been reduced during that period.

4. Where the product has been used in the Community for less than 15 years, but is otherwise eligible for simplified registration, the Member State where the application for traditional-use registration has been submitted shall refer the product to the Committee for Herbal Medicinal Products. The Member State shall submit relevant documentation supporting the referral.

The Committee shall consider whether the other criteria for a simplified registration as referred to in Article 16a are fully complied with. If the Committee considers it possible, it shall establish a Community herbal monograph as referred to in Article 16h(3) which shall be taken into account by the Member State when taking its final decision.

Article 16d

1. Without prejudice to Article 16h(1), Chapter 4 of Title III shall apply by analogy to registrations granted in accordance with Article 16a, provided that:

(a) a Community herbal monograph has been established in accordance with Article 16h(3), or

(b) the herbal medicinal product consists of herbal substances, preparations or combinations thereof contained in the list referred to in Article 16f.

2. For other herbal medicinal products as referred to in Article 16a, each Member State shall, when evaluating an application for traditional-use registration, take due account of registrations granted by another Member State in accordance with this chapter.

Article 16e

1. Traditional-use registration shall be refused if the application does not comply with Articles 16a, 16b or 16c or if at least one of the following conditions is fulfilled:

(a) the qualitative and/or quantitative composition is not as declared;

(b) the indications do not comply with the conditions laid down in Article 16a;

(c) the product could be harmful under normal conditions of use;

(d) the data on traditional use are insufficient, especially if pharmacological effects or efficacy are not plausible on the basis of long-standing use and experience;

(e) the pharmaceutical quality is not satisfactorily demonstrated.

2. The competent authorities of the Member States shall notify the applicant, the Commission and any competent authority that requests it, of any decision they take to refuse traditional-use registration and the reasons for the refusal.

Article 16f

1. A list of herbal substances, preparations and combinations thereof for use in traditional herbal medicinal products shall be established in accordance with the procedure referred to in Article 121(2). The list shall contain, with regard to each herbal substance, the indication, the specified strength and the posology, the route of administration and any other information necessary for the safe use of the herbal substance as a traditional medicinal product.

2. If an application for traditional-use registration relates to a herbal substance, preparation or a combination thereof contained in the list referred to in paragraph 1, the data specified in Article 16c(1)(b)(c) and (d) do not need to be provided. Article 16e(1)(c) and (d) shall not apply.

3. If a herbal substance, preparation or a combination thereof ceases to be included in the list referred to in paragraph 1, registrations pursuant to paragraph 2 for herbal medicinal products containing this substance shall be revoked unless the particulars and documents

referred to in Article 16c(1) are submitted within three months.

Article 16g

1. Articles 3(1) and (2), 4(4), 6(1), 12, 17(1), 19, 20, 23, 24, 25, 40 to 52, 70 to 85, 101 to 108, 111(1) and (3), 112, 116 to 118, 122, 123, 125, 126, second subparagraph, and 127 of this Directive as well as Commission Directive 91/356/EEC²⁹ shall apply, by analogy, to traditional-use registration granted under this chapter.

2. In addition to the requirements of Articles 54 to 65, any labelling and user package leaflet shall contain a statement to the effect that:

(a) the product is a traditional herbal medicinal product for use in specified indication(s) exclusively based upon long-standing use; and

(b) the user should consult a doctor or a qualified health care practitioner if the symptoms persist during the use of the medicinal product or if adverse effects not mentioned in the package leaflet occur.

A Member State may require that the labelling and the user package leaflet shall also state the nature of the tradition in question.

3. In addition to the requirements of Articles 86 to 99, any advertisement for a medicinal product registered under this chapter shall contain the following statement: Traditional herbal medicinal product for use in specified indication(s) exclusively based upon long-standing use.

Article 16h

1. A Committee for Herbal Medicinal Products is hereby established. That Committee shall be part of the Agency and shall have the following competence:

(a) as regards simplified registrations, to:

- perform the tasks arising from Article 16c(1) and (4),

- perform the tasks arising from Article 16d,

- prepare a draft list of herbal substances, preparations and combinations thereof, as referred to in Article 16f(1), and

- establish Community monographs for traditional herbal medicinal products, as referred to in paragraph 3 of this Article;

(b) as regards authorisations of herbal medicinal products, to establish Community herbal monographs for herbal medicinal products, as referred to in paragraph 3 of this Article;

(c) as regards referrals to the Agency under Chapter 4 of Title III, in relation to herbal medicinal products as referred to in Article 16a, to perform the tasks set out in Article 32;

(d) where other medicinal products containing herbal substances are referred to the Agency under Chapter 4 of Title III, to give an opinion on the herbal substance where appropriate.

Finally, the Committee for Herbal Medicinal Products shall perform any other task conferred upon it by Community law.

The appropriate coordination with the Committee for Human Medicinal Products shall be ensured by a procedure to be determined by the Executive Director of the Agency in accordance with Article 57(2) of Regulation (EEC) No 2309/93.

2. Each Member State shall appoint, for a three-year term which may be renewed, one member and one alternate to the Committee for Herbal Medicinal Products.

The alternates shall represent and vote for the members in their absence. Members and alternates shall be chosen for their role and experience in the evaluation of herbal medicinal products and shall represent the competent national authorities.

²⁹ OJ L 193, 17.7.1991, p. 30.

Article 16i

The said Committee may co-opt a maximum of five additional members chosen on the basis of their specific scientific competence. These members shall be appointed for a term of three years, which may be renewed, and shall not have alternates.

With a view to the co-opting of such members, the said Committee shall identify the specific complementary scientific competence of the additional member(s). Co-opted members shall be chosen among experts nominated by Member States or the Agency.

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

3. The Committee for Herbal Medicinal Products shall establish Community herbal monographs for herbal medicinal products with regard to the application of Article 10(1)(a)(ii) as well as traditional herbal medicinal products. The said Committee shall fulfil further responsibilities conferred upon it by provisions of this chapter and other Community law.

When Community herbal monographs within the meaning of this paragraph have been established, they shall be taken into account by the Member States when examining an application. Where no such Community herbal monograph has yet been established, other appropriate monographs, publications or data may be referred to.

When new Community herbal monographs are established, the registration holder shall consider whether it is necessary to modify the registration dossier accordingly. The registration holder shall notify any such modification to the competent authority of the Member State concerned.

The herbal monographs shall be published.

4. The general provisions of Regulation (EEC) No 2309/93 relating to the Committee for Human Medicinal Products shall apply by analogy to the Committee for Herbal Medicinal Products.

Before 30 April 2007, the Commission shall submit a report to the European Parliament and to the Council concerning the application of the provisions of this chapter.

The report shall include an assessment on the possible extension of traditional-use registration to other categories of medicinal products.

CHAPTER 3

Procedures relevant to the marketing authorisation

Article 17

1. Member States shall take all appropriate measures to ensure that the procedure for granting a marketing authorisation for medicinal products is completed within a maximum of 210 days after the submission of a valid application.

Applications for marketing authorisations in two or more Member States in respect of the same medicinal product 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 Articles 27 to 39 apply.

Article 18

Where a Member State is informed in accordance with Article 8(3)(1) 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 was submitted in compliance with Articles 27 to 39.

Article 19

In order to examine the application submitted in accordance with Articles 8, 10, 10a, 10b and 10c, the competent authority of the Member State:

1. must verify whether the particulars submitted in support of the application comply with the said Articles 8, 10, 10a, 10b and 10c and examine whether the conditions for issuing an authorization to place medicinal products on the market (marketing authorization) are complied with.

2. may submit the medicinal product, its starting materials and, if need be, its intermediate products or other constituent materials, for testing by an Official Medicines Control Laboratory or a laboratory that a Member State has designed for that purpose in order to ensure that the control methods employed by the manufacturer and described in the particulars accompanying the application in accordance with Article 8(3)(h) are satisfactory.

3. may, where appropriate, require the applicant to supplement the particulars accompanying the application in respect of the items listed in the Articles 8(3), 10, 10a, 10b and 10c. Where the competent authority avails itself of this option, the time limits laid down in Article 17 shall be suspended until such time as the supplementary information required has been provided. Likewise, these time limits shall be suspended for the time allowed the applicant, where appropriate, for giving oral or written explanation.

Article 20

Member States shall take all appropriate measures to ensure that:

(a) the competent authorities verify that manufacturers and importers of medicinal products coming from third countries are able to carry out manufacture in compliance with the particulars supplied pursuant to Article 8(3)(d), and/or to carry out controls according to the methods described in the particulars

accompanying the application in accordance with Article 8(3)(h);

(b) the competent authorities may allow manufacturers and importers of medicinal products coming from third countries, in justifiable cases, to have certain stages of manufacture and/or certain of the controls referred to in (a) carried out by third parties; in such cases, the verifications by the competent authorities shall also be made in the establishment designated.

Article 21

1. When the marketing authorization is issued, the holder shall be informed, by the competent authorities of the Member State concerned, of the summary of the product characteristics as approved by it.

2. The competent authorities shall take all necessary measures to ensure that the information given in the summary is in conformity with that accepted when the marketing authorization is issued or subsequently.

3. The competent authorities shall make publicly available without delay the marketing authorisation together with the summary of the product characteristics for each medicinal product which they have authorised.

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.

The competent authorities shall make publicly accessible without delay the assessment report, together with the reasons for their opinion, after deletion of any information of a commercially confidential nature. The justification shall be

provided separately for each indication applied for.

Article 22

In exceptional circumstances and following consultation with the applicant, the authorisation may be granted subject to a requirement for the applicant to meet certain conditions, in particular concerning the safety of the medicinal product, notification to the competent authorities of any incident relating to its use, and action to be taken. This authorisation may be granted only for objective, verifiable reasons and must be based on one of the grounds set out in Annex I. Continuation of the authorisation shall be linked to the annual reassessment of these conditions. The list of these conditions shall be made publicly accessible without delay, together with deadlines and dates of fulfilment.

Article 23

After an authorization has been issued, the authorization holder must, in respect of the methods of manufacture and control provided for in Article 8(3)(d) and (h), take account of scientific and technical progress and introduce any changes that may be required to enable the medicinal product to be manufactured and checked by means of generally accepted scientific methods.

These changes shall be subject to the approval of the competent authority of the Member State concerned.

The authorisation holder shall forthwith supply to the competent authority any new information which might entail the amendment of the particulars or documents referred to in Articles 8(3), 10, 10a, 10b and 11, or 32(5), or Annex I.

In particular, he shall forthwith inform the competent authority of any prohibition or restriction imposed by the competent authorities of any country in which the medicinal product for human use is marketed and of any other new information which might influence the evaluation of the benefits and risks of the medicinal product for human use concerned.

In order that the risk-benefit balance may be continuously assessed, the competent authority may at any time ask the holder of the marketing authorisation to forward data demonstrating that the risk-benefit balance remains favourable.

Article 23a

After a marketing authorisation has been granted, the holder of the authorisation shall inform the competent authority of the authorising Member State of the date of actual marketing of the medicinal product for human use in that Member State, taking into account the various presentations authorised.

The holder shall also notify the competent authority if the product ceases to be placed on the market of the Member State, either temporarily or permanently. Such notification shall, otherwise than in exceptional circumstances, be made no less than 2 months before the interruption in the placing on the market of the product.

Upon request by the competent authority, particularly in the context of pharmacovigilance, the marketing authorisation holder shall provide the competent authority with all data relating to the volume of sales of the medicinal product, and any data in his possession relating to the volume of prescriptions.

Article 24

1. Without prejudice to paragraphs 4 and 5, a marketing authorisation shall be valid for five years.

2. The marketing authorisation may be renewed after five years on the basis of a re-evaluation of the risk-benefit balance by the competent authority of the authorising Member State.

To this end, the marketing authorisation holder shall provide the competent authority with a consolidated version of the file in respect of quality, safety and efficacy, including all variations introduced since the marketing authorisation was granted, at least six months

before the marketing authorisation ceases to be valid in accordance with paragraph 1.

3. Once renewed, the marketing authorisation shall be valid for an unlimited period, unless the competent authority decides, on justified grounds relating to pharmacovigilance, to proceed with one additional five-year renewal in accordance with paragraph 2.

4. Any authorisation which within three years of its granting is not followed by the actual placing on the market of the authorised product in the authorising Member State shall cease to be valid.

5. 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 three consecutive years, the authorisation for that product shall cease to be valid.

6. The competent authority may, in exceptional circumstances and on public health grounds grant exemptions from paragraphs 4 and 5. Such exemptions must be duly justified.

Article 25

Authorization shall not affect the civil and criminal liability of the manufacturer and, where applicable, of the marketing authorization holder.

Article 26

1. The marketing authorisation shall be refused if, after verification of the particulars and documents listed in Articles 8, 10, 10a, 10b and 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.

2. Authorisation shall likewise be refused if any particulars or documents submitted in support of the application do not comply with Articles 8, 10, 10a, 10b and 10c.

3. The applicant or the holder of a marketing authorisation shall be responsible for the accuracy of the documents and the data submitted.

CHAPTER 4

Mutual recognition procedure and decentralised procedure

Article 27

1. A coordination group shall be 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 renewable period of three years. 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 has been given by the Commission. These Rules of Procedure shall be made public.

Article 28

1. With a view to the granting 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 Articles 8, 10, 10a, 10b, 10c and 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 in accordance with paragraphs 2 or 3.

2. Where the medicinal product has already received a marketing authorisation at the time of application, the concerned Member States 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 90 days of receipt of a valid application. The assessment report together with the approved summary of product characteristics, labelling and package leaflet shall be sent to the concerned Member States 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 after 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 accordingly. The reference Member State shall record the agreement of all parties, close the procedure and inform the applicant accordingly.

5. Each Member State in which 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 after 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 potential serious 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. Guidelines to be adopted by the Commission shall define a potential serious risk to public health.

3. 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 point of view known orally or in writing. If, within 60 days of the communication of the points of disagreement, the Member States reach an agreement, the reference Member State shall record the agreement, close the procedure and inform the applicant accordingly. Article 28(5) shall apply.

4. If the Member States fail to reach an agreement within the 60-day period laid down in paragraph 3, the Agency shall be immediately informed, with a view to the application of the procedure under Articles 32, 33 and 34. 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.

5. As soon as the applicant is informed that the matter has been referred to the Agency, he shall forthwith forward to the Agency a copy of the information and documents referred to in the first subparagraph of Article 28(1).

6. In the circumstances referred to in paragraph 4, 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 Articles 8, 10, 10a, 10b, 10c and 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 revocation, a Member State, the Commission or the applicant or the marketing authorisation holder may refer the matter to the Committee for Medicinal Products for Human Use, hereinafter referred to as “the Committee”, for the application of the procedure laid down in Articles 32, 33 and 34.

2. In order to promote harmonisation of authorisations for medicinal products authorised in the Community, Member States shall, 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 to the Committee in accordance with paragraph 1.

Article 31

1. The Member States or the Commission or the applicant or the marketing authorisation holder shall, 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 Articles 32, 33 and 34 before any decision is reached on a request for a marketing authorisation or on the suspension or revocation 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 shall appoint one of its members to act as

rappporteur. 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 within a time limit which it shall specify.

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 revoked.

Within 15 days after receipt of the opinion, the applicant or the marketing authorisation holder may notify the Agency in writing of his intention to request a re-examination of the opinion. In

that case, he shall forward to the Agency the detailed grounds for the request within 60 days after receipt of the opinion.

Within 60 days following receipt of the grounds for the request, the Committee shall re-examine its opinion in accordance with the fourth subparagraph of Article 62(1) of Regulation (EC) No 726/2004. The reasons for the conclusion reached shall be annexed to the assessment report referred to in paragraph 5 of this Article.

5. Within 15 days after 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 paragraph 4(c);

(c) details of any recommended conditions or restrictions with regard to the safe and effective use of the medicinal product;

(d) the proposed text of the labelling and leaflet.

Article 33

Within 15 days of the receipt of the opinion, the Commission shall prepare a draft of the decision to be taken in respect of the application, taking into account Community law.

In the event of a draft decision which envisages the granting of marketing authorization, the documents referred to in Article 32(5), second subparagraph shall be annexed.

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

The draft decision shall be forwarded to the Member States and the applicant or the marketing authorisation holder.

Article 34

1. The Commission shall take a final decision in accordance with, and within 15 days after the end of, the procedure referred to in Article 121(3).

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 under 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 have 22 days to forward their written observations on the draft decision to the Commission. However, if a decision has to be taken urgently, a shorter time-limit may be set by the Chairman according to the degree of urgency involved. This time-limit shall not, otherwise than in exceptional circumstances, be shorter than 5 days;

(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 concerned Member States and the reference Member State shall either grant or revoke the 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.

Article 35

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

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

These arrangements shall be adopted by the Commission in the form of an implementing Regulation in accordance with the procedure referred to in Article 121(2).

2. In case of arbitration submitted to the Commission, the procedure laid down in Articles 32, 33 and 34 shall apply by analogy to variations made to marketing authorizations.

Article 36

1. Where a Member State considers that the variation of a marketing authorization which has been granted in accordance with the provisions of this Chapter or its suspension or withdrawal is necessary for the protection of public health, the Member State concerned shall forthwith refer the

matter to the Agency for the application of the procedures laid down in Articles 32, 33 and 34.

2. Without prejudice to the provisions of Article 31, in exceptional cases, where urgent action is essential to protect public health, until a definitive decision is adopted a Member State may suspend the marketing and the use of the medicinal product concerned on its territory. It shall inform the Commission and the other Member States no later than the following working day of the reasons for its action.

Article 37

Articles 35 and 36 shall apply by analogy to medicinal products authorized by Member States following an opinion of the Committee given in accordance with Article 4 of Directive 87/22/EEC before 1 January 1995.

Article 38

1. The Agency shall publish an annual report on the operation of the procedures laid down in this Chapter and shall forward that report to the European Parliament and the Council for information.

2. At least every ten years 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. The Commission shall submit this report to the European Parliament and to the Council.

Article 39

Article 29(4), (5) and (6) and Articles 30 to 34 shall not apply to the homeopathic medicinal products referred to in Article 14.

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

TITLE IV

MANUFACTURE AND IMPORTATION

Article 40

1. Member States shall take all appropriate measures to ensure that the manufacture of the medicinal products within their territory is subject to the holding of an authorization. This manufacturing authorization shall be required notwithstanding that the medicinal products manufactured are intended for export.

2. The authorization referred to in paragraph 1 shall be required for both total and partial manufacture, and for the various processes of dividing up, packaging or presentation.

However, such authorization shall not be required for preparation, dividing up, changes in packaging or presentation where these processes are carried out, solely for retail supply, by pharmacists in dispensing pharmacies or by persons legally authorized in the Member States to carry out such processes.

3. Authorization referred to in paragraph 1 shall also be required for imports coming from third countries into a Member State; this Title and Article 118 shall have corresponding application to such imports as they have to manufacture.

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 Community database referred to in Article 111(6).

Article 41

In order to obtain the manufacturing authorization, the applicant shall meet at least the following requirements:

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

(b) have at his disposal, for the manufacture or import of the above, suitable and sufficient premises, technical equipment and control facilities complying with the legal requirements which the Member State concerned lays down as regards both manufacture and control and the storage of medicinal products, in accordance with Article 20;

(c) have at his disposal the services of at least one qualified person within the meaning of Article 48.

The applicant shall provide particulars in support of the above in his application.

Article 42

1. The competent authority of the Member State shall issue the manufacturing authorization only after having made sure of the accuracy of the particulars supplied pursuant to Article 41, by means of an inquiry carried out by its agents.

2. In order to ensure that the requirements referred to in Article 41 are complied with, authorization may be made conditional on the carrying out of certain obligations imposed either when authorization is granted or at a later date.

3. The authorization shall apply only to the premises specified in the application and to the medicinal products and pharmaceutical forms specified in that same application.

Article 43

The Member States shall take all appropriate measures to ensure that the time taken for the procedure for granting the manufacturing authorization does not exceed 90 days from the day on which the competent authority receives the application.

Article 44

If the holder of the manufacturing authorization requests a change in any of the particulars referred to in points (a) and (b) of the first paragraph of Article 41, the time taken for the

procedure relating to this request shall not exceed 30 days. In exceptional cases this period of time may be extended to 90 days.

Article 45

The competent authority of the Member State may require from the applicant further information concerning the particulars supplied pursuant to Article 41 and concerning the qualified person referred to in Article 48; where the competent authority concerned exercises this right, application of the time-limits referred to in Article 43 and 44 shall be suspended until the additional data required have been supplied.

Article 46

The holder of a manufacturing authorization shall at least be obliged:

(a) to have at his disposal the services of staff who comply with the legal requirements existing in the Member State concerned both as regards manufacture and controls;

(b) to dispose of the authorized medicinal products only in accordance with the legislation of the Member States concerned;

(c) to give prior notice to the competent authority of any changes he may wish to make to any of the particulars supplied pursuant to Article 41; the competent authority shall, in any event, be immediately informed if the qualified person referred to in Article 48 is replaced unexpectedly;

(d) to allow the agents of the competent authority of the Member State concerned access to his premises at any time;

(e) to enable the qualified person referred to in Article 48 to carry out his duties, for example by placing at his disposal all the necessary facilities;

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

guidelines on good manufacturing practice for starting materials.

This point shall also be applicable to certain excipients, the list of which as well as the specific conditions of application shall be established by a Directive adopted by the Commission in accordance with the procedure referred to in Article 121(2).

Article 46a

1. For the purposes 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 Part I, point 3.2.1.1 (b) 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).

Article 47

The principles and guidelines of good manufacturing practices for medicinal products referred to in Article 46(f) shall be adopted in the form of a directive, in accordance with the procedure referred to in Article 121(2).

Detailed guidelines in line with those principles will be published by the Commission and revised necessary to take account of technical and scientific progress.

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 form and content of the authorisation referred to in Article 40(1), on the reports referred to in Article 111(3) and on the form and content of the

certificate of good manufacturing practice referred to in Article 111(5).

Article 48

1. Member States shall take all appropriate measures to ensure that the holder of the manufacturing authorization has permanently and continuously at his disposal the services of at least one qualified person, in accordance with the conditions laid down in Article 49, responsible in particular for carrying out the duties specified in Article 51.

2. If he personally fulfils the conditions laid down in Article 49, the holder of the authorization may himself assume the responsibility referred to in paragraph 1.

Article 49

1. Member States shall ensure that the qualified person referred to in Article 48 fulfils the conditions of qualification set out in paragraphs 2 and 3.

2. A qualified person shall be in possession of a diploma, certificate or other evidence of formal qualifications awarded on completion of a university course of study, or a course recognized as equivalent by the Member State concerned, extending over a period of at least four years of theoretical and practical study in one of the following scientific disciplines: pharmacy, medicine, veterinary medicine, chemistry, pharmaceutical chemistry and technology, biology.

However, the minimum duration of the university course may be three and a half years where the course is followed by a period of theoretical and practical training of a minimum duration of one year and including a training period of at least six months in a pharmacy open to the public, corroborated by an examination at university level.

Where two university courses or two courses recognized by the State as equivalent co-exist in a Member State and where one of these extends over four years and the other over three years,

the three-year course leading to a diploma, certificate or other evidence of formal qualifications awarded on completion of a university course or its recognized equivalent shall be considered to fulfil the condition of duration referred to in the second subparagraph in so far as the diplomas, certificates or other evidence of formal qualifications awarded on completion of both courses are recognized as equivalent by the State in question.

The course shall include theoretical and practical study bearing upon at least the following basic subjects:

- Experimental physics
- General and inorganic chemistry
- Organic chemistry
- Analytical chemistry
- Pharmaceutical chemistry, including analysis of medicinal products
- General and applied biochemistry (medical)
- Physiology
- Microbiology
- Pharmacology
- Pharmaceutical technology
- Toxicology
- Pharmacognosy (study of the composition and effects of the natural active substances of plant and animal origin).

Studies in these subjects should be so balanced as to enable the person concerned to fulfil the obligations specified in Article 51.

In so far as certain diplomas, certificates or other evidence of formal qualifications mentioned in the first subparagraph do not fulfil the criteria laid down in this paragraph, the competent authority of the Member State shall ensure that

the person concerned provides evidence of adequate knowledge of the subjects involved.

3. The qualified person shall have acquired practical experience over at least two years, in one or more undertakings which are authorized to manufacture medicinal products, in the activities of qualitative analysis of medicinal products, of quantitative analysis of active substances and of the testing and checking necessary to ensure the quality of medicinal products.

The duration of practical experience may be reduced by one year where a university course lasts for at least five years and by a year and a half where the course lasts for at least six years.

Article 50

1. A person engaging in the activities of the person referred to in Article 48 from the time of the application of Directive 75/319/EEC, in a Member State without complying with the provisions of Article 49 shall be eligible to continue to engage in those activities within the Community.

2. The holder of a diploma, certificate or other evidence of formal qualifications awarded on completion of a university course - or a course recognized as equivalent by the Member State concerned - in a scientific discipline allowing him to engage in the activities of the person referred to in Article 48 in accordance with the laws of that State may - if he began his course prior to 21 May 1975 - be considered as qualified to carry out in that State the duties of the person referred to in Article 48 provided that he has previously engaged in the following activities for at least two years before 21 May 1985 following notification of this directive in one or more undertakings authorized to manufacture: production supervision and/or qualitative and quantitative analysis of active substances, and the necessary testing and checking under the direct authority of the person referred to in Article 48 to ensure the quality of the medicinal products.

If the person concerned has acquired the practical experience referred to in the first subparagraph before 21 May 1965, a further one year's practical experience in accordance with the conditions referred to in the first subparagraph will be required to be completed immediately before he engages in such activities.

Article 51

1. Member States shall take all appropriate measures to ensure that the qualified person referred to in Article 48, without prejudice to his relationship with the holder of the manufacturing authorization, is responsible, in the context of the procedures referred to in Article 52, for securing:

(a) in the case of medicinal products manufactured within the Member States concerned, that each batch of medicinal products has been manufactured and checked in compliance with the laws in force in that Member State and in accordance with the requirements of the marketing authorisation;

(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 substances and all the other tests or checks necessary to ensure the quality of medicinal products in accordance with the requirements of the marketing authorisation.

The batches of medicinal products which have undergone such controls in a Member State shall be exempt from the controls if they are marketed in another Member State, accompanied by the control reports signed by the qualified person.

2. In the case of medicinal products imported from a third country, where appropriate arrangements have been made by the Community with the exporting country to ensure that the manufacturer of the medicinal product applies standards of good manufacturing practice

at least equivalent to those laid down by the Community, and to ensure that the controls referred to under point (b) of the first subparagraph of paragraph 1 have been carried out in the exporting country, the qualified person may be relieved of responsibility for carrying out those controls.

3. In all cases and particularly where the medicinal products are released for sale, the qualified person must certify in a register or equivalent document provided for that purpose, that each production batch satisfies the provisions of this Article; the said register or equivalent document must be kept up to date as operations are carried out and must remain at the disposal of the agents of the competent authority for the period specified in the provisions of the Member State concerned and in any event for at least five years.

Article 52

Member States shall ensure that the duties of qualified persons referred to in Article 48 are fulfilled, either by means of appropriate administrative measures or by making such persons subject to a professional code of conduct.

Member States may provide for the temporary suspension of such a person upon the commencement of administrative or disciplinary procedures against him for failure to fulfil his obligations.

Article 53

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

TITLE V

LABELLING AND PACKAGE LEAFLET

Article 54

The following particulars shall appear on the outer packaging of medicinal products or, where

there is no outer packaging, on the immediate packaging:

(a) the name of the medicinal product followed by its strength and pharmaceutical form, and, if appropriate, whether it is intended for babies, children or adults; where the product contains up to three active substances, the international non-proprietary name (INN) shall be included, or, if one does not exist, the common name;

(b) a statement of the active substances expressed qualitatively and quantitatively per dosage unit or according to the form of administration for a given volume or weight, using their common names;

(c) the pharmaceutical form and the contents by weight, by volume or by number of doses of the product;

(d) a list of those excipients known to have a recognized action or effect and included in the detailed guidance published pursuant to Article 65. However, if the product is injectable, or a topical or eye preparation, all excipients must be stated;

(e) the method of administration and, if necessary, the route of administration. Space shall be provided for the prescribed dose to be indicated;

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

(g) a special warning, if this is necessary for the medicinal product;

(h) the expiry date in clear terms (month/year);

(i) special storage precautions, if any;

(j) specific precautions relating to the disposal of unused medicinal products or waste derived from medicinal products, where appropriate, as well as reference to any appropriate collection system in place;

(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;

(l) the number of the authorization for placing the medicinal product on the market;

(m) the manufacturer's batch number;

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

Article 55

1. The particulars laid down in Article 54 shall appear on immediate packagings other than those referred to in paragraphs 2 and 3.

2. The following particulars at least shall appear on immediate packagings which take the form of blister packs and are placed in an outer packaging that complies with the requirements laid down in Articles 54 and 62:

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

- the name of the holder of the authorization for placing the product on the market,

- the expiry date,

- the batch number.

3. The following particulars at least shall appear on small immediate packaging units on which the particulars laid down in Articles 54 and 62 cannot be displayed:

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

- the method of administration,

- the expiry date,

- the batch number,

- the contents by weight, by volume or by unit.

Article 56

The particulars referred to in Articles 54, 55 and 62 shall be easily legible, clearly comprehensible and indelible.

Article 56a

The name of the medicinal product, as referred to in Article 54, point (a) must also be expressed in Braille format on the packaging. The marketing authorisation holder shall ensure that the package information leaflet is made available on request from patients' organisations in formats appropriate for the blind and partially-sighted.

Article 57

Notwithstanding Article 60, Member States may require the use of certain forms of labelling of the medicinal product making it possible to ascertain:

- the price of the medicinal product,
- the reimbursement conditions of social security organizations,
- the legal status for supply to the patient, in accordance with Title VI,
- identification and authenticity.

For medicinal products authorised under Regulation (EC) No 726/2004, Member States shall, when applying this Article, observe the detailed guidance referred to in Article 65 of this Directive.

Article 58

The inclusion in the packaging of all medicinal products of a package leaflet shall be obligatory unless all the information required by Articles 59 and 62 is directly conveyed on the outer packaging or on the immediate packaging.

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, and, if appropriate, whether it is intended for babies, children or adults. 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 the medicinal product is taken:

(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) 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 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;

(viii) a specific recommendation to consult the doctor or the pharmacist, as appropriate, for any clarification on the use of the product;

(e) 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;

(f) a reference to the expiry date indicated on the label, with:

(i) a warning against using the product after that date;

(ii) where appropriate, special storage precautions;

(iii) if necessary, a warning concerning 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;

(vii) the name and address of the manufacturer;

(g) where the medicinal product is authorised in accordance with 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.

3. The package leaflet shall reflect the results of consultations with target patient groups to ensure that it is legible, clear and easy to use.

Article 60

Member States may not prohibit or impede the placing on the market of medicinal products within their territory on grounds connected with labelling or the package leaflet where these comply with the requirements of this Title.

Article 61

1. One or more mock-ups of the outer packaging and the immediate packaging of a medicinal product, together with the draft package leaflet, shall be submitted to the authorities competent for authorising marketing when the marketing authorisation is requested. The results of assessments carried out in cooperation with target patient groups shall also be provided to the competent authority.

2. The competent authority shall refuse the marketing authorization if the labelling or the package leaflet do not comply with the provisions of this Title or if they are not in accordance with the particulars listed in the summary of product characteristics.

3. All proposed changes to an aspect of the labelling or the package leaflet covered by this Title and not connected with the summary of product characteristics shall be submitted to the authorities competent for authorizing marketing. If the competent authorities have not opposed a proposed change within 90 days following the introduction of the request, the applicant may put the change into effect.

4. The fact that the competent authority does not refuse a marketing authorization pursuant to paragraph 2 or a change to the labelling or the package leaflet pursuant to paragraph 3 does not alter the general legal liability of the manufacturer and the marketing authorization holder.

Article 62

The outer packaging and the package leaflet may include symbols or pictograms designed to clarify certain information mentioned in Articles 54 and 59(1) and other information compatible with the summary of the product characteristics which is useful for the patient, to the exclusion of any element of a promotional nature.

Article 63

1. The particulars for labelling listed in Articles 54, 59 and 62 shall appear in the official

language or languages of the Member State where the product is placed on the market.

The first subparagraph shall not prevent these particulars from being indicated in several languages, provided that the same particulars appear in all the languages used.

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

2. The package leaflet must be written and designed to be clear and understandable, enabling the users to act appropriately, when necessary with the help of health professionals. The package leaflet must be clearly legible in the official language or languages of the Member State in which the medicinal product is placed on the market.

The first subparagraph shall not prevent the package leaflet from being printed in several languages, provided that the same information is given in all the languages used.

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 in which the product is placed on the market.

Article 64

Where the provisions of this Title are not complied with, and a notice served on the person concerned has remained without effect, the competent authorities of the Member States may suspend the marketing authorization, until the labelling and the package leaflet of the medicinal product in question have been made to comply with the requirements of this Title.

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 non-prescription medicinal products;
- (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.

Article 66

1. The outer carton and the container of medicinal products containing radionuclides shall be labelled in accordance with the regulations for the safe transport of radioactive materials laid down by the International Atomic Energy Agency. Moreover, the labelling shall comply with the provisions set out in paragraphs 2 and 3.

2. The label on the shielding shall include the particulars mentioned in Article 54. In addition, the labelling on the shielding shall explain in full, the codings used on the vial and shall indicate, where necessary, for a given time and date, the amount of radioactivity per dose or per vial and the number of capsules, or, for liquids, the number of millilitres in the container.

3. The vial shall be labelled with the following information:

- the name or code of the medicinal product, including the name or chemical symbol of the radionuclide,
- the batch identification and expiry date,

- the international symbol for radioactivity,
- the name and address of the manufacturer,
- the amount of radioactivity as specified in paragraph 2.

Article 67

The competent authority shall ensure that a detailed instruction leaflet is enclosed with the packaging of radiopharmaceuticals, radionuclide generators, radionuclide kits or radionuclide precursors. The text of this leaflet shall be established in accordance with the provisions of Article 59. In addition, the leaflet shall include any precautions to be taken by the user and the patient during the preparation and administration of the medicinal product and special precautions for the disposal of the packaging and its unused contents.

Article 68

Without prejudice to the provisions of Article 69, homeopathic medicinal products shall be labelled in accordance with the provisions of this title and shall be identified by a reference on their labels, in clear and legible form, to their homeopathic nature.

Article 69

1. In addition to the clear mention of the words 'homeopathic medicinal product', the labelling and, where appropriate, the package insert for the medicinal products referred to in Article 14(1) shall bear the following, and no other, information:

- 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 supplemented by an invented name,
- name and address of the registration holder and, where appropriate, of the manufacturer,

- method of administration and, if necessary, route,
- expiry date, in clear terms (month, year),
- pharmaceutical form,
- contents of the sales presentation,
- special storage precautions, if any,
- a special warning if necessary for the medicinal product,
- manufacturer's batch number,
- registration number,
- 'homeopathic medicinal product without approved therapeutic indications',
- a warning advising the user to consult a doctor if the symptoms persist.

2. Notwithstanding paragraph 1, Member States may require the use of certain types of labelling in order to show:

- the price of the medicinal product,
- the conditions for refunds by social security bodies.

TITLE VI

CLASSIFICATION OF MEDICINAL PRODUCTS

Article 70

1. When a marketing authorization is granted, the competent authorities shall specify the classification of the medicinal product into:

- a medicinal product subject to medical prescription,
- a medicinal product not subject to medical prescription.

To this end, the criteria laid down in Article 71(1) shall apply.

2. The competent authorities may fix sub-categories for medicinal products which are available on medical prescription only. In that case, they shall refer to the following classification:

- (a) medicinal products on medical prescription for renewable or non-renewable delivery;
- (b) medicinal products subject to special medical prescription;
- (c) medicinal products on "restricted" medical prescription, reserved for use in certain specialised areas.

Article 71

1. Medicinal products shall be subject to medical prescription where they:

- are likely to present a danger either directly or indirectly, even when used correctly, if utilized without medical supervision, or
- are frequently and to a very wide extent used incorrectly, and as a result are likely to present a direct or indirect danger to human health, or
- contain substances or preparations thereof, the activity and/or adverse reactions of which require further investigation, or
- are normally prescribed by a doctor to be administered parenterally.

2. Where Member States provide for the sub-category of medicinal products subject to special medical prescription, they shall take account of the following factors:

- the medicinal product contains, in a non-exempt quantity, a substance classified as a narcotic or a psychotropic substance within the meaning of the international conventions in force, such as the United Nations Conventions of 1961 and 1971, or

- the medicinal product is likely, if incorrectly used, to present a substantial risk of medicinal abuse, to lead to addiction or be misused for illegal purposes, or

- the medicinal product contains a substance which, by reason of its novelty or properties, could be considered as belonging to the group envisaged in the second indent as a precautionary measure.

3. Where Member States provide for the sub-category of medicinal products subject to restricted prescription, they shall take account of the following factors:

- the medicinal product, because of its pharmaceutical characteristics or novelty or in the interests of public health, is reserved for treatments which can only be followed in a hospital environment,

- the medicinal product is used in the treatment of conditions which must be diagnosed in a hospital environment or in institutions with adequate diagnostic facilities, although administration and follow-up may be carried out elsewhere, or

- the medicinal product is intended for outpatients but its use may produce very serious adverse reactions requiring a prescription drawn up as required by a specialist and special supervision throughout the treatment.

4. A competent authority may waive application of paragraphs 1, 2 and 3 having regard to:

(a) the maximum single dose, the maximum daily dose, the strength, the pharmaceutical form, certain types of packaging; and/or

(b) other circumstances of use which it has specified.

5. If a competent authority does not designate medicinal products into sub-categories referred to in Article 70(2), it shall nevertheless take into account the criteria referred to in paragraphs 2 and 3 of this Article in determining whether any

medicinal product shall be classified as a prescription-only medicine.

Article 72

Medicinal products not subject to prescription shall be those which do not meet the criteria listed in Article 71.

Article 73

The competent authorities shall draw up a list of the medicinal products subject, on their territory, to medical prescription, specifying, if necessary, the category of classification. They shall update this list annually.

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.

Article 74a

Where a change of classification of a medicinal product has been authorised on the basis of significant pre-clinical tests or clinical trials, the competent authority shall not refer to the results of those tests or trials when examining an application by another applicant for or holder of marketing authorisation for a change of classification of the same substance for one year after the initial change was authorised.

Article 75

Each year, Member States shall communicate to the Commission and to the other Member States, the changes that have been made to the list referred to in Article 73.

TITLE VII

WHOLESALE DISTRIBUTION OF MEDICINAL PRODUCTS

Article 76

1. Without prejudice to Article 6, Member States shall take all appropriate action to ensure that only medicinal products in respect of which a marketing authorization has been granted in accordance with Community law are distributed on their territory.

2. In the case of wholesale distribution and storage, medicinal products shall be covered by a marketing authorisation granted pursuant to Regulation (EC) No 726/2004 or by the competent authorities of a Member State in accordance with this Directive.

3. Any distributor, not being the marketing authorisation holder, who imports a product from another Member State, shall notify the marketing authorisation holder and the competent authority in the Member State to which the product will be imported of his intention to import it. In the case of products which have not been granted an authorisation pursuant to Regulation (EC) No 726/2004, the notification to the competent authority shall be without prejudice to additional procedures provided for in the legislation of that Member State.

Article 77

1. Member States shall take all appropriate measures to ensure that the wholesale distribution of medicinal products is subject to the possession of an authorization to engage in activity as a wholesaler in medicinal products, stating the place for which it is valid.

2. Where persons authorized or entitled to supply medicinal products to the public may also, under national law, engage in wholesale business, such persons shall be subject to the authorization provided for in paragraph 1.

3. Possession of a manufacturing authorization shall include authorization to distribute by

wholesale the medicinal products covered by that authorization. Possession of an authorization to engage in activity as a wholesaler in medicinal products shall not give dispensation from the obligation to possess a manufacturing authorization and to comply with the conditions set out in that respect, even where the manufacturing or import business is secondary.

4. At the request of the Commission or any Member State, Member States shall supply all appropriate information concerning the individual authorizations which they have granted under paragraph 1.

5. Checks on the persons authorized to engage in the activity of wholesaler in medicinal products and the inspection of their premises shall be carried out under the responsibility of the Member State which granted the authorization.

6. The Member State which granted the authorization referred to in paragraph 1 shall suspend or revoke that authorization if the conditions of authorization cease to be met. It shall forthwith inform the other Member States and the Commission thereof.

7. Should a Member State consider that, in respect of a person holding an authorization granted by another Member State under the terms of paragraph 1, the conditions of authorization are not, or are no longer met, it shall forthwith inform the Commission and the other Member State involved. The latter shall take the measures necessary and shall inform the Commission and the first Member State of the decisions taken and the reasons for those decisions.

Article 78

Member States shall ensure that the time taken for the procedure for examining the application for the distribution authorization does not exceed 90 days from the day on which the competent authority of the Member State concerned receives the application.

The competent authority may, if need be, require the applicant to supply all necessary information

concerning the conditions of authorization. Where the authority exercises this option, the period laid down in the first paragraph shall be suspended until the requisite additional data have been supplied.

Article 79

In order to obtain the distribution authorization, applicants must fulfil the following minimum requirements:

(a) they must have suitable and adequate premises, installations and equipment, so as to ensure proper conservation and distribution of the medicinal products;

(b) they must have staff, and in particular, a qualified person designated as responsible, meeting the conditions provided for by the legislation of the Member State concerned;

(c) they must undertake to fulfil the obligations incumbent on them under the terms of Article 80.

Article 80

Holders of the distribution authorization must fulfil the following minimum requirements:

(a) they must make the premises, installations and equipment referred to in Article 79(a) accessible at all times to the persons responsible for inspecting them;

(b) they must obtain their supplies of medicinal products only from persons who are themselves in possession of the distribution authorization or who are exempt from obtaining such authorization under the terms of Article 77(3);

(c) they must supply medicinal products only to persons who are themselves in possession of the distribution authorization or who are authorized or entitled to supply medicinal products to the public in the Member State concerned;

(d) they must have an emergency plan which ensures effective implementation of any recall from the market ordered by the competent

authorities or carried out in cooperation with the manufacturer or marketing authorization holder for the medicinal product concerned;

(e) they must keep records either in the form of purchase/sales invoices, or on computer, or in any other form, giving for any transaction in medicinal products received or dispatched at least the following information:

- date,

- name of the medicinal product,

- quantity received or supplied,

- name and address of the supplier or consignee, as appropriate;

(f) they must keep the records referred to under (e) available to the competent authorities, for inspection purposes, for a period of five years;

(g) they must comply with the principles and guidelines of good distribution practice for medicinal products as laid down in Article 84.

Article 81

With regard to the supply of medicinal products to pharmacists and persons authorised or entitled to supply medicinal products to the public, Member States shall not impose upon the holder of a distribution authorisation which has been granted by another Member State any obligation, in particular public service obligations, more stringent than those they impose on persons whom they have themselves authorised to engage in equivalent activities.

The holder of a marketing authorisation for a medicinal product and the distributors of the said medicinal product actually placed on the market in a Member State shall, within the limits of their responsibilities, ensure appropriate and continued supplies of that medicinal product to pharmacies and persons authorised to supply medicinal products so that the needs of patients in the Member State in question are covered.

The arrangements for implementing this Article should, moreover, be justified on grounds of public health protection and be proportionate in relation to the objective of such protection, in compliance with the Treaty rules, particularly those concerning the free movement of goods and competition.

Article 82

For all supplies of medicinal products to a person authorized or entitled to supply medicinal products to the public in the Member State concerned, the authorized wholesaler must enclose a document that makes it possible to ascertain:

- the date,
- the name and pharmaceutical form of the medicinal product,
- the quantity supplied,
- the name and address of the supplier and consignor.

Member States shall take all appropriate measures to ensure that persons authorized or entitled to supply medicinal products to the public are able to provide information that makes it possible to trace the distribution path of every medicinal product.

Article 83

The provisions of this Title shall not prevent the application of more stringent requirements laid down by Member States in respect of the wholesale distribution of:

- narcotic or psychotropic substances within their territory,
- medicinal products derived from blood,
- immunological medicinal products,
- radiopharmaceuticals.

Article 84

The Commission shall publish guidelines on good distribution practice. To this end, it shall consult the Committee for Medicinal Products for Human Use and the Pharmaceutical Committee established by Council Decision 75/320/EEC³⁰.

Article 85

This Title shall apply to homeopathic medicinal products.

TITLE VIII

ADVERTISING

Article 86

1. 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 or consumption of medicinal products; it shall include in particular:

- the advertising of medicinal products to the general public,
- advertising of medicinal products to persons qualified to prescribe or supply them,
- visits by medical sales representatives to persons qualified to prescribe medicinal products,
- the supply of samples,
- the provision of inducements to prescribe or supply medicinal products by the gift, offer or promise of any benefit or bonus, whether in money or in kind, except when their intrinsic value is minimal,
- sponsorship of promotional meetings attended by persons qualified to prescribe or supply medicinal products,

³⁰ OJ L 147, 9.6.1975, p. 23.

- sponsorship of scientific congresses attended by persons qualified to prescribe or supply medicinal products and in particular payment of their travelling and accommodation expenses in connection therewith.

2. The following are not covered by this Title:

- the labelling and the accompanying package leaflets, which are subject to the provisions of Title V,

- correspondence, possibly accompanied by material of a non-promotional nature, needed to answer a specific question about a particular medicinal product,

- factual, informative announcements and reference material relating, for example, to pack changes, adverse-reaction warnings as part of general drug precautions, trade catalogues and price lists, provided they include no product claims,

- information relating to human health or diseases, provided that there is no reference, even indirect, to medicinal products.

Article 87

1. Member States shall prohibit any advertising of a medicinal product in respect of which a marketing authorization has not been granted in accordance with Community law.

2. All parts of the advertising of a medicinal product must comply with the particulars listed in the summary of product characteristics.

3. The advertising of a medicinal product:

- shall encourage the rational use of the medicinal product, by presenting it objectively and without exaggerating its properties,

- shall not be misleading.

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. 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.

3. Member States shall be entitled to ban, on their territory, advertising to the general public of medicinal products the cost of which may be reimbursed.

4. 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.

5. The prohibition referred to in paragraph 1 shall apply without prejudice to Article 14 of Directive 89/552/EEC.

6. Member States shall prohibit the direct distribution of medicinal products to the public by the industry for promotional purposes.

TITLE VIIIa

INFORMATION AND ADVERTISING

Article 88a

Within three years of the entry into force of Directive 2004/726/EC, the Commission shall, following consultations with patients' and consumers' organisations, doctors' and pharmacists' organisations, Member States and

other interested parties, present to the European Parliament and the Council a report on current practice with regard to information provision — particularly on the Internet — and its risks and benefits for patients.

Following analysis of the above data, the Commission shall, if appropriate, put forward proposals setting out an information strategy to ensure good-quality, objective, reliable and non-promotional information on medicinal products and other treatments and shall address the question of the information source's liability.

Article 89

1. Without prejudice to Article 88, all advertising to the general public of a medicinal product shall:

(a) be set out in such a way that it is clear that the message is an advertisement and that the product is clearly identified as a medicinal product;

(b) include the following minimum information:

- the name of the medicinal product, as well as the common name if the medicinal product contains only one active substance,

- the information necessary for correct use of the medicinal product,

- an express, legible invitation to read carefully the instructions on the package leaflet or on the outer packaging, as the case may be.

2. Member States may decide that the advertising of a medicinal product to the general public may, notwithstanding paragraph 1, include only the name of the medicinal product or its international non-proprietary name, where this exists, or the trademark if it is intended solely as a reminder.

Article 90

The advertising of a medicinal product to the general public shall not contain any material which:

(a) gives the impression that a medical consultation or surgical operation is unnecessary, in particular by offering a diagnosis or by suggesting treatment by mail;

(b) suggests that the effects of taking the medicine are guaranteed, are unaccompanied by adverse reactions or are better than, or equivalent to, those of another treatment or medicinal product;

(c) suggests that the health of the subject can be enhanced by taking the medicine;

(d) suggests that the health of the subject could be affected by not taking the medicine; this prohibition shall not apply to the vaccination campaigns referred to in Article 88(4);

(e) is directed exclusively or principally at children;

(f) refers to a recommendation by scientists, health professionals or persons who are neither of the foregoing but who, because of their celebrity, could encourage the consumption of medicinal products;

(g) suggests that the medicinal product is a foodstuff, cosmetic or other consumer product;

(h) suggests that the safety or efficacy of the medicinal product is due to the fact that it is natural;

(i) could, by a description or detailed representation of a case history, lead to erroneous self-diagnosis;

(j) refers, in improper, alarming or misleading terms, to claims of recovery;

(k) uses, in improper, alarming or misleading terms, pictorial representations of changes in the human body caused by disease or injury, or of the action of a medicinal product on the human body or parts thereof.

Article 91

1. Any advertising of a medicinal product to persons qualified to prescribe or supply such products shall include:

- essential information compatible with the summary of product characteristics;
- the supply classification of the medicinal product.

Member States may also require such advertising to include the selling price or indicative price of the various presentations and the conditions for reimbursement by social security bodies.

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, or its international non-proprietary name, where this exists, or the trademark, if it is intended solely as a reminder.

Article 92

1. Any documentation relating to a medicinal product which is transmitted as part of the promotion of that product to persons qualified to prescribe or supply it shall include, as a minimum, the particulars listed in Article 91(1) and shall state the date on which it was drawn up or last revised.

2. All the information contained in the documentation referred to in paragraph 1 shall be accurate, up-to-date, verifiable and sufficiently complete to enable the recipient to form his or her own opinion of the therapeutic value of the medicinal product concerned.

3. Quotations as well as tables and other illustrative matter taken from medical journals or other scientific works for use in the documentation referred to in paragraph 1 shall be faithfully reproduced and the precise sources indicated.

Article 93

1. Medical sales representatives shall be given adequate training by the firm which employs them and shall have sufficient scientific knowledge to be able to provide information which is precise and as complete as possible about the medicinal products which they promote.

2. During each visit, medical sales representatives shall give the persons visited, or have available for them, summaries of the product characteristics of each medicinal product they present together, if the legislation of the Member State so permits, with details of the price and conditions for reimbursement referred to in Article 91(1).

3. Medical sales representatives shall transmit to the scientific service referred to in Article 98(1) any information about the use of the medicinal products they advertise, with particular reference to any adverse reactions reported to them by the persons they visit.

Article 94

1. Where medicinal products are being promoted to persons qualified to prescribe or supply them, no gifts, pecuniary advantages or benefits in kind may be supplied, offered or promised to such persons unless they are inexpensive and relevant to the practice of medicine or pharmacy.

2. Hospitality at sales promotion events shall always be strictly limited to their main purpose and must not be extended to persons other than health-care professionals.

3. Persons qualified to prescribe or supply medicinal products shall not solicit or accept any inducement prohibited under paragraph 1 or contrary to paragraph 2.

4. Existing measures or trade practices in Member States relating to prices, margins and discounts shall not be affected by paragraphs 1, 2 and 3.

Article 95

The provisions of Article 94(1) shall not prevent hospitality being offered, directly or indirectly, at events for purely professional and scientific purposes; such hospitality shall always be strictly limited to the main scientific objective of the event; it must not be extended to persons other than health-care professionals.

Article 96

1. Free samples shall be provided on an exceptional basis only to persons qualified to prescribe them and on the following conditions:

(a) the number of samples for each medicinal product each year on prescription shall be limited;

(b) any supply of samples shall be in response to a written request, signed and dated, from the prescribing agent;

(c) those supplying samples shall maintain an adequate system of control and accountability;

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

(e) each sample shall be marked 'free medical sample – not for sale' or shall show some other wording having the same meaning;

(f) each sample shall be accompanied by a copy of the summary of product characteristics;

(g) no samples of medicinal products containing psychotropic or narcotic substances within the meaning of international conventions, such as the United Nations Conventions of 1961 and 1971, may be supplied.

2. Member States may also place further restrictions on the distribution of samples of certain medicinal products.

Article 97

1. Member States shall ensure that there are adequate and effective methods to monitor the

advertising of medicinal products. Such methods, which may be based on a system of prior vetting, shall in any event include legal provisions under which persons or organizations regarded under national law as having a legitimate interest in prohibiting any advertisement inconsistent with this Title, may take legal action against such advertisement, or bring such advertisement before administrative authority competent either to decide on complaints or to initiate appropriate legal proceedings.

2. Under the legal provisions referred to in paragraph 1, Member States shall confer upon the courts or administrative authorities powers enabling them, in cases where they deem such measures to be necessary, taking into account all the interests involved, and in particular the public interest:

- to order the cessation of, or to institute appropriate legal proceedings for an order for the cessation of, misleading advertising, or

- if misleading advertising has not yet been published but publication is imminent, to order the prohibition of, or to institute appropriate legal proceedings for an order for the prohibition of, such publication,

even without proof of actual loss or damage or of intention or negligence on the part of the advertiser.

3. Member States shall make provision for the measures referred to in the second subparagraph to be taken under an accelerated procedure, either with interim effect or with definitive effect.

It shall be for each Member State to decide which of the two options set out in the first subparagraph to select.

4. Member States may confer upon the courts or administrative authorities powers enabling them, with a view to eliminating the continuing effects of misleading advertising the cessation of which has been ordered by a final decision:

- to require publication of that decision in full or in part and in such form as they deem adequate,

- to require in addition the publication of a corrective statement.

5. Paragraphs 1 to 4 shall not exclude the voluntary control of advertising of medicinal products by self-regulatory bodies and recourse to such bodies, if proceedings before such bodies are possible in addition to the judicial or administrative proceedings referred to in paragraph 1.

Article 98

1. The marketing authorization holder shall establish, within his undertaking, a scientific service in charge of information about the medicinal products which he places on the market.

2. The marketing authorization holder shall:

- keep available for, or communicate to, the authorities or bodies responsible for monitoring advertising of medicinal products, a sample of all advertisements emanating from his undertaking together with a statement indicating the persons to whom it is addressed, the method of dissemination and the date of first dissemination,

- ensure that advertising of medicinal products by his undertaking conforms to the requirements of this Title,

- verify that medical sales representatives employed by his undertaking have been adequately trained and fulfil the obligations imposed upon them by Article 93(2) and (3),

- supply the authorities or bodies responsible for monitoring advertising of medicinal products with the information and assistance they require to carry out their responsibilities,

- ensure that the decisions taken by the authorities or bodies responsible for monitoring advertising of medicinal products are immediately and fully complied with.

3. The Member States shall not prohibit the co-promotion of a medicinal product by the holder of the marketing authorisation and one or more companies nominated by him.

Article 99

Member States shall take the appropriate measures to ensure that the provisions of this Title are applied and shall determine in particular what penalties shall be imposed should the provisions adopted in the execution of Title be infringed.

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.

TITLE IX

PHARMACOVIGILANCE

Article 101

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

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.

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 (l) of the second subparagraph of Article 57(1) of Regulation (EC) No 726/2004 and shall be permanently accessible to all Member States and without delay to the public.

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.

Article 102a

The management of funds intended for activities connected with pharmacovigilance, the operation of communication networks and market surveillance shall be under the permanent control of the competent authorities in order to guarantee their independence.

Article 103

The marketing authorization holder shall have permanently and continuously at his disposal an appropriately qualified person responsible for pharmacovigilance.

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

(a) the establishment and maintenance of a system which ensures that information about all suspected adverse reactions which are reported to the personnel of the company, and to medical representatives, is collected and collated in order to be accessible at least at one point within the Community;

(b) the preparation for the competent authorities of the reports referred to in Article 104, in such form as may be laid down by those authorities, in accordance with the guidance referred to in Article 106(1);

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

(d) the provision to the competent authorities, of any other information relevant to the evaluation of the benefits and risks afforded by a medicinal product, including appropriate information on post-authorization safety studies.

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 in accordance with 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 promptly to the competent authority of the Member State on whose territory the incident occurred and no later than 15 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, promptly to the competent authority of the Member State in whose territory the

incident occurred, and no later than 15 days following the receipt of the information.

4. The marketing authorisation holder shall ensure that all suspected serious unexpected adverse reactions and any suspected transmission via a medicinal product of any infectious agent occurring in the territory of a third country are reported promptly in accordance with the guidelines referred to in Article 106(1), so that the Agency and the competent authorities of the Member States in which the medicinal product is authorised are informed of them, and no later than 15 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 for the granting of the marketing 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, immediately upon request or at least every six months after authorisation and until the placing on the market. Periodic safety update reports shall also be submitted immediately upon request or at least every six months during the first two years following the initial placing on the market and once a year for the following two years. Thereafter, the reports shall be submitted at three-yearly intervals, or immediately upon request.

The periodic safety update reports shall include a scientific evaluation of the risk-benefit balance of the medicinal product.

7. The Commission may lay down provisions to amend paragraph 6 in view of experience gained through its operation. The Commission shall adopt the provisions in accordance with the procedure referred to in Article 121(2).

8. Following the granting of a marketing authorisation, the marketing authorisation holder may request the amendment of the periods referred to in paragraph 6 in accordance with the procedure laid down by Commission Regulation (EC) No 1084/2003³¹.

9. The holder of a marketing authorisation may not communicate information relating to pharmacovigilance concerns to the general public in relation to its authorised medicinal product without giving prior or simultaneous notification to the competent authority.

In any case, the marketing authorisation holder shall ensure that such information is presented objectively and is not misleading.

Member States shall take the necessary measures to ensure that a marketing authorisation holder who fails to discharge these obligations is subject to effective, proportionate and dissuasive penalties.

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 in order 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

³¹ OJ L 159, 27.6.2003, p. 1.

promptly made available to the Agency and the other Member States, and in any case within 15 days after 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 promptly made available to the marketing authorisation holder and in any case within 15 days after 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, revoked 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 in relation to suspensions and revocation, 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. In relation to variations, the Committee may upon request from a Member State prepare an opinion.

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

The final measures shall be adopted in accordance with the procedure referred to in Article 121(3).

Article 108

Any amendments which may be necessary to update provisions of Articles 101 to 107 to take account of scientific and technical progress shall be adopted in accordance with the procedure referred to in Article 121(2).

TITLE X

SPECIAL PROVISIONS ON MEDICINAL PRODUCTS DERIVED FROM HUMAN BLOOD AND PLASMA

Article 109

For the collection and testing of human blood and human plasma, Directive 2002/98/EC of the European Parliament and of the Council of 27 January 2003 setting standards of quality and

safety for the collection, testing, processing, storage and distribution of human blood and blood components and amending Directive 2001/83/EC³² shall apply.

Article 110

Member States shall take the necessary measures to promote Community self-sufficiency in human blood or human plasma. For this purpose, they shall encourage the voluntary unpaid donation of blood and plasma and shall take the necessary measures to develop the production and use of products derived from human blood or human plasma coming from voluntary unpaid donations. They shall notify the Commission of such measures.

TITLE XI

SUPERVISION AND SANCTIONS

Article 111

1. The competent authority of the Member State concerned shall ensure, by means of repeated inspections, and if necessary unannounced inspections, and, where appropriate, by asking an Official Medicines Control Laboratory or a laboratory designated for that purpose to carry out tests on samples, that the legal requirements governing medicinal products are complied with.

The competent authority may also carry out unannounced inspections at the premises of manufacturers of active substances used as starting materials, or at the premises of marketing authorisation holders whenever it considers that there are grounds for suspecting non-compliance with the principles and guidelines of good manufacturing 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 Pharmacopoeia³³ (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 that 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 including with a view to independent tests being carried out by an Official Medicines Control Laboratory or a laboratory designated for that purpose by a Member State;

(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 description of the manufacturing method;

(d) inspect the premises, records and documents 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.

2. Member States shall take all appropriate steps to ensure that the manufacturing processes used in the manufacture of immunological products are properly validated and attain batch-to-batch consistency.

³² OJ L 33, 8.2.2003, p. 30.

³³ OJ L 158, 25.6.1994, p. 19.

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.

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 database 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 database as referred to in paragraph 6.

Article 112

Member States shall take all appropriate measures to ensure that the holder of the marketing authorization for a medicinal product and, where appropriate, the holder of the manufacturing authorization, furnish proof of the controls carried out on the medicinal product and/or the ingredients and of the controls carried out at an intermediate stage of the manufacturing process, in accordance with the methods laid down in Article 8(3)(h).

Article 113

For the purpose of implementing Article 112, Member States may require manufacturers of immunological products to submit to a competent authority copies of all the control reports signed by the qualified person in accordance with Article 51.

Article 114

1. Where it considers it necessary in the interests of public health, a Member State may require the holder of an authorization for marketing:

- live vaccines,
- immunological medicinal products used in the primary immunization of infants or of other groups at risk,
- immunological medicinal products used in public health immunization programmes,
- new immunological medicinal products or immunological medicinal products manufactured using new or altered kinds of technology or new for a particular manufacturer, during a transitional period normally specified in the marketing authorization,

to submit samples from each batch of the bulk and/or the medicinal product for examination by an Official Medicines Control Laboratory or a laboratory that a Member State has designated for that purpose before release on to the market unless, in the case of a batch manufactured in another Member State, the competent authority

of that Member State has previously examined the batch in question and declared it to be in conformity with the approved specifications. Member States shall ensure that any such examination is completed within 60 days of the receipt of the samples.

2. Where, in the interests of public health, the laws of a Member State so provide, the competent authorities may require the marketing authorization holder for medicinal products derived from human blood or human plasma to submit samples from each batch of the bulk and/or the medicinal product for testing by an Official Medicines Control Laboratory or a laboratory that a Member State has designated for that purpose before being released into free circulation, unless the competent authorities of another Member State have previously examined the batch in question and declared it to be in conformity with the approved specifications. Member States shall ensure that any such examination is completed within 60 days of the receipt of the samples.

Article 115

Member States shall take all necessary measures to ensure that the manufacturing and purifying processes used in the preparation of medicinal products derived from human blood or human plasma are properly validated, attain batch-to-batch consistency and guarantee, insofar as the state of technology permits, the absence of specific viral contamination. To this end manufacturers shall notify the competent authorities of the method used to reduce or eliminate pathogenic viruses liable to be transmitted by medicinal products derived from human blood or human plasma. The competent authority may submit samples of the bulk and/or the medicinal product for testing by a State laboratory or a laboratory designated for that purpose, either during the examination of the application pursuant to Article 19, or after a marketing authorization has been granted.

Article 116

The competent authorities shall suspend, revoke, withdraw or vary a marketing authorisation 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 normal 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, revoked, withdrawn or varied where the particulars supporting the application as provided for in Article 8 or Articles 10, 10a, 10b, 10c and 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.

Article 117

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.

2. The competent authority may limit the prohibition to supply the product, or its withdrawal from the market, to those batches which are the subject of dispute.

Article 118

1. The competent authority shall suspend or revoke the marketing authorization for a category of preparations or all preparations where any one of the requirements laid down in Article 41 is no longer met.

2. In addition to the measures specified in Article 117, the competent authority may suspend manufacture or imports of medicinal products coming from third countries, or suspend or revoke the manufacturing authorization for a category of preparations or all preparations where Articles 42, 46, 51 and 112 are not complied with.

Article 119

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

TITLE XII

STANDING COMMITTEE

Article 120

Any changes which are necessary in order to adapt Annex I to take account of scientific and technical progress shall be adopted in accordance with the procedure referred to in Article 121(2).

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.

2. Where reference is made to this paragraph, Articles 5 and 7 of Decision 1999/468/EC shall apply, having regard to the provisions of Article 8 thereof.

The period laid down in Article 5(6) of Decision 1999/468/EC shall be set at three months.

3. Where reference is made to this paragraph, Articles 4 and 7 of Decision 1999/468/EC shall apply, having regard to the provisions of Article 8 thereof.

The period laid down in Article 4(3) of Decision 1999/468/EC shall be set at one month.

4. The Standing Committee shall adopt its own rules of procedure which shall be made public.

TITLE XIII

GENERAL PROVISIONS

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 Articles 40 and 77, 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 in accordance with Article 111(1) 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. The Agency shall inform the Member States concerned.

When the Commission is informed of these divergences of opinion, 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 which are not parties to the disagreement.

Article 123

1. Each Member State shall take all the appropriate measures to ensure that decisions authorizing marketing, refusing or revoking a marketing authorization, cancelling a decision refusing or revoking a marketing authorization, prohibiting supply, or withdrawing a product from the market, together with the reasons on which such decisions are based, are brought to the attention of the Agency forthwith.

2. The marketing authorization holder shall be obliged to notify the Member States concerned forthwith of any action taken by him to suspend the marketing of a medicinal product or to withdraw a medicinal product from the market, together with the reasons for such action if the latter concerns the efficacy of the medicinal product or the protection of public health. Member States shall ensure that this information is brought to the attention of the Agency.

3. Member States shall ensure that appropriate information about action taken pursuant to paragraphs 1 and 2 which may affect the protection of public health in third countries is forthwith brought to the attention of the World Health Organization, with a copy to the Agency.

4. The Commission shall publish annually a list of the medicinal products which are prohibited in the Community.

Article 124

Member States shall communicate to each other all the information necessary to guarantee the quality and safety of homeopathic medicinal products manufactured and marketed within the Community, and in particular the information referred to in Articles 122 and 123.

Article 125

Every decision referred to in this Directive which is taken by the competent authority of a Member State shall state in detail the reasons on which it is based.

Such decision shall be notified to the party concerned, together with information as to the redress available to him under the laws in force and of the time-limit allowed for access to such redress.

Decisions to grant or revoke a marketing authorisation shall be made publicly available.

Article 126

An authorization to market a medicinal product shall not be refused, suspended or revoked except on the grounds set out in this Directive.

No decision concerning suspension of manufacture or of importation of medicinal products coming from third countries, prohibition of supply or withdrawal from the market of a medicinal product may be taken except on the grounds set out in Articles 117 and 118.

Article 126a

1. In the absence of a marketing authorisation or of a pending application for a medicinal product authorised in another Member State in accordance with this Directive, a Member State may for justified public health reasons authorise the placing on the market of the said medicinal product.

2. When a Member State avails itself of this possibility, it shall adopt the necessary measures in order to ensure that the requirements of this Directive are complied with, in particular those referred to in Titles V, VI, VIII, IX and XI.

3. Before granting such an authorisation a Member State shall:

(a) notify the marketing authorisation holder, in the Member State in which the medicinal

product concerned is authorised, of the proposal to grant an authorisation under this Article in respect of the product concerned; and

(b) request the competent authority in that State to furnish a copy of the assessment report referred to in Article 21(4) and of the marketing authorisation in force in respect of the said medicinal product.

4. The Commission shall set up a publicly accessible register of medicinal products authorised under paragraph 1. Member States shall notify the Commission if any medicinal product is authorised, or ceases to be authorised, under paragraph 1, including the name or corporate name and permanent address of the authorisation holder. The Commission shall amend the register of medicinal products accordingly and make this register available on their website.

5. No later than 30 April 2008, the Commission shall present a report to the European Parliament and the Council concerning the application of this provision with a view to proposing any necessary amendments.

Article 126b

In order to guarantee independence and transparency, the Member States shall ensure that members of staff of the competent authority responsible for granting authorisations, rapporteurs and experts concerned with the authorisation and surveillance of medicinal products have no financial or other interests in the pharmaceutical industry which could affect their impartiality. These persons shall make an annual declaration of their financial interests.

In addition, the Member States shall ensure that the competent authority makes publicly accessible its rules of procedure and those of its committees, agendas for its meetings and records of its meetings, accompanied by decisions taken, details of votes and explanations of votes, including minority opinions.

Article 127

1. At the request of the manufacturer, the exporter or the authorities of an importing third country, Member States shall certify that a manufacturer of medicinal products is in possession of the manufacturing authorization. When issuing such certificates Member States shall comply with the following conditions:

(a) they shall have regard to the prevailing administrative arrangements of the World Health Organization;

(b) for medicinal products intended for export which are already authorized on their territory, they shall supply the summary of the product characteristics as approved in accordance with Article 21.

2. When the manufacturer is not in possession of a marketing authorization he shall provide the authorities responsible for establishing the certificate referred to in paragraph 1, with a declaration explaining why no marketing authorization is available.

Article 127a

When a medicinal product is to be authorised in accordance with Regulation (EC) No 726/2004 and the Scientific Committee in its opinion refers to recommended conditions or restrictions with regard to the safe and effective use of the medicinal product as provided for in Article 9(4)(c) of that Regulation, a decision addressed to the Member States shall be adopted in accordance with the procedure provided for in Articles 33 and 34 of this Directive, for the implementation of those conditions or restrictions.

Article 127b

Member States shall ensure that appropriate collection systems are in place for medicinal products that are unused or have expired.

TITLE XIV

FINAL PROVISIONS

Article 128

Directives 65/65/EEC, 75/318/EEC, 75/319/EEC, 89/342/EEC, 89/343/EEC, 89/381/EEC, 92/25/EEC, 92/26/EEC, 92/27/EEC, 92/28/EEC and 92/73/EEC, amended by the Directives referred to in Annex II, Part A, are repealed, without prejudice to the obligations of the Member States concerning the time-limits for implementation set out in Annex II, Part B.

References to the repealed Directives shall be construed as references to this Directive and shall be read in accordance with the correlation table in Annex III.

Article 129

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

Article 130

This Directive is addressed to the Member States.

Done at Brussels, 6 November 2001

<i>For the European Parliament</i>	<i>For the Council</i>
<i>The President</i>	<i>The President</i>
N. FONTAINE	D. REYNDERS

DEAD-LINES FOR THE TRANSPOSITION OF AMENDING DIRECTIVES:

Directive 2002/98/EC:

Article 32

1. Member States shall bring into force the laws, regulations and administrative provisions necessary to comply with this Directive not later

than 8 February 2005. They shall forthwith inform the Commission thereof.

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

2. Member States shall communicate to the Commission the texts of the provisions of national law that they have already adopted or which they adopt in the field governed by this Directive.

Directive 2004/24/EC:

Article 2

1. The Member States shall take the necessary measures to comply with this Directive by 30 October 2005. They shall forthwith inform the Commission thereof.

When Member States adopt these measures, they shall contain a reference to this Directive or shall be accompanied by such a reference on the occasion of their official publication. The methods of making such reference shall be laid down by the Member States.

2. For the traditional herbal medicinal products as referred to in Article 1, which are already on the market on the entry into force of this Directive, the competent authorities shall apply the provisions of this Directive within seven years after its entry into force.

Directive 2004/27/EC:

Article 2

The periods of protection provided for in Article 1, point 8, which amends Article 10(1) of Directive 2001/83/EC, shall not apply to reference medicinal products for which an application for authorisation has been submitted

before the date of transposition to in Article 3 first paragraph.

Article 3

Member States shall bring into force the laws, regulations and administrative provisions necessary to comply with this Directive no later than 30 October 2005. They shall immediately inform the Commission thereof.

When Member States adopt these measures, they shall contain a reference to this Directive or shall be accompanied by such a reference on the occasion of their official publication. The methods of making such reference shall be laid down by the Member States.