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Compendium of EU pharmaceutical law

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Preface

2015 marks the 50th anniversary of pharmaceutical legislation in the EU, which began with Directive 65/65 in 1965 in the wake of the Thalidomide disaster.

The EU legal framework for medicinal products for human use guarantees high standards of quality and safety of medicinal products and intends to promote the functioning of the internal market, with measures which encourage innovation and competiveness in Europe. It is based on the principle that medicinal products may be placed on the market only following a marketing authorisation granted by the competent authorities.

A large body of legislation has developed around this principle, with the progressive harmonisation of requirements for the granting of marketing authorisations since the 1960s, implemented across the whole European Economic Area.

Nowadays, medicinal products may be either authorised centrally by the European Commission or nationally by Member States' competent authorities. The European Medicines Agency, established in 1995, underpins the centralised authorisation procedure and supports coordination between national competent authorities. The Agency is the hub of a European medicines network comprising over 40 national regulatory authorities guaranteeing a constant exchange and flow of information regarding the scientific assessment of medicinal products in the EU.

The EU legal framework is definitely not an area in which the law stands still. Quite the contrary, its history is marked by a constant ambition to improve its functioning or tackling shortcomings in order to guarantee the right balance between early access of patients to new medicines and high standards of quality and safety. Moreover, over the past 50 years science has developed. New technologies and further knowledge about diseases led to the introduction of new concepts or re-shaping of existing medical therapies that were subsequently mirrored in legislation.

The pharmaceutical sector is characterised by an abundance of guidelines intended to help and support the key players in the application of the EU legal framework. Still, the guidance documents would be nothing without the basic legislation on which they build.

To understand the EU legal framework for medicinal products it is important to know the applicable provisions of the legislation itself. This E-Book is intended to support readers in this regard by putting together the most recent versions of the key legal instruments on medicinal products for human use. It provides a useful overview for stakeholders, especially the pharmaceutical industry, regulatory authorities, legal practitioners, but also interested citizens, patients and healthcare professionals.

This E-Book reflects the law as it stands on 1 January 2015.

Directive 2001/83/EC - Medicinal products for human use

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

This text of Directive 2001/83/EC integrates the following successive amendments and corrigenda:

Directive 2002/98/EC of the European Parliament and of the Council of 27 January 2003

OJ L 33, p. 30, 8.2.2003

Commission directive 2003/63/EC Text with EEA relevance of 25 June 2003

OJ L 159; p. 46, 27.6.2003

Directive 2004/24/EC of the European Parliament and of the Council of 31 March 2004

OJ L 136, p. 85, 30.4.2004

Directive 2004/27/EC of the European Parliament and of the Council of 31 March 2004

OJ L 136, p. 34, 30.4.2004

Regulation (EC) No 1901/2006 of the European Parliament and of the Council of 12 December 2006

OJ L 378, p. 1, 27.12.2006

Regulation (EC) No 1394/2007 of the European Parliament and of the Council of 13 November 2007

OJ L 324, p. 121, 10.12.2007

Directive 2008/29/EC of the European Parliament and of the Council of 11 March 2008

OJ L 81, p. 51, 20.3.2008

Directive 2009/53/EC of the European Parliament and of the Council Text with EEA relevance of 18 June 2009

OJ L 168, p. 33, 30.6.2009

Commission Directive 2009/120/EC Text with EEA relevance of 14 September 2009

OJ L 242, p. 3, 15.9.2009

Directive 2010/84/EU of the European Parliament and of the Council Text with EEA relevance of 15 December 2010

OJ L 348, p. 74, 31.12.2010

Directive 2011/62/EU of the European Parliament and of the Council Text with EEA relevance of 8 June 2011

OJ L 174, p. 74, 1. 7. 2011

Directive 2012/26/EU of the European Parliament and of the Council Text with EEA relevance of 25 October 2012

OJ L 299, p. 1, 27.10.2012

Corrigendum, OJ L 087, 31.3.2009, p. 174 (1394/2007)

Corrigendum, OJ L 276, 21.10.2011, p. 63 (2010/84)

THE EUROPEAN PARLIAMENT AND THE COUNCIL OF THE EUROPEAN UNION,

Having regard to the Treaty establishing the European Community, and in particular Article 95 thereof,
Having regard to the proposal from the Commission;
Having regard to the opinion of the Economic and Social Committee [1],
Acting in accordance with the procedure laid down in Article 251 of the Treaty [2],

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 products [3], Council Directive 75/318/EEC of 20 May 1975 on the approximation of the laws of Member States relating to analytical, pharmacotoxicological and clinical standards and protocols in respect of the testing of proprietary medicinal products [4], Council Directive 75/319/EEC of 20 May 1975 on the approximation of provisions laid down by law, regulation or administrative action relating to proprietary medicinal products [5], 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 allergens [6], 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 radiopharmaceuticals [7], 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 plasma [8], Council Directive 92/25/EEC of 31 March 1992 on the wholesale distribution of medicinal products for human use [9], Council Directive 92/26/EEC of 31 March 1992 concerning the classification for the supply of medicinal products for human use [10], Council Directive 92/27/EEC of 31 March 1992 on the labelling of medicinal products for human use and on package leaflets [11], Council Directive 92/28/EEC of 31 March 1992 on the advertising of medicinal products for human use [12], Council Directive 92/73/EEC of 22 September 1992 widening the scope of Directives 65/65/EEC and 75/319/EEC on the

[1] OJ C 368, 20.12.1999, p. 3

[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.

approximation of provisions laid down by law, regulation or administrative action relating to medicinal products and laying down additional provisions on homeopathic medicinal products [13] 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 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

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[13] OJ L 297, 13.10.1992, p. 8.

(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 super¬vision of medicinal products for human and veterinary use and establishing a European Agency for the Evaluation of Medicinal Products [14] 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 above mentioned Regulation (EEC) No 2309/93.

(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 above mentioned 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.

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[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).

(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 treatment [15]. Account should also 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 radiation [16], 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 treated, as regards registration and marketing authorization, in the same way as homeopathic medicinal products.

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[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).

[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).

(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 fulfillls 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 trans-actions 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 advertising[17].

(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 activities[18] 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.

(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

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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).

(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 Commission[19].

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

(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.

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19 OJ L 184, 17.7.1999, p. 23.

HAVE ADOPTED THIS DIRECTIVE:

TITLE I - DEFINITIONS

Article 1

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

1	…
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.*
3a	**Active substance** Any substance or mixture of substances intended to be used in the manufacture of a medicinal product and that, when used in its production, becomes an active ingredient of that product intended to exert a pharmacological, immunological or metabolic action with a view to restoring, correcting or modifying physiological functions or to make a medical diagnosis.
3b	**Excipient** Any constituent of a medicinal product other than the active substance and the packaging material.
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.
4a	**Advanced therapy medicinal product** A product as defined in Article 2 of Regulation (EC) No 1394/2007 of the European Parliament and of the Council of 13 November 2007 on advanced therapy medicinal products.
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 reconsitituted or combined with radionuclides in the final radiopharmaceutical, usually prior to its administration.
9	**Radionuclide precursor** Any other radionuclide produced for the radio-labelling of another substance prior to administration.
10	**Medicinal products derived from human blood or human plasma** Medicinal products based on blood constitutents 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.
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.
15	**Post-authorisation safety study** Any study relating to an authorised medicinal product conducted with the aim of identifying, characterising or quantifying a safety hazard, confirming the safety profile of the medicinal product, or of measuring the effectiveness of risk management measures.
16	**Abuse of medicinal products** Persistent or sporadic, intentional excessive use of medicinal products which is accompanied by harmful physical or psychological effets.
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.
17a	**Brokering of medicinal products** All activities in relation to the sale or purchase of medicinal products, except for wholesale distribution, that do not include physical handling and that consist of negotiating independently and on behalf of another legal or natural person.
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 726/2004.
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.
28b	**Risk management system** A set of pharmacovigilance activities and interventions designed to identify, characterise, prevent or minimise risks relating to a medicinal product, including the assessment of the effectiveness of those activities and interventions.
28c	**Risk management plan** A detailed description of the risk management system.
28d	**Pharmacovigilance system** A system used by the marketing authorisation holder and by Member States to fulfill the tasks and responsibilities listed in Title IX and designed to monitor the safety of authorised medicinal products and detect any change to their risk-benefit balance.
28e	**Pharmacovigilance system master file** A detailed description of the pharmacovigilance system used by the marketing authorisation holder with respect to one or more authorised medicinal products.
29	**Traditional herbal medicinal product** A herbal medicinal product that fulfills 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.

33	**Falsified medicinal product** Any medicinal product with a false representation of: (a) its identity, including its packaging and labelling, its name or its composition as regards any of the ingredients including excipients and the strength of those ingredients; (b) its source, including its manufacturer, its country of manufacturing, its country of origin or its marketing authorisation holder; or (c) its history, including the records and documents relating to the distribution channels used. This definition does not include unintentional quality defects and is without prejudice to infringements of intellectual property rights. <

TITLE II - SCOPE

Article 2

1. This Directive shall apply to medicinal products for human use intended to be placed on the market in Member States and either prepared industrially or manufactured by a method involving an industrial process.
2. 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 of this Article and Article 3(4), Title IV of this Directive shall apply to the manufacture of medicinal products intended only for export and to intermediate products, active substances and excipients.
4. Paragraph 1 shall be without prejudice to Articles 52b and 85a.

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 use[20].
4. Intermediate products intended for further processing by an authorized manufacturer.

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20 OJ L 121, 1.5.2001, p. 34.

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.
7. Any advanced therapy medicinal product, as defined in Regulation (EC) No 1394/2007, which is prepared on a non-routine basis according to specific quality standards, and used within the same Member State in a hospital under the exclusive professional responsibility of a medical practitioner, in order to comply with an individual medical prescription for a custom-made product for an individual patient.

   Manufacturing of these products shall be authorised by the competent authority of the Member State. Member States shall ensure that national traceability and pharmacovigilance requirements as well as the specific quality standards referred to in this paragraph are equivalent to those provided for at Community level in respect of advanced therapy medicinal products for which authorisation is required pursuant to Regulation (EC) No 726/2004 of the European Parliament and of the Council of 31 March 2004 laying down Community procedures for the authorisation and supervision of medicinal products for human and veterinary use and establishing a European Medicines Agency[21].

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 Origin[22]
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.
5. This Directive and all Regulations referred to therein shall not affect the application of national legislation prohibiting or restricting the use of any specific type of human or animal cells, or the sale, supply or use of medicinal products containing, consisting of or derived from these cells, on grounds not dealt with in the aforementioned Community legislation. The Member States shall communicate the national legislation concerned to the Commission. The Commission shall make this information publicly available in a register.

Article 5

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21 OJ L 136, 30.4.2004, p. 1. Regulation as amended by Regulation (EC) No 1901/2006 (OJ L 378, 27.12.2006, p. 1).

22 OJ L 207, 30.7.1986, p. 1.

1. A Member State may, in accordance with legislation in force and to fulfill 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.
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 products[23], shall not be affected by paragraph 3.

[23] 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).

TITLE III - PLACING ON THE MARKET

CHAPTER 1 - Marketing authorization

Article 6

1. No medicinal product may be placed on the market of a Member State unless a marketing authorisation has been issued by the competent authorities of that Member State in accordance with this Directive or an authorisation has been granted in accordance with Regulation (EC) No 726/2004, read in conjunction with Regulation (EC) No 1901/2006 of the European Parliament and of the Council of 12 December 2006 on medicinal products for paediatric use[24] and Regulation (EC) No 1394/2007.

   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).

   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, 1 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, 2 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.

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24 OJ L 378, 27.12.2006, p. 1.

(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.

(c)(a)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.

(h)(a)A written confirmation that the manufacturer of the medicinal product has verified compliance of the manufacturer of the active substance with principles and guidelines of good manufacturing practice by conducting audits, in accordance with point (f) of Article 46. The written confirmation shall contain a reference to the date of the audit and a declaration that the outcome of the audit confirms that the manufacturing complies with the principles and guidelines of good manufacturing practice.

(i) Results of:

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

(i)(a)A summary of the applicant's pharmacovigilance system which shall include the following elements

- proof that the applicant has at his disposal a qualified person responsible for pharmacovigilance,
- the Member States in which the qualified person resides and carries out his/her tasks,
- the contact details of the qualified person,
- a statement signed by the applicant to the effect that the applicant has the necessary means to fulfill the tasks and responsibilities listed in Title IX,
- a reference to the location where the pharmacovigilance system master file for the medicinal product is kept.

(a) The risk management plan describing the risk management system which the applicant will introduce for the medicinal product concerned, together with a summary thereof.

(i)(b)A statement to the effect that clinical trials carried out outside the European Union meet 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 the following:

- any authorisation, obtained in another Member State or in a third country, to place the medicinal product on the market, a summary of the safety data including the data contained in the periodic safety update reports, where available, and suspected adverse reactions reports, together with a list of those Member States in which an application for authorisation submitted in accordance with this Directive is under examination;
- 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 and 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 authorisation, whether in the Union or in a third country, and the reasons for such a decision.

(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 products[25], accompanied by a copy of the relevant Agency opinion.

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.

The risk management system referred to in point (i)(a)(a) of the first subparagraph shall be proportionate to the identified risks and the potential risks of the medicinal product, and the need for post-authorisation safety data.

The information referred to in the first subparagraph shall be updated where and when appropriate.

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25 OJ L 18, 22.1.2000, p. 1.

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.

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 Annex I 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 Annex I. 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.

For medicinal products included on the list referred to in Article 23 of Regulation (EC) No 726/2004, the summary of product characteristics shall include the statement: 'This medicinal product is subject to additional monitoring'. This statement shall be preceded by the black symbol referred to in Article 23 of Regulation (EC) No 726/2004 and followed by an appropriate standardised explanatory sentence.

For all medicinal products, a standard text shall be included expressly asking healthcare professionals to report any suspected adverse reaction in accordance with the national spontaneous reporting system referred to in Article 107a(1). Different ways of reporting, including electronic reporting, shall be available in compliance with the second subparagraph of Article 107a(1).

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 10000 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. That measure, designed to amend non-essential elements of this Directive, shall be adopted in accordance with the regulatory procedure with scrutiny referred to in Article 121(2a).

    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 preclinical 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 practiced 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 fulfilll 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 fulfills 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) 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 fulfillled:
    (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. Article 3(1) and (2), Article 4(4), Article 6(1), Article 12, Article 17(1), Articles 19, 20, 23, 24, 25, 40 to 52, 70 to 85, 101 to 108b, Article 111(1) and (3), Articles 112, 116, 117, 118, 122, 123, 125, the second paragraph of Article 126, and Article 127 of this Directive as well as Commission Directive 2003/94/EC of 8 October 2003 laying down the principles and guidelines of good manufacturing practice in respect of medicinal products for human use and investigational medicinal products for human use[26] 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;

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[26] OJ L 262, 14.10.2003, p. 22.

(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.

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

   With a view to the coopting of such members, the said Committee shall identify the specific complementary scientific competence of the additional member(s). Coopted 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 fulfilll 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.

Article 16i

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 authorization

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 28 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 28 to 39 apply.

The Member State concerned shall inform the other Member State and the applicant of its decision to suspend detailed examination of the application in question. As soon as it has completed the examination of the application and reached a decision, the other Member State shall forward a copy of its assessment report to the Member State concerned.

Article 18

Where a Member State is informed in accordance with Article 8(3)(l) that another Member State has authorized a medicinal product which is the subject of an application for authorization in the Member State concerned, that Member State shall forthwith request the authorities of the Member State which has granted the authorization to forward to it the assessment report referred to in Article 21(4).

Within 90 days of the receipt of the assessment report, the Member State concerned shall either recognize the decision of the first Member State and the summary of the product characteristics as approved by it or, if it considers that there are grounds for supposing that the authorization of the medicinal product concerned may present a risk to public health, it shall apply the procedures set out in Articles 29 to 34.

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 designated 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[5], 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 national competent authorities shall, without delay, make publicly available the marketing authorisation together with the package leaflet, the summary of the product characteristics and any conditions established in accordance with Articles 21a, 22 and 22a, together with any deadlines for the fulfilllment of those conditions for each medicinal product which they have authorised.
4. The national competent authorities shall draw up an assessment report and make comments on the file as regards the results of the pharmaceutical and pre-clinical tests, the clinical trials, the risk management system and the pharmacovigilance system of the medicinal product concerned. The assessment report shall be updated whenever new information becomes available which is important for the evaluation of the quality, safety or efficacy of the medicinal product concerned.

   The national competent authorities shall make the assessment report publicly accessible without delay, 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.

   The public assessment report shall include a summary written in a manner that is understandable to

the public. The summary shall contain, in particular, a section relating to the conditions of use of the medicinal product.

Article 21a

In addition to the provisions laid down in Article 19, a marketing authorisation for a medicinal product may be granted subject to one or more of the following conditions:

(a) to take certain measures for ensuring the safe use of the medicinal product to be included in the risk management system;
(b) to conduct post-authorisation safety studies;
(c) to comply with obligations on the recording or reporting of suspected adverse reactions which are stricter than those referred to in Title IX;
(d) any other conditions or restrictions with regard to the safe and effective use of the medicinal product;
(e) the existence of an adequate pharmacovigilance system;
(f) to conduct post-authorisation efficacy studies where concerns relating to some aspects of the efficacy of the medicinal product are identified and can be resolved only after the medicinal product has been marketed. Such an obligation to conduct such studies shall be based on the delegated acts adopted pursuant to Article 22b while taking into account the scientific guidance referred to in Article 108a.

The marketing authorisation shall lay down deadlines for the fulfilllment of these conditions where necessary.

Article 22

In exceptional circumstances and following consultation with the applicant, the marketing authorisation may be granted subject to certain conditions, in particular relating to the safety of the medicinal product, notification to the national competent authorities of any incident relating to its use, and action to be taken.
The marketing authorisation may be granted only when the applicant can show that he is unable to provide comprehensive data on the efficacy and safety of the medicinal product under normal conditions of use, for objective, verifiable reasons and must be based on one of the grounds set out in Annex I.
Continuation of the marketing authorisation shall be linked to the annual reassessment of these conditions

Article 22a

1. After the granting of a marketing authorisation, the national competent authority may impose an obligation on the marketing authorisation holder:
   (a) to conduct a post-authorisation safety study if there are concerns about the risks of an authorised medicinal product. If the same concerns apply to more than one medicinal product, the national competent authority shall, following consultation with the Pharmacovigilance Risk Assessment Committee, encourage the marketing authorisation holders concerned to conduct a joint post-authorisation safety study;

(b) to conduct a post-authorisation efficacy study when the understanding of the disease or the clinical methodology indicate that previous efficacy evaluations might have to be revised significantly. The obligation to conduct the post-authorisation efficacy study shall be based on the delegated acts adopted pursuant to Article 22b while taking into account the scientific guidance referred to in Article 108a.

The imposition of such an obligation shall be duly justified, notified in writing, and shall include the objectives and timeframe for submission and conduct of the study.

2. The national competent authority shall provide the marketing authorisation holder with an opportunity to present written observations in response to the imposition of the obligation within a time limit which it shall specify, if the marketing authorisation holder so requests within 30 days of receipt of the written notification of the obligation.
3. On the basis of the written observations submitted by the marketing authorisation holder, the national competent authority shall withdraw or confirm the obligation. Where the national competent authority confirms the obligation, the marketing authorisation shall be varied to include the obligation as a condition of the marketing authorisation and the risk management system shall be updated accordingly.

Article 22b

1. In order to determine the situations in which post-authorisation efficacy studies may be required under Articles 21a and 22a of this Directive, the Commission may adopt, by means of delegated acts in accordance with Article 121a, and subject to the conditions of Articles 121b and 121c, measures supplementing the provisions in Articles 21a and 22a.
2. When adopting such delegated acts, the Commission shall act in accordance with the provisions of this Directive.

Article 22c

1. The marketing authorisation holder shall incorporate any conditions referred to in Articles 21a, 22 or 22a in his risk management system.
2. The Member States shall inform the Agency of the marketing authorisations that they have granted subject to conditions pursuant to Articles 21a, 22 or 22a.

Article 23

1. After a marketing authorisation has been granted, the marketing authorisation holder shall, 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. Those changes shall be subject to the approval of the competent authority of the Member State concerned.
2. The marketing authorisation holder shall forthwith provide the national competent authority with any new information which might entail the amendment of the particulars or documents referred to in

Article 8(3), Articles 10, 10a, 10b and 11, or Article 32(5), or Annex I

In particular, the marketing authorisation holder shall forthwith inform the national competent authority of any prohibition or restriction imposed by the competent authorities of any country in which the medicinal product is marketed and of any other new information which might influence the evaluation of the benefits and risks of the medicinal product concerned. The information shall include both positive and negative results of clinical trials or other studies in all indications and populations, whether or not included in the marketing authorisation, as well as data on the use of the medicinal product where such use is outside the terms of the marketing authorisation.

3. The marketing authorisation holder shall ensure that the product information is kept up to date with the current scientific knowledge, including the conclusions of the assessment and recommendations made public by means of the European medicines web-portal established in accordance with Article 26 of Regulation (EC) No 726/2004.
4. In order to be able to continuously assess the risk-benefit balance, the national competent authority may at any time ask the marketing authorisation holder to forward data demonstrating that the risk-benefit balance remains favourable. The marketing authorisation holder shall answer fully and promptly any such request.

   The national competent authority may at any time ask the marketing authorisation holder to submit a copy of the pharmacovigilance system master file. The marketing authorisation holder shall submit the copy at the latest 7 days after receipt of the request.

Article 23a

After a marketing authorisation has b 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 23b

1. The Commission shall adopt appropriate arrangements for the examination of variations to the terms of marketing authorisations granted in accordance with this Directive.
2. The Commission shall adopt the arrangements referred to in paragraph 1 in the form of an implementing regulation. That measure, designed to amend non-essential elements of this Directive, by supplementing it, shall be adopted in accordance with the regulatory procedure with scrutiny referred to in Article 121(2a).
3. When adopting the arrangements referred to in paragraph 1, the Commission shall make efforts to make it possible to submit a single application for one or more identical changes made to the terms of a number of marketing authorisations.
4. A Member State may continue to apply national provisions on variations applicable at the time of entry into force of the implementing regulation to marketing authorisations granted before 1 January 1998 to medicinal products authorised only in that Member State. Where a medicinal product subject to national provisions in accordance with this Article is subsequently granted a marketing authorisation in another Member State, the implementing regulation shall apply to that medicinal product from that date.

5. Where a Member State decides to continue to apply national provisions pursuant to paragraph 4, it shall notify the Commission thereof. If a notification has not been made by 20 January 2011, the implementing regulation shall apply.

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 national competent authority with a consolidated version of the file in respect of quality, safety and efficacy, including the evaluation of data contained in suspected adverse reactions reports and periodic safety update reports submitted in accordance with Title IX, and information on all variations introduced since the marketing authorisation was granted, at least 9 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 national competent authority decides, on justified grounds relating to pharmacovigilance, including exposure of an insufficient number of patients to the medicinal product concerned, 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.

Article 27

1. A coordination group shall be set up for the following purposes:
   (a) the examination of any question relating to a marketing authorisation of a medicinal product in two or more Member States in accordance with the procedures laid down in Chapter 4;
   (b) the examination of questions related to the pharmacovigilance of medicinal products authorised by the Member States, in accordance with Articles 107c, 107e, 107g, 107k and 107q;
   (c) the examination of questions relating to variations of marketing authorisations granted by the Member States, in accordance with Article 35(1).

   The Agency shall provide the secretariat of this coordination group. For the fulfillment of its pharmacovigilance tasks, including approving risk management systems and monitoring their effectiveness, the coordination group shall rely on the scientific assessment and the recommendations of the Pharmacovigilance Risk Assessment Committee provided for in Article 56(1)(aa) of Regulation (EC) No 726/2004.
2. The coordination group shall be composed of one representative per Member State appointed for a renewable period of 3 years. Member States may appoint an alternate for a renewable period of 3 years. Members of the coordination group may arrange to be accompanied by experts.
   Members of the coordination group and experts shall, for the fulfillment of their tasks, rely on the scientific and regulatory resources available to national competent authorities. Each national competent authority shall monitor the level of expertise of the evaluations carried out and facilitate the activities of nominated coordination group members and experts.
   Article 63 of Regulation (EC) No 726/2004 shall apply to the coordination group as regards transparency and the independence of its members.
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.
4. The Executive Director of the Agency or his representative and representatives of the Commission shall be entitled to attend all meetings of the coordination group.
5. The members of the coordination group shall ensure that there is appropriate coordination between the tasks of that group and the work of national competent authorities, including the consultative bodies concerned with the marketing authorisation.
6. Save where otherwise provided for in this Directive, the Member States represented within the coordination group shall use their best endeavours to reach a position by consensus on the action to be taken. If such a consensus cannot be reached, the position of the majority of the Member States represented within the coordination group shall prevail.
7. Members of the coordination group shall be required, even after their duties have ceased, not to disclose information of the kind covered by the obligation of professional secrecy.

CHAPTER 4 - Mutual recognition and decentralised procedure

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.

   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, the Commission, the applicant or the marketing authorisation holder shall, in specific cases where the interests of the Union 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 an application for a marketing authorisation or on the suspension or revocation of a marketing authorisation, or on any other variation of the marketing authorisation which appears necessary.

   Where the referral results from the evaluation of data relating to pharmacovigilance of an authorised medicinal product, the matter shall be referred to the Pharmacovigilance Risk Assessment Committee and Article 107j(2) may be applied. The Pharmacovigilance Risk Assessment Committee shall issue a

recommendation according to the procedure laid down in Article 32. The final recommendation shall be forwarded to the Committee for Medicinal Products for Human Use or to the coordination group, as appropriate, and the procedure laid down in Article 107k shall apply.

However, where one of the criteria listed in Article 107i(1) is met, the procedure laid down in Articles 107i to 107k shall apply.

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.

   Where the scope of the procedure initiated under this Article concerns a range of medicinal products or a therapeutic class, medicinal products authorised in accordance with Regulation (EC) No 726/2004 which belong to that range or class shall also be included in the procedure.

3. Without prejudice to paragraph 1, a Member State may, where urgent action is necessary to protect public health at any stage of the procedure, suspend the marketing authorisation and prohibit the use of the medicinal product concerned on its territory until a definitive decision is adopted. It shall inform the Commission, the Agency and the other Member States, no later than the following working day, of the reasons for its action.

4. Where the scope of the procedure initiated under this Article, as determined in accordance with paragraph 2, includes medicinal products authorised in accordance with Regulation (EC) No 726/2004, the Commission may, where urgent action is necessary to protect public health, at any stage of the procedure, suspend the marketing authorisations and prohibit the use of the medicinal products concerned until a definitive decision is adopted. The Commission shall inform the Agency and the Member States no later than the following working day of the reasons for its action.

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 rapporteur. The Committee may also appoint individual experts to advise it on specific questions. When appointing experts, the Committee shall define their tasks and specify the time-limit for the completion of these tasks.

3. Before issuing its opinion, the Committee shall provide the applicant or the marketing authorisation holder with an opportunity to present written or oral explanations 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) 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.

   Where the scope of the procedure initiated under Article 31 includes medicinal products authorised in accordance with Regulation (EC) No 726/2004 pursuant to the third subparagraph of Article 31(2) of this Directive, the Commission shall, where necessary, adopt decisions to vary, suspend or revoke the marketing authorisations or to refuse the renewal of the marketing authorisations concerned.

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.

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 37

Article 35 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 nothwithstanding 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. Member States shall enter the information relating to the authorisation referred to in paragraph 1 of this Article in the Union 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 only active substances, which have been manufactured in accordance with good manufacturing practice for active substances and distributed in accordance with good distribution practices for active substances. To this end, the holder of the manufacturing authorisation shall verify compliance by the manufacturer and distributors of active substances with good manufacturing practice and good distribution practices by conducting audits at the manufacturing and distribution sites of the manufacturer and distributors of active substances. The holder of the manufacturing authorisation shall verify such compliance either by himself or, without prejudice to his responsibility as provided for in this Directive, through an entity acting on his behalf under a contract.

The holder of the manufacturing authorisation shall ensure that the excipients are suitable for use in medicinal products by ascertaining what the appropriate good manufacturing practice is. This shall be ascertained on the basis of a formalised risk assessment in accordance with the applicable guidelines referred to in the fifth paragraph of Article 47. Such risk assessment shall take into account requirements under other appropriate quality systems as well as the source and intended use of the excipients and previous instances of quality defects. The holder of the manufacturing authorisation shall ensure that the appropriate good manufacturing practice so ascertained, is applied. The holder of the manufacturing authorisation shall document the measures taken under this paragraph;

(g) to inform the competent authority and the marketing authorisation holder immediately if he obtains information that medicinal products which come under the scope of his manufacturing authorisation are, or are suspected of being, falsified irrespective of whether those medicinal products were distributed within the legal supply chain or by illegal means, including illegal sale by means of information society services;

(h) to verify that the manufacturers, importers or distributors from whom he obtains active substances are registered with the competent authority of the Member State in which they are established;

(i) to verify the authenticity and quality of the active substances and the excipients.

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. The Commission shall be empowered to adapt paragraph 1 to take account of scientific and technical progress. That measure, designed to amend non-essential elements of this Directive, shall be adopted in accordance with the regulatory procedure with scrutiny referred to in Article 121(2a).

Article 46b

1. Member States shall take appropriate measures to ensure that the manufacture, import and distribution on their territory of active substances, including active substances that are intended for export, comply with good manufacturing practice and good distribution practices for active substances.
2. Active substances shall only be imported if the following conditions are fulfilled:
    (a) the active substances have been manufactured in accordance with standards of good manufacturing practice at least equivalent to those laid down by the Union pursuant to the third paragraph of Article 47; and
    (b) the active substances are accompanied by a written confirmation from the competent authority of the exporting third country of the following:
        (I) the standards of good manufacturing practice applicable to the plant manufacturing the exported active substance are at least equivalent to those laid down by the Union pursuant to the third paragraph of Article 47;
        (II) the manufacturing plant concerned is subject to regular, strict and transparent controls and to the effective enforcement of good manufacturing practice, including repeated and unannounced inspections, so as to ensure a protection of public health at least equivalent to that in the Union; and
        (III) in the event of findings relating to non-compliance, information on such findings is supplied by the exporting third country to the Union without any delay.

    This written confirmation shall be without prejudice to the obligations set out in Article 8 and in point (f) of Article 46.
3. The requirement set out in point (b) of paragraph 2 of this Article shall not apply if the exporting country is included in the list referred to in Article 111b.
4. Exceptionally and where necessary to ensure the availability of medicinal products, when a plant manufacturing an active substance for export has been inspected by a Member State and was found to comply with the principles and guidelines of good manufacturing practice laid down pursuant to the third paragraph of Article 47, the requirement set out in point (b) of paragraph 2 of this Article may be waived by any Member State for a period not exceeding the validity of the certificate of Good Manufacturing Practice. Member States that make use of the possibility of such waiver, shall communicate this to the Commission.

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. That measure, designed to amend non-essential elements of this Directive by supplementing it, shall be adopted in accordance with the regulatory procedure with scrutiny referred to in Article 121(2a).

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 Commission shall adopt, by means of delegated acts in accordance with Article 121a and subject to the conditions laid down in Articles 121b and 121c, the principles and guidelines of good manufacturing practice for active substances referred to in the first paragraph of point (f) of Article 46 and in Article 46b.

The principles of good distribution practices for active substances referred to in the first paragraph of point (f) of Article 46 shall be adopted by the Commission in the form of guidelines.

The Commission shall adopt guidelines on the formalised risk assessment for ascertaining the appropriate good manufacturing practice for excipients referred to in the second paragraph of point (f) of Article 46.

Article 47a

1. The safety features referred to in point (o) of Article 54 shall not be removed or covered, either fully or partially, unless the following conditions are fulfilled:
   (a) the manufacturing authorisation holder verifies, prior to partly or fully removing or covering those safety features, that the medicinal product concerned is authentic and that it has not been tampered with;
   (b) the manufacturing authorisation holder complies with point (o) of Article 54 by replacing those safety features with safety features which are equivalent as regards the possibility to verify the authenticity, identification and to provide evidence of tampering of the medicinal product. Such replacement shall be conducted without opening the immediate packaging as defined in point 23 of Article 1.

   Safety features shall be considered equivalent if they:
      (i) comply with the requirements set out in the delegated acts adopted pursuant to Article 54a(2); and
      (ii) are equally effective in enabling the verification of authenticity and identification of medicinal products and in providing evidence of tampering with medicinal products;
   (c) the replacement of the safety features is conducted in accordance with applicable good manufacturing practice for medicinal products; and
   (d) the replacement of the safety features is subject to supervision by the competent authority.
2. Manufacturing authorisation holders, including those performing the activities referred to in paragraph 1 of this Article, shall be regarded as producers and therefore held liable for damages in the cases and under the conditions set forth in Directive 85/374/EEC.

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 fulfills 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 authorization;

(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 qualified person referred to in Article 48 shall in the case of medicinal products intended to be placed on the market in the Union, ensure that the safety features referred to in point (o) of Article 54 have been affixed on the packaging.

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 fulfill his obligations.

Article 52a

1. Importers, manufacturers and distributors of active substances who are established in the Union shall register their activity with the competent authority of the Member State in which they are established.
2. The registration form shall include, at least, the following information:
    (i) name or corporate name and permanent address;
    (ii) the active substances which are to be imported, manufactured or distributed;

(iii) particulars regarding the premises and the technical equipment for their activity.

3. The persons referred to in paragraph 1 shall submit the registration form to the competent authority at least 60 days prior to the intended commencement of their activity.
4. The competent authority may, based on a risk assessment, decide to carry out an inspection. If the competent authority notifies the applicant within 60 days of the receipt of the registration form that an inspection will be carried out, the activity shall not begin before the competent authority has notified the applicant that he may commence the activity. If within 60 days of the receipt of the registration form the competent authority has not notified the applicant that an inspection will be carried out, the applicant may commence the activity.
5. The persons referred to in paragraph 1 shall communicate annually to the competent authority an inventory of the changes which have taken place as regards the information provided in the registration form. Any changes that may have an impact on the quality or safety of the active substances that are manufactured, imported or distributed must be notified immediately.
6. Persons referred to in paragraph 1 who had commenced their activity before 2 January 2013 shall submit the registration form to the competent authority by 2 March 2013.
7. Member States shall enter the information provided in accordance with paragraph 2 of this Article in the Union database referred to in Article 111(6).
8. This Article shall be without prejudice to Article 111.

Article 52b

1. Notwithstanding Article 2(1), and without prejudice to Title VII, Member States shall take the necessary measures in order to prevent medicinal products that are introduced into the Union, but are not intended to be placed on the market of the Union, from entering into circulation if there are sufficient grounds to suspect that those products are falsified.
2. In order to establish what the necessary measures referred to in paragraph 1 of this Article are, the Commission may adopt, by means of delegated acts in accordance with Article 121a, and subject to the conditions laid down in Articles 121b and 121c, measures supplementing paragraph 1 of this Article as regards the criteria to be considered and the verifications to be made when assessing the potential falsified character of medicinal products introduced into the Union but not intended to be placed on the market.

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;
(o) for medicinal products other than radiopharmaceuticals referred to in Article 54a(1), safety features enabling wholesale distributors and persons authorised or entitled to supply medicinal products to the public to:
    - verify the authenticity of the medicinal product, and
    - identify individual packs, as well as a device allowing verification of whether the outer packaging has been tampered with.

Article 54 a

1. Medicinal products subject to prescription shall bear the safety features referred to in point (o) of Article 54, unless they have been listed in accordance with the procedure pursuant to point (b) of paragraph 2 of this Article.

   Medicinal products not subject to prescription shall not bear the safety features referred to in point (o) of

Article 54, unless, by way of exception, they have been listed in accordance with the procedure pursuant to point (b) of paragraph 2 of this Article, after having been assessed to be at risk of falsification.

2. The Commission shall adopt, by means of delegated acts in accordance with Article 121a and subject to the conditions laid down in Articles 121b and 121c, measures supplementing point (o) of Article 54 with the objective of establishing the detailed rules for the safety features referred to in point (o) of Article 54. Those delegated acts shall set out:
   (a) the characteristics and technical specifications of the unique identifier of the safety features referred to in point (o) of Article 54 that enables the authenticity of medicinal products to be verified and individual packs to be identified. When establishing the safety features due consideration shall be given to their cost-effectiveness;
   (b) the lists containing the medicinal products or product categories which, in the case of medicinal products subject to prescription shall not bear the safety features, and in the case of medicinal products not subject to prescription shall bear the safety features referred to in point (o) of Article 54. Those lists shall be established considering the risk of and the risk arising from falsification relating to medicinal products or categories of medicinal products. To this end, at least the following criteria shall be applied:
      (i) the price and sales volume of the medicinal product;
      (ii) the number and frequency of previous cases of falsified medicinal products being reported within the Union and in third countries and the evolution of the number and frequency of such cases to date;
      (iii) the specific characteristics of the medicinal products concerned;
      (iv) the severity of the conditions intended to be treated;
      (v) other potential risks to public health;
   (c) the procedures for the notification to the Commission provided for in paragraph 4 and a rapid system for evaluating and deciding on such notification for the purpose of applying point (b);
   (d) the modalities for the verification of the safety features referred to in point (o) of Article 54 by the manufacturers, wholesalers, pharmacists and persons authorised or entitled to supply medicinal products to the public and by the competent authorities. Those modalities shall allow the verification of the authenticity of each supplied pack of the medicinal products bearing the safety features referred to in point (o) of Article 54 and determine the extent of such verification. When establishing those modalities, the particular characteristics of the supply chains in Member States, and the need to ensure that the impact of verification measures on particular actors in the supply chains is proportionate, shall be taken into account;
   (e) provisions on the establishment, management and accessibility of the repositories system in which information on the safety features, enabling the verification of the authenticity and identification of medicinal products, as provided for in point (o) of Article 54, shall be contained. The costs of the repositories system shall be borne by the manufacturing authorisation holders of medicinal products bearing the safety features.
3. When adopting the measures referred to in paragraph 2, the Commission shall take due account of at least the following:

(a) the protection of personal data as provided for in Union law;
(b) the legitimate interests to protect information of a commercially confidential nature;
(c) the ownership and confidentiality of the data generated by the use of the safety features; and
(d) the cost-effectiveness of the measures.

4. The national competent authorities shall notify the Commission of non-prescription medicinal products which they judge to be at risk of falsification and may inform the Commission of medicinal products which they deem not to be at risk according to the criteria set out in point (b) of paragraph 2 of this Article.
5. Member States may, for the purposes of reimbursement or pharmacovigilance, extend the scope of application of the unique identifier referred to in point (o) of Article 54 to any medicinal product subject to prescription or subject to reimbursement

   Member States may, for the purposes of reimbursement, pharmacovigilance or pharmacoepidemiology, use the information contained in the repositories system referred to in point (e) of paragraph 2 of this Article.

   Member States may, for the purposes of patient safety, extend the scope of application of the anti-tampering device referred to in point (o) of Article 54 to any medicinal product.

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,
- authenticity and identification in accordance with Article 54a(5).

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;

(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.

For medicinal products included in the list referred to in Article 23 of Regulation (EC) No 726/2004, the following additional statement shall be included 'This medicinal product is subject to additional monitoring'. This statement shall be preceded by the black symbol referred to in Article 23 of Regulation (EC) No 726/2004 and followed by an appropriate standardised explanatory sentence.
For all medicinal products, a standardised text shall be included, expressly asking patients to communicate any suspected adverse reaction to his/her doctor, pharmacist, healthcare professional or directly to the national spontaneous reporting system referred to in Article 107a(1), and specifying the different ways of reporting available (electronic reporting, postal address and/or others) in compliance with the second subparagraph of Article 107a(1).

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.
4. By 1 January 2013, the Commission shall present to the European Parliament and the Council an assessment report on current shortcomings in the summary of product characteristics and the package leaflet and how they could be improved in order to better meet the needs of patients and healthcare professionals. The Commission shall, if appropriate, and on the basis of the report, and consultation with appropriate stakeholders, present proposals in order to improve the readability, layout and content of these documents.

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 do 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 >2 to 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 an official language or official languages of the Member State where the medicinal product is placed on the market, as specified, for the purposes of this Directive, by that Member State.

   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 in such a way as to be clear and understandable, enabling users to act appropriately, when necessary with the help of health professionals. The package leaflet must be clearly legible in an official language or official languages of the Member State where the medicinal product is placed on the market, as specified, for the purposes of this Directive, by that Member State.

   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. Where the medicinal product is not intended to be delivered directly to the patient, or where there are severe problems in respect of the availability of the medicinal product, the competent authorities may, subject to measures they consider necessary to safeguard human health, grant an exemption to the obligation that certain particulars should appear on the labelling and in the package leaflet. They may also grant a full or partial exemption to the obligation that the labelling and the package leaflet must be in an official language or official languages of the Member State where the medicinal product is placed on the market, as specified, for the purposes of this Directive, by that Member State.

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 AND BROKERING 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 medicinal product from another Member State shall notify the marketing authorisation holder and the competent authority in the Member State to which the medicinal product will be imported of his intention to import that product. In the case of medicinal 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 and to fees payable to the competent authority for examining the notification.
4. In the case of medicinal products which have been granted an authorisation pursuant to Regulation (EC) No 726/2004, the distributor shall submit the notification in accordance with paragraph 3 of this Article to the marketing authorisation holder and the Agency. A fee shall be payable to the Agency for checking that the conditions laid down in Union legislation on medicinal products and in the marketing authorisations are observed.

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 authorisation to engage in activity as a wholesaler in medicinal products, stating the premises located on their territory 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. Member States shall enter the information relating to the authorisations referred to in paragraph 1 of this Article in the Union database referred to in Article 111(6). At the request of the Commission or any Member State, Member States shall provide all appropriate information concerning the individual authorisations which they have granted under paragraph 1 of this Article.
5. Checks on the persons authorised to engage in activity as a wholesaler in medicinal products, and the inspection of their premises, shall be carried out under the responsibility of the Member State which granted the authorisation for premises located on its territory.
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 verify that the medicinal products received are not falsified by checking the safety features on the outer packaging, in accordance with the requirements laid down in the delegated acts referred to in Article 54a(2);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, dispatched or brokered at least the following information:
    - date,
    - name of the medicinal product,
    - quantity received, supplied or brokered,
    - name and address of the supplier or consignee, as appropriate,
    - batch number of the medicinal products at least for products bearing the safety features referred to in point (o) of Article 54;
(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;
(h) they must maintain a quality system setting out responsibilities, processes and risk management measures in relation to their activities;
(i) they must immediately inform the competent authority and, where applicable, the marketing authorisation holder, of medicinal products they receive or are offered which they identify as falsified or suspect to be falsified.

For the purposes of point (b), where the medicinal product is obtained from another wholesale distributor, wholesale distribution authorisation holders must verify compliance with the principles and guidelines of

good distribution practices by the supplying wholesale distributor. This includes verifying whether the supplying wholesale distributor holds a wholesale distribution authorisation.

Where the medicinal product is obtained from the manufacturer or importer, wholesale distribution authorisation holders must verify that the manufacturer or importer holds a manufacturing authorisation.

Where the medicinal product is obtained through brokering, the wholesale distribution authorisation holders must verify that the broker involved fulfils the requirements set out in this Directive.

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,
- batch number of the medicinal products at least for products bearing the safety features referred to in point (o) of Article 54.

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/EEC[27].

Article 85

This Title shall apply to homeopathic medicinal products.

Article 85a

In the case of wholesale distribution of medicinal products to third countries, Article 76 and point (c) of the first paragraph of Article 80 shall not apply. Moreover, points (b) and (ca) of the first paragraph of Article 80 shall not apply where a product is directly received from a third country but not imported. However, in that case wholesale distributors shall ensure that the medicinal products are obtained only from persons who are authorised or entitled to supply medicinal products in accordance with the applicable legal and administrative provisions of the third country concerned. Where wholesale distributors supply medicinal products to persons in third countries, they shall ensure that such supplies are only made to persons who are authorised or entitled to receive medicinal products for wholesale distribution or supply to the public in accordance with the applicable legal and administrative provisions of the third country concerned. The requirements set out in Article 82 shall apply to the supply of medicinal products to persons in third countries authorised or entitled to supply medicinal products to the public.

Article 85b

1. Persons brokering medicinal products shall ensure that the brokered medicinal products are 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.

   Persons brokering medicinal products shall have a permanent address and contact details in the Union, so as to ensure accurate identification, location, communication and supervision of their activities by competent authorities.

   The requirements set out in points (d) to (i) of Article 80 shall apply *mutatis mutandis* to the brokering of medicinal products.

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27 OJ L 147, 9.6.1975, p. 23.

2. Persons may only broker medicinal products if they are registered with the competent authority of the Member State of their permanent address referred to in paragraph 1. Those persons shall submit, at least, their name, corporate name and permanent address in order to register. They shall notify the competent authority of any changes thereof without unnecessary delay.

   Persons brokering medicinal products who had commenced their activity before 2 January 2013 shall register with the competent authority by 2 March 2013.

   The competent authority shall enter the information referred to in the first subparagraph in a register that shall be publicly accessible.
3. The guidelines referred to in Article 84 shall include specific provisions for brokering.
4. This Article shall be without prejudice to Article 111. Inspections referred to in Article 111 shall be carried out under the responsibility of the Member State where the person brokering medicinal products is registered.

   If a person brokering medicinal products does not comply with the requirements set out in this Article, the competent authority may decide to remove that person from the register referred to in paragraph 2. The competent authority shall notify that person thereof.

TITLE VIIA - SALE AT A DISTANCE TO THE PUBLIC

Article 85c

1. Without prejudice to national legislation prohibiting the offer for sale at a distance of prescription medicinal products to the public by means of information society services, Member States shall ensure that medicinal products are offered for sale at a distance to the public by means of information society services as defined in Directive 98/34/EC of the European Parliament and of the Council of 22 June 1998 laying down a procedure for the provision of information in the field of technical standards and regulations and of rules on Information Society services[28] under the following conditions:
   (a) the natural or legal person offering the medicinal products is authorised or entitled to supply medicinal products to the public, also at a distance, in accordance with national legislation of the Member State in which that person is established;
   (b) the person referred to in point (a) has notified the Member State in which that person is established of at least the following information:
      (i) name or corporate name and permanent address of the place of activity from where those medicinal products are supplied;
      (ii) the starting date of the activity of offering medicinal products for sale at a distance to the public by means of information society services;
      (iii) the address of the website used for that purpose and all relevant information necessary to identify that website;

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28 OJ L 204, 21.7.1998, p. 37.

(iv) if applicable, the classification in accordance with Title VI of the medicinal products offered for sale at a distance to the public by means of information society services. Where appropriate, that information shall be updated;

(c) the medicinal products comply with the national legislation of the Member State of destination in accordance with Article 6(1);

(d) without prejudice to the information requirements set out in Directive 2000/31/EC of the European Parliament and of the Council of 8 June 2000 on certain legal aspects of information society services, in particular electronic commerce, in the Internal Market (Directive on electronic commerce)[29], the website offering the medicinal products contains at least:

(i) the contact details of the competent authority or the authority notified pursuant to point (b);

(ii) a hyperlink to the website referred to in paragraph 4 of the Member State of establishment;

(iii) the common logo referred to in paragraph 3 clearly displayed on every page of the website that relates to the offer for sale at a distance to the public of medicinal products. The common logo shall contain a hyperlink to the entry of the person in the list referred to in point (c) of paragraph 4.

2. Member States may impose conditions, justified on grounds of public health protection, for the retail supply on their territory of medicinal products for sale at a distance to the public by means of information society services.

3. A common logo shall be established that is recognisable throughout the Union, while enabling the identification of the Member State where the person offering medicinal products for sale at a distance to the public is established. That logo shall be clearly displayed on websites offering medicinal products for sale at a distance to the public in accordance with point (d) of paragraph 1.

In order to harmonise the functioning of the common logo, the Commission shall adopt implementing acts regarding:

(a) the technical, electronic and cryptographic requirements for verification of the authenticity of the common logo;

(b) the design of the common logo.

Those implementing acts shall, where necessary, be amended to take account of technical and scientific progress. Those implementing acts shall be adopted in accordance with the procedure referred to in Article 121(2).

4. Each Member State shall set up a website providing at least the following:

(a) information on the national legislation applicable to the offering of medicinal products for sale at a distance to the public by means of information society services, including information on the fact that there may be differences between Member States regarding classification of medicinal products and the conditions for their supply;

(b) information on the purpose of the common logo;

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29 OJ L 178, 17.7.2000, p. 1.

(c) the list of persons offering the medicinal products for sale at a distance to the public by means of information society services in accordance with paragraph 1 as well as their website addresses;

(d) background information on the risks related to medicinal products supplied illegally to the public by means of information society services.

This website shall contain a hyperlink to the website referred to in paragraph 5.

5. The Agency shall set up a website providing the information referred to in points (b) and (d) of paragraph 4, information on the Union legislation applicable to falsified medicinal products as well as hyperlinks to the Member States' websites referred to in paragraph 4. The Agency's website shall explicitly mention that the Member States' websites contain information on persons authorised or entitled to supply medicinal products at a distance to the public by means of information society services in the Member State concerned.
6. Without prejudice to Directive 2000/31/EC and the requirements set out in this Title, Member States shall take the necessary measures to ensure that other persons than those referred to in paragraph 1 that offer medicinal products for sale at a distance to the public by means of information society services and that operate on their territory are subject to effective, proportionate and dissuasive penalties.

Article 85d

Without prejudice to the competences of the Member States, the Commission shall, in cooperation with the Agency and Member State authorities, conduct or promote information campaigns aimed at the general public on the dangers of falsified medicinal products. Those campaigns shall raise consumer awareness of the risks related to medicinal products supplied illegally at a distance to the public by means of information society services and of the functioning of the common logo, the Member States' websites and the Agency's website.

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,
- 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 an 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 fulfill 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

Chapter 1 - General provisions

Article 101

1. Member States shall operate a pharmacovigilance system for the fulfilment of their pharmacovigilance tasks and their participation in Union pharmacovigilance activities.

   The pharmacovigilance system shall be used to collect information on the risks of medicinal products as regards patients' or public health. That information shall in particular refer to adverse reactions in human beings, arising from use of the medicinal product within the terms of the marketing authorisation as well as from use outside the terms of the marketing authorisation, and to adverse reactions associated with occupational exposure.

2. Member States shall, by means of the pharmacovigilance system referred to in paragraph 1, evaluate all information scientifically, consider options for risk minimisation and prevention and take regulatory action concerning the marketing authorisation as necessary. They shall perform a regular audit of their pharmacovigilance system and report the results to the Commission on 21 September 2013 at the latest and then every 2 years thereafter.
3. Each Member State shall designate a competent authority for the performance of pharmacovigilance tasks.
4. The Commission may request Member States to participate, under the coordination of the Agency, in international harmonisation and standardisation of technical measures in relation to pharmacovigilance.

Article 102

The Member States shall:

(a) take all appropriate measures to encourage patients, doctors, pharmacists and other healthcare professionals to report suspected adverse reactions to the national competent authority; for these tasks, organisations representing consumers, patients and healthcare professionals may be involved as appropriate;

(b) facilitate patient reporting through the provision of alternative reporting formats in addition to web-based formats;

(c) take all appropriate measures to obtain accurate and verifiable data for the scientific evaluation of suspected adverse reaction reports;

(d) ensure that the public is given important information on pharmacovigilance concerns relating to the use of a medicinal product in a timely manner through publication on the web-portal and through other means of publicly available information as necessary;

(e) ensure, through the methods for collecting information and where necessary through the follow-up of suspected adverse reaction reports, that all appropriate measures are taken to identify clearly any biological medicinal product prescribed, dispensed, or sold in their territory which is the subject of a suspected adverse reaction report, with due regard to the name of the medicinal product, in accordance with Article 1(20), and the batch number;

(f) take the necessary measures to ensure that a marketing authorisation holder who fails to discharge the obligations laid down in this Title is subject to effective, proportionate and dissuasive penalties.

For the purposes of point (a) and (e) of the first paragraph the Member States may impose specific obligations on doctors, pharmacists and other health-care professionals.

Article 103

A Member State may delegate any of the tasks entrusted to it under this Title to another Member State subject to a written agreement of the latter. Each Member State may represent no more than one other Member State.

The delegating Member State shall inform the Commission, the Agency and all other Member States of the delegation in writing. The delegating Member State and the Agency shall make that information public.

Article 104

1. The marketing authorisation holder shall operate a pharmacovigilance system for the fulfilment of his pharmacovigilance tasks equivalent to the relevant Member State's pharmacovigilance system provided for under Article 101(1).
2. The marketing authorisation holder shall by means of the pharmacovigilance system referred to in paragraph 1 evaluate all information scientifically, consider options for risk minimisation and prevention and take appropriate measures as necessary.

   The marketing authorisation holder shall perform a regular audit of his pharmacovigilance system. He shall place a note concerning the main findings of the audit on the pharmacovigilance system master file and, based on the audit findings, ensure that an appropriate corrective action plan is prepared and implemented. Once the corrective actions have been fully implemented, the note may be removed.
3. As part of the pharmacovigilance system, the marketing authorisation holder shall:
   (a) have permanently and continuously at his disposal an appropriately qualified person responsible for pharmacovigilance;
   (b) maintain and make available on request a pharmacovigilance system master file;
   (c) operate a risk management system for each medicinal product;
   (d) monitor the outcome of risk minimisation measures which are contained in the risk management plan or which are laid down as conditions of the marketing authorisation pursuant to Articles 21a, 22 or 22a;
   (e) update the risk management system and monitor pharmacovigilance data to determine whether there are new risks or whether risks have changed or whether there are changes to the benefit-risk balance of medicinal products.

   The qualified person referred to in point (a) of the first subparagraph shall reside and operate in the Union and shall be responsible for the establishment and maintenance of the pharmacovigilance system. The marketing authorisation holder shall submit the name and contact details of the qualified person to the competent authority and the Agency.
4. Notwithstanding the provisions of paragraph 3, national competent authorities may request the nomination of a contact person for pharmacovigilance issues at national level reporting to the qualified person responsible for pharmacovigilance activities.

Article 104a

1. Without prejudice to paragraphs 2, 3 and 4 of this Article, holders of marketing authorisations granted before 21 July 2012 shall, by way of derogation from Article 104(3)(c), not be required to operate a risk management system for each medicinal product.
2. The national competent authority may impose an obligation on a marketing authorisation holder to operate a risk management system, as referred to in Article 104(3)(c), if there are concerns about the risks affecting the risk-benefit balance of an authorised medicinal product. In that context, the national

competent authority shall also oblige the marketing authorisation holder to submit a detailed description of the risk-management system which he intends to introduce for the medicinal product concerned.

The imposition of such obligations shall be duly justified, notified in writing and shall include the timeframe for submission of the detailed description of the risk-management system.

3. The national competent authority shall provide the marketing authorisation holder with an opportunity to present written observations in response to the imposition of the obligation within a time limit which it shall specify, if the marketing authorisation holder so requests within 30 days of receipt of the written notification of the obligation.
4. On the basis of the written observations submitted by the marketing authorisation holder, the national competent authority shall withdraw or confirm the obligation. Where the national competent authority confirms the obligation, the marketing authorisation shall be varied accordingly to include the measures to be taken as part of the risk management system as conditions of the marketing authorisation referred to in point (a) of Article 21a.

Article 105

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 national competent authorities in order to guarantee their independence in the performance of those pharmacovigilance activities.

The first paragraph shall not preclude the national competent authorities from charging fees to marketing authorisation holders for performing those activities by the national competent authorities on the condition that their independence in the performance of those pharmacovigilance activities is strictly guaranteed.

CHAPTER 2 - Transparency and communications

Article 106

Each Member State shall set up and maintain a national medicines web-portal which shall be linked to the European medicines web-portal established in accordance with Article 26 of Regulation (EC) No 726/2004. By means of the national medicines web-portals, the Member States shall make publicly available at least the following:

(a) public assessment reports, together with a summary thereof;
(b) summaries of product characteristics and package leaflets;
(c) summaries of risk management plans for medicinal products authorised in accordance with this Directive;
(d) the list of medicinal products referred to in Article 23 of Regulation (EC) No 726/2004;
(e) information on the different ways of reporting suspected adverse reactions to medicinal products to national competent authorities by healthcare professionals and patients, including the web-based structured forms referred to in Article 25 of Regulation (EC) No 726/2004.

Article 106a

1. As soon as the marketing authorisation holder intends to make a public announcement relating to information on pharmacovigilance concerns in relation to the use of a medicinal product, and in any event at the same time or before the public announcement is made, he shall be required to inform the national competent authorities, the Agency and the Commission.
   The marketing authorisation holder shall ensure that information to the public is presented objectively and is not misleading.
2. Unless urgent public announcements are required for the protection of public health, the Member States, the Agency and the Commission shall inform each other not less than 24 hours prior to a public announcement relating to information on pharmacovigilance concerns.
3. For active substances contained in medicinal products authorised in more than one Member State, the Agency shall be responsible for the coordination between national competent authorities of safety announcements and shall provide timetables for the information being made public.
   Under the coordination of the Agency, the Member States shall make all reasonable efforts to agree on a common message in relation to the safety of the medicinal product concerned and the timetables for their distribution. The Pharmacovigilance Risk Assessment Committee shall, at the request of the Agency, provide advice on those safety announcements.
4. When the Agency or national competent authorities make public information referred to in paragraphs 2 and 3, any information of a personal or commercially confidential nature shall be deleted unless its public disclosure is necessary for the protection of pu blic health.

CHAPTER 3 - Recording, reporting and assessment of pharmacovigilance data

Section 1 - Recording and reporting of suspected adverse reactions

Article 107

1. Marketing authorisation holders shall record all suspected adverse reactions in the Union or in third countries which are brought to their attention, whether reported spontaneously by patients or healthcare professionals, or occurring in the context of a post-authorisation study.
   Marketing authorisation holders shall ensure that those reports are accessible at a single point within the Union.
   By way of derogation from the first subparagraph, suspected adverse reactions occurring in the context of a clinical trial shall be recorded and reported in accordance with Directive 2001/20/EC.
2. Marketing authorisation holders shall not refuse to consider reports of suspected adverse reactions received electronically or by any other appropriate means from patients and healthcare professionals.
3. Marketing authorisation holders shall submit electronically to the database and data-processing network referred to in Article 24 of Regulation (EC) No 726/2004 (hereinafter referred to as the 'Eudravigilance database') information on all serious suspected adverse reactions that occur in the Union and in third countries within 15 days following the day on which the marketing authorisation

holder concerned gained knowledge of the event.

Marketing authorisation holders shall submit electronically to the Eudravigilance database information on all non-serious suspected adverse reactions that occur in the Union, within 90 days following the day on which the marketing authorisation holder concerned gained knowledge of the event.

For medicinal products containing the active substances referred to in the list of publications monitored by the Agency pursuant to Article 27 of Regulation (EC) No 726/2004, marketing authorisation holders shall not be required to report to the Eudravigilance database the suspected adverse reactions recorded in the listed medical literature, but they shall monitor all other medical literature and report any suspected adverse reactions.

4. Marketing authorisation holders shall establish procedures in order to obtain accurate and verifiable data for the scientific evaluation of suspected adverse reaction reports. They shall also collect follow-up information on these reports and submit the updates to the Eudravigilance database.
5. Marketing authorisation holders shall collaborate with the Agency and the Member States in the detection of duplicates of suspected adverse reaction reports.

Article 107a

1. Each Member State shall record all suspected adverse reactions that occur in its territory which are brought to its attention from healthcare professionals and patients. Member States shall involve patients and healthcare professionals, as appropriate, in the follow-up of any reports they receive in order to comply with Article 102(c) and (e).

   Member States shall ensure that reports of such reactions may be submitted by means of the national medicines web-portals or by other means.
2. For reports submitted by a marketing authorisation holder, Member States on whose territory the suspected adverse reaction occurred may involve the marketing authorisation holder in the follow-up of the reports.
3. Member States shall collaborate with the Agency and the marketing authorisation holders in the detection of duplicates of suspected adverse reaction reports.
4. Member States shall, within 15 days following the receipt of the reports of serious suspected adverse reactions referred to in paragraph 1, submit the reports electronically to the Eudravigilance database.

   They shall, within 90 days from the receipt of reports referred to in paragraph 1, submit reports of non-serious suspected adverse reactions electronically to the Eudravigilance database.

   Marketing authorisation holders shall access those reports through the Eudravigilance database.
5. Member States shall ensure that reports of suspected adverse reactions arising from an error associated with the use of a medicinal product that are brought to their attention are made available to the Eudravigilance database and to any authorities, bodies, organisations and/or institutions, responsible for patient safety within that Member State. They shall also ensure that the authorities responsible for medicinal products within that Member State are informed of any suspected adverse reactions brought to the attention of any other authority within that Member State. These reports shall be appropriately identified in the forms referred to in Article 25 of Regulation (EC) No 726/2004.

6. Unless there are justifiable grounds resulting from pharmacovigilance activities, individual Member States shall not impose any additional obligations on marketing authorisation holders for the reporting of suspected adverse reactions.

Section 2 - Periodic safety update reports

Article 107b

1. Marketing authorisation holders shall submit to the Agency periodic safety update reports containing:
   (a) summaries of data relevant to the benefits and risks of the medicinal product, including results of all studies with a consideration of their potential impact on the marketing authorisation;
   (b) a scientific evaluation of the risk-benefit balance of the medicinal product;
   (c) all data relating to the volume of sales of the medicinal product and any data in possession of the marketing authorisation holder relating to the volume of prescriptions, including an estimate of the population exposed to the medicinal product.

   The evaluation referred to in point (b) shall be based on all available data, including data from clinical trials in unauthorised indications and populations.

   The periodic safety update reports shall be submitted electronically.
2. The Agency shall make available the reports referred to in paragraph 1 to the national competent authorities, the members of the Pharmacovigilance Risk Assessment Committee, the Committee for Medicinal Products for Human Use and the coordination group by means of the repository referred to in Article 25a of Regulation (EC) No 726/2004.
3. By way of derogation from paragraph 1 of this Article, the holders of marketing authorisations for medicinal products referred to in Article 10(1), or Article 10a, and the holders of registrations for medicinal products referred to in Articles 14 or 16a, shall submit periodic safety update reports for such medicinal products in the following cases:
   (a) where such obligation has been laid down as a condition in the marketing authorisation in accordance with Article 21a or Article 22; or
   (b) when requested by a competent authority on the basis of concerns relating to pharmacovigilance data or due to the lack of periodic safety update reports relating to an active substance after the marketing authorisation has been granted. The assessment reports of the requested periodic safety update reports shall be communicated to the Pharmacovigilance Risk Assessment Committee, which shall consider whether there is a need for a single assessment report for all marketing authorisations for medicinal products containing the same active substance and inform the coordination group or the Committee for Medicinal Products for Human Use accordingly, in order to apply the procedures laid down in Article 107c(4) and Article 107e.

Article 107c

1. The frequency with which the periodic safety update reports are to be submitted shall be specified in the marketing authorisation.

   The dates of submission according to the specified frequency shall be calculated from the date of the authorisation.

2. Holders of marketing authorisations which were granted before 21 July 2012, and for which the frequency and dates of submission of the periodic safety update reports are not laid down as a condition to the marketing authorisation, shall submit the periodic safety update reports in accordance with the second subparagraph of this paragraph until another frequency or other dates of submission of the reports are laid down in the marketing authorisation or determined in accordance with paragraphs 4, 5 or 6.

   Periodic safety update reports shall be submitted to the competent authorities immediately upon request or in accordance with the following:

   (a) where a medicinal product has not yet been placed on the market, at least every 6 months following authorisation and until the placing on the market;

   (b) where a medicinal product has been placed on the market, at least every 6 months during the first 2 years following the initial placing on the market, once a year for the following 2 years and at three-yearly intervals thereafter.

3. Paragraph 2 shall also apply to medicinal products which are authorised only in one Member State and for which paragraph 4 does not apply.

4. Where medicinal products that are subject to different marketing authorisations contain the same active substance or the same combination of active substances, the frequency and dates of submission of the periodic safety update reports resulting from the application of paragraphs 1 and 2 may be amended and harmonised to enable a single assessment to be made in the context of a periodic safety update report work-sharing procedure and to set a Union reference date from which the submission dates are calculated.

   This harmonised frequency for the submission of the reports and the Union reference date may be determined, after consultation of the Pharmacovigilance Risk Assessment Committee, by one of the following:

   (a) the Committee for Medicinal Products for Human Use, where at least one of the marketing authorisations for the medicinal products containing the active substance concerned has been granted in accordance with the centralised procedure provided for in Chapter 1 of Title II of Regulation (EC) No 726/2004;

   (b) the coordination group, in other cases than those referred to in point (a).

   The harmonised frequency for the submission of the reports determined pursuant to the first and second subparagraphs shall be made public by the Agency. Marketing authorisation holders shall submit an application for a variation of the marketing authorisation accordingly.

5. For the purposes of paragraph 4, the Union reference date for medicinal products containing the same active substance or the same combination of active substances shall be one of the following:

   (a) the date of the first marketing authorisation in the Union of a medicinal product containing that active substance or that combination active substances;

(b) if the date referred to in point (a) cannot be ascertained, the earliest of the known dates of the marketing authorisations for a medicinal product containing that active substance or that combination of active substances.

6. Marketing authorisation holders shall be allowed to submit requests to the Committee for Medicinal Products for Human Use or the coordination group, as appropriate, to determine Union reference dates or to change the frequency of submission periodic safety update reports on one of the following grounds:
    (a) for reasons relating to public health;
    (b) in order to avoid a duplication of the assessment;
    (c) in order to achieve international harmonisation.

    Such requests shall be submitted in writing and shall be duly justified. The Committee for Medicinal Products for Human Use or the coordination group shall, following the consultation with the Pharmacovigilance Risk Assessment Committee, shall either approve or deny such requests. Any change in the dates or the frequency of submission of periodic safety update reports shall be made public by the Agency. The marketing authorisation holders shall accordingly submit an application for a variation of the marketing authorisation.
7. The Agency shall make public a list of Union reference dates and frequency of submission of periodic safety update reports by means of the European medicines web-portal.

    Any change to the dates of submission and frequency of periodic safety update reports specified in the marketing authorisation as a result of the application of paragraphs 4, 5 and 6 shall take effect 6 months after the date of such publication.

Article 107d

The national competent authorities shall assess periodic safety update reports to determine whether there are new risks or whether risks have changed or whether there are changes to the risk-benefit balance of medicinal products.

Article 107e

1. A single assessment of periodic safety update reports shall be performed for medicinal products authorised in more than one Member State and, in the cases of paragraphs 4 to 6 of Article 107c, for all medicinal products containing the same active substance or the same combination of active substances and for which a Union reference date and frequency of periodic safety update reports has been established.

    The single assessment shall be conducted by either of the following:
    (a) a Member State appointed by the coordination group where none of the marketing authorisations concerned has been granted in accordance with the centralised procedure provided for in Chapter 1 of Title II of Regulation (EC) No 726/2004; or
    (b) a rapporteur appointed by the Pharmacovigilance Risk Assessment Committee, where at least one of the marketing authorisations concerned has been granted in accordance with the centralised procedure provided for in Chapter 1 of Title II of Regulation (EC) No 726/2004.

When selecting the Member State in accordance with point (a) of the second subparagraph, the coordination group shall take into account whether any Member State is acting as a reference Member State, in accordance with Article 28(1).

2. The Member State or rapporteur, as appropriate, shall prepare an assessment report within 60 days of receipt of the periodic safety update report and send it to the Agency and to the Member States concerned. The Agency shall send the report to the marketing authorisation holder.

   Within 30 days of receipt of the assessment report, the Member States and the marketing authorisation holder may submit comments to the Agency and to the rapporteur or Member State.

3. Following the receipt of the comments referred to in paragraph 2, the rapporteur or Member State shall within 15 days update the assessment report taking into account any comments submitted, and forward it to the Pharmacovigilance Risk Assessment Committee. The Pharmacovigilance Risk Assessment Committee shall adopt the assessment report with or without further changes at its next meeting and issue a recommendation. The recommendation shall mention the divergent positions with the grounds on which they are based. The Agency shall include the adopted assessment report and the recommendation in the repository set up under Article 25a of Regulation (EC) No 726/2004 and forward both to the marketing authorisation holder.

Article 107f

Following the assessment of periodic safety update reports, the national competent authorities shall consider whether any action concerning the marketing authorisation for the medicinal product concerned is necessary.

They shall maintain, vary, suspend or revoke the marketing authorisation as appropriate.

Article 107g

1. In the case of a single assessment of periodic safety update reports that recommends any action concerning more than one marketing authorisation in accordance with Article 107e(1) which does not include any marketing authorisation granted in accordance with the centralised procedure provided for in Chapter 1 of Title II of Regulation (EC) No 726/2004, the coordination group shall, within 30 days of receipt of the report of the Pharmacovigilance Risk Assessment Committee, consider the report and reach a position on the maintenance, variation, suspension or revocation of the marketing authorisations concerned, including a timetable for the implementation of the agreed position.
2. If, within the coordination group, the Member States represented reach agreement on the action to be taken by consensus, the chairman shall record the agreement and send it to the marketing authorisation holder and the Member States. The Member States shall adopt necessary measures to maintain, vary, suspend or revoke the marketing authorisations concerned in accordance with the timetable for implementation determined in the agreement.

   In the event of a variation, the marketing authorisation holder shall submit to the national competent authorities an appropriate application for a modification, including an updated summary of product characteristics and package leaflet within the determined timetable for implementation.

   If an agreement by consensus cannot be reached, the position of the majority of the Member States

represented within the coordination group shall be forwarded to the Commission which shall apply the procedure laid down in Articles 33 and 34.

Where the agreement reached by the Member States represented within the coordination group or the position of the majority of Member States differs from the recommendation of the Pharmacovigilance Risk Assessment Committee, the coordination group shall attach to the agreement or the majority position a detailed explanation of the scientific grounds for the differences together with the recommendation.

3. In the case of a single assessment of periodic safety update reports that recommends any action concerning more than one marketing authorisation in accordance with Article 107e(1) which includes at least one marketing authorisation granted in accordance with the centralised procedure provided for in Chapter 1 of Title II of Regulation (EC) No 726/2004, the Committee for Medicinal Products for Human Use shall, within 30 days of receipt of the report of the Pharmacovigilance Risk Assessment Committee, consider the report and adopt an opinion on the maintenance, variation, suspension or revocation of the marketing authorisations concerned, including a timetable for the implementation of the opinion.

   Where this opinion of the Committee for Medicinal Products for Human Use differs from the recommendation of the Pharmacovigilance Risk Assessment Committee, the Committee for Medicinal Products for Human Use shall attach to its opinion a detailed explanation of the scientific grounds for the differences together with the recommendation.

4. On the basis of the opinion of the Committee for Medicinal Products for Human Use referred to in paragraph 3, the Commission shall:

   (a) adopt a decision addressed to the Member States concerning the measures to be taken in respect of marketing authorisations granted by the Member States and concerned by the procedure provided for in this section; and

   (b) where the opinion states that regulatory action concerning the marketing authorisation is necessary, adopt a decision to vary, suspend or revoke the marketing authorisations granted in accordance with the centralised procedure provided for in Regulation (EC) No 726/2004 and concerned by the procedure provided for in this section.

Articles 33 and 34 of this Directive shall apply to the adoption of the decision referred to in point (a) of the first subparagraph of this paragraph and to its implementation by the Member States.

Article 10 of Regulation (EC) No 726/2004 shall apply to the decision referred to in point (b) of the first subparagraph of this paragraph. Where the Commission adopts such decision, it may also adopt a decision addressed to the Member States pursuant to Article 127a of this Directive.

Section 3 - Signal detection

Article 107h

1. Regarding medicinal products authorised in accordance with this Directive, national competent authorities in collaboration with the Agency, shall take the following measures:

   (a) monitor the outcome of risk minimisation measures contained in risk management plans and of the conditions referred to in Articles 21a, 22 or 22a;

   (b) assess updates to the risk management system;

(c) monitor the data in the Eudravigilance database to determine whether there are new risks or whether risks have changed and whether those risks impact on the risk-benefit balance.

2. The Pharmacovigilance Risk Assessment Committee shall perform the initial analysis and prioritisation of signals of new risks or risks that have changed or changes to the risk-benefit balance. Where it considers that follow-up action may be necessary, the assessment of those signals and agreement on any subsequent action concerning the marketing authorisation shall be conducted in a timescale commensurate with the extent and seriousness of the issue.

3. The Agency and national competent authorities and the marketing authorisation holder shall inform each other in the event of new risks or risks that have changed or changes to the risk-benefit balance being detected.

   Member States shall ensure that marketing authorisation holders inform the Agency and national competent authorities in the event of new risks or risks that have changed or when changes to the risk-benefit balance have been detected.

Section 4 - Urgent Union procedure

Article 107i

1. A Member State or the Commission, as appropriate, shall, on the basis of concerns resulting from the evaluation of data from pharmacovigilance activities, initiate the procedure provided for in this section by informing the other Member States, the Agency and the Commission where:
   (a) it considers suspending or revoking a marketing authorisation;
   (b) it considers prohibiting the supply of a medicinal product;
   (c) it considers refusing the renewal of a marketing authorisation; or
   (d) it is informed by the marketing authorisation holder that, on the basis of safety concerns, the holder has interrupted the placing on the market of a medicinal product or has taken action to have a marketing authorisation withdrawn, or intends to take such action or has not applied for the renewal of a marketing authorisation.

   1.(a). A Member State or the Commission, as appropriate, shall, on the basis of concerns resulting from the evaluation of data from pharmacovigilance activities, inform the other Member States, the Agency and the Commission where it considers that a new contraindication, a reduction in the recommended dose or a restriction to the indications of a medicinal product is necessary. The information shall outline the action considered and the reasons therefor.

   Any Member State or the Commission, as appropriate, shall, when urgent action is considered necessary, initiate the procedure provided for in this section in any of the cases referred to in this paragraph.

   Where the procedure provided for in this section is not initiated, for medicinal products authorised in accordance with the procedures laid down in Chapter 4 of Title III, the case shall be brought to the attention of the coordination group.

   Article 31 shall be applicable where the interests of the Union are involved.

1.(b) Where the procedure provided for in this section is initiated, the Agency shall verify whether the safety concern relates to medicinal products other than the one covered by the information, or whether it is common to all products belonging to the same range or therapeutic class.

Where the medicinal product involved is authorised in more than one Member State, the Agency shall without undue delay inform the initiator of the procedure of the outcome of this verification, and the procedures laid down in Articles 107j and 107k shall apply. Otherwise, the safety concern shall be addressed by the Member State concerned. The Agency or the Member State, as applicable, shall make the information that the procedure has been initiated available to marketing authorisation holders.

2. Without prejudice to the provisions of$_1$ paragraphs 1 and 1a of this Article, and Articles 107j and 107k, a Member State may, where urgent action is necessary to protect public health, suspend the marketing authorisation and prohibit the use of the medicinal product concerned on its territory until a definitive decision is adopted. It shall inform the Commission, the Agency and the other Member States no later than the following working day of the reasons for its action.
3. At any stage of the procedure laid down in Articles 107j to 107k, the Commission may request Member States in which the medicinal product is authorised to take temporary measures immediately.
   Where the scope of the procedure, as determined$_2$ in accordance with paragraphs 1 and 1a, includes medicinal products authorised in accordance with Regulation (EC) No 726/2004, the Commission may, at any stage of the procedure initiated under this section, take temporary measures immediately in relation to those marketing authorisations.
4. The information referred to in this Article may relate to individual medicinal products or to a range of medicinal products or a therapeutic class.
   If the Agency identifies that the safety concern relates to more medicinal products than those which are covered by the information or that it is common to all medicinal products belonging to the same range or therapeutic class, it shall extend the scope of the procedure accordingly.
   Where the scope of the procedure initiated under this Article concerns a range of medicinal products or therapeutic class, medicinal products authorised in accordance with Regulation (EC) No 726/2004 which belong to that range or class shall also be included in the procedure.
5. At the time of the information referred to$_3$ in paragraphs 1 and 1a, the Member State shall make available to the Agency all relevant scientific information that it has at its disposal and any assessment by the Member State.

Article 107j

1. Following receipt of the information referred to$_4$ in paragraphs 1 and 1a of Article 107i, the Agency shall publicly announce the initiation of the procedure by means of the European medicines web-portal. In parallel,
   Member States may publicly announce the initiation on their national medicines web-portals.
   The announcement shall specify the matter submitted to the Agency in accordance with Article 107i, and the medicinal products and, where applicable, the active substances concerned. It shall contain information

on the right of the marketing authorisation holders, healthcare professionals and the public to submit to the Agency information relevant to the procedure and it shall state how such information may be submitted.

2. The Pharmacovigilance Risk Assessment Committee shall assess the matter which has been submitted to the Agency in accordance with Article 107i. The rapporteur shall closely collaborate with the rapporteur appointed by the Committee for Medicinal Products for Human Use and the Reference Member State for the medicinal products concerned.

   For the purposes of that assessment, the marketing authorisation holder may submit comments in writing.

   Where the urgency of the matter permits, the Pharmacovigilance Risk Assessment Committee may hold public hearings, where it considers that this is appropriate on justified grounds particularly with regard to the extent and seriousness of the safety concern. The hearings shall be held in accordance with the modalities specified by the Agency and shall be announced by means of the European medicines web-portal. The announcement shall specify the modalities of participation.

   In the public hearing, due regard shall be given to the therapeutic effect of the medicinal product.

   The Agency shall, in consultation with the parties concerned, draw up Rules of Procedure on the organisation and conduct of public hearings, in accordance with Article 78 of Regulation (EC) No 726/2004.

   Where a marketing authorisation holder or another person intending to submit information has confidential data relevant to the subject matter of the procedure, he may request permission to present that data to the Pharmacovigilance Risk Assessment Committee in a non-public hearing.

3. Within 60 days of the information being submitted, the Pharmacovigilance Risk Assessment Committee shall make a recommendation, stating the reasons on which it is based, having due regard to the therapeutic effect of the medicinal product. The recommendation shall mention the divergent positions and the grounds on which they are based. In the case of urgency, and on the basis of a proposal by its chairman, the Pharmacovigilance Risk Assessment Committee may agree to a shorter deadline. The recommendation shall include any or a combination of the following conclusions:

   (a) no further evaluation or action is required at Union level;
   (b) the marketing authorisation holder should conduct further evaluation of data together with the follow-up of the results of that evaluation;
   (c) the marketing authorisation holder should sponsor a post-authorisation safety study together with the follow up evaluation of the results of that study;
   (d) the Member States or marketing authorisation holder should implement risk minimisation measures;
   (e) the marketing authorisation should be suspended, revoked or not renewed;
   (f) the marketing authorisation should be varied.

   For the purposes of point (d) of the first subparagraph, the recommendation shall specify the risk minimisation measures recommended and any conditions or restrictions to which the marketing authorisation should be made subject.

   Where, in the cases referred to in point (f) of the first subparagraph, it is recommended to change or add information in the summary of product characteristics or the labelling or package leaflet, the

recommendation shall suggest the wording of such changed or added information and where in the summary of the product characteristics, labelling or package leaflet such wording should be placed.

Article 107k

1. Where the scope of the procedure, as determined in accordance with Article 107i(4), does not include any marketing authorisation granted in accordance with the centralised procedure provided for in Chapter 1 of Title II of Regulation (EC) No 726/2004, the coordination group shall, within 30 days of receipt of the recommendation of the Pharmacovigilance Risk Assessment Committee, consider the recommendation and reach a position on the maintenance, variation, suspension, revocation or refusal of the renewal of the marketing authorisation concerned, including a timetable for the implementation of the agreed position. Where an urgent adoption of the position is necessary, and on the basis of a proposal by its chairman, the coordination group may agree to a shorter deadline.
2. If, within the coordination group, the Member States represented reach agreement on the action to be taken by consensus, the chairman shall record the agreement and send it to the marketing authorisation holder and the Member States. The Member States shall adopt necessary measures to maintain, vary, suspend, revoke or refuse renewal of the marketing authorisation concerned in accordance with the implementation timetable determined in the agreement.

   In the event that a variation is agreed upon, the marketing authorisation holder shall submit to the national competent authorities an appropriate application for a variation, including an updated summary of product characteristics and package leaflet within the determined timetable for implementation.

   If an agreement by consensus cannot be reached, the position of the majority of the Member States represented within the coordination group shall be forwarded to the Commission which shall apply the procedure laid down in Articles 33 and 34. However, by way of derogation from Article 34(1), the procedure referred to in Article 121(2) shall apply.

   Where the agreement reached by the Member States represented within the coordination group or the position of the majority of the Member States represented within the coordination group differs from the recommendation of the Pharmacovigilance Risk Assessment Committee, the coordination group shall attach to the agreement or majority position a detailed explanation of the scientific grounds for the differences together with the recommendation.
3. Where the scope of the procedure, as determined in accordance with Article 107i(4), includes at least one marketing authorisation granted in accordance with the centralised procedure provided for in Chapter 1 of Title II of Regulation (EC) No 726/2004, the Committee for Medicinal Products for Human Use shall, within 30 days of receipt of the recommendation of the Pharmacovigilance Risk Assessment Committee, consider the recommendation and adopt an opinion on the maintenance, variation, suspension, revocation or refusal of the renewal of the marketing authorisations concerned. Where an urgent adoption of the opinion is necessary, and on the basis of a proposal by its chairman, the Committee for Medicinal Products for Human Use may agree to a shorter deadline.

   Where the opinion of the Committee for Medicinal Products for Human Use differs from the recommendation of the Pharmacovigilance Risk Assessment Committee, the Committee for Medicinal

Products for Human Use shall attach to its opinion a detailed explanation of the scientific grounds for the differences together with the recommendation.

4. On the basis of the opinion of the Committee for Medicinal Products for Human Use referred to in paragraph 3, the Commission shall:
    (a) adopt a decision addressed to the Member States concerning the measures to be taken in respect of marketing authorisations that are granted by the Member States and that are subject to the procedure provided for in this section; and
    (b) where the opinion is that regulatory action is necessary, adopt a decision to vary, suspend, revoke or refuse renewal of the marketing authorisations granted in accordance with Regulation (EC) No 726/2004 and subject to the procedure provided for in this section.

    Articles 33 and 34 of this Directive shall apply to the adoption of the decision referred to in point (a) of the first subparagraph of this paragraph and to its implementation by the Member States. However, by way of derogation from Article 34(1) of this Directive, the procedure referred to in Article 121(2) thereof shall apply.

    Article 10 of Regulation (EC) No 726/2004 shall apply to the decision referred to in point (b) of the first subparagraph of this paragraph. However, by way of derogation from Article 10(2) of that Regulation, the procedure referred to in Article 87(2) thereof shall apply. Where the Commission adopts such decision, it may also adopt a decision addressed to the Member States pursuant to Article 127a of this Directive.

Section 5 - Publication of assessments

Article 107l

The Agency shall make public the final assessment conclusions, recommendations, opinions and decisions referred to in Articles 107b to 107k by means of the European medicines web-portal.

CHAPTER 4 - Supervision of post-authorisation safety studies

Article 107m

1. This Chapter applies to non-interventional post-authorisation safety studies which are initiated, managed or financed by the marketing authorisation holder voluntarily or pursuant to obligations imposed in accordance with Articles 21a or 22a, and which involve the collection of safety data from patients or healthcare professionals.
2. This Chapter is without prejudice to national and Union requirements for ensuring the well-being and rights of participants in non-interventional post-authorisation safety studies.
3. The studies shall not be performed where the act of conducting the study promotes the use of a medicinal product.
4. Payments to healthcare professionals for participating in non-interventional post-authorisation safety studies shall be restricted to the compensation for time and expenses incurred.

5. The national competent authority may require the marketing authorisation holder to submit the protocol and the progress reports to the competent authorities of the Member States in which the study is conducted.
6. The marketing authorisation holder shall send the final report to the competent authorities of the Member States in which the study was conducted within 12 months of the end of data collection.
7. While a study is being conducted, the marketing authorisation holder shall monitor the data generated and consider its implications for the risk-benefit balance of the medicinal product concerned.
   Any new information which might influence the evaluation of the risk-benefit balance of the medicinal product shall be communicated to the competent authorities of the Member State in which the medicinal product has been authorised in accordance with Article 23.
   The obligation laid down in the second subparagraph is without prejudice to the information on the results of studies that the marketing authorisation holder shall make available by means of the periodic safety update reports as laid down in Article 107b.
8. Articles 107n to 107q shall apply exclusively to studies referred to in paragraph 1 which are conducted pursuant to an obligation imposed in accordance with Articles 21a or 22a.

Article 107n

1. Before a study is conducted, the marketing authorisation holder shall submit a draft protocol to the Pharmacovigilance Risk Assessment Committee, except for studies to be conducted in only one Member State that requests the study according to Article 22a. For such studies, the marketing authorisation holder shall submit a draft protocol to the national competent authority of the Member State in which the study is conducted.
2. Within 60 days of the submission of the draft protocol the national competent authority or the Pharmacovigilance Risk Assessment Committee, as appropriate, shall issue:
   (a) a letter endorsing the draft protocol;
   (b) a letter of objection, which shall set out in detail the grounds for the objection, in any of the following cases:
      i) it considers that the conduct of the study promotes the use of a medicinal product;
      ii) it considers that the design of the study does not fulfil the study objectives; or
   (c) a letter notifying the marketing authorisation holder that the study is a clinical trial falling under the scope of Directive 2001/20/EC.
3. The study may commence only when the written endorsement from the national competent authority or the Pharmacovigilance Risk Assessment Committee, as appropriate, has been issued.
   Where a letter of endorsement as referred to in paragraph 2(a) has been issued, the marketing authorisation holder shall forward the protocol to the competent authorities of the Member States in which the study is to be conducted and may thereafter commence the study according to the endorsed protocol.

Article 107o

After a study has been commenced, any substantial amendments to the protocol shall be submitted, before their implementation, to the national competent authority or to the Pharmacovigilance Risk Assessment Committee, as appropriate. The national competent authority or the Pharmacovigilance Risk Assessment Committee, as appropriate, shall assess the amendments and inform the marketing authorisation holder of its endorsement or objection. Where applicable, the marketing authorisation holder shall inform Member States in which the study is conducted.

Article 107p

1. Upon completion of the study, a final study report shall be submitted to the national competent authority or the Pharmacovigilance Risk Assessment Committee within 12 months of the end of data collection unless a written waiver has been granted by the national competent authority or the Pharmacovigilance Risk Assessment Committee, as appropriate.
2. The marketing authorisation holder shall evaluate whether the results of the study have an impact on the marketing authorisation and shall, if necessary, submit to the national competent authorities an application to vary the marketing authorisation.
3. Together with the final study report, the marketing authorisation holder shall electronically submit an abstract of the study results to the national competent authority or the Pharmacovigilance Risk Assessment Committee.

Article 107q

1. Based on the results of the study and after consultation of the marketing authorisation holder, the Pharmacovigilance Risk Assessment Committee may make recommendations concerning the marketing authorisation, stating the reasons on which they are based. The recommendations shall mention the divergent positions and the grounds on which they are based.
2. When recommendations for the variation, suspension or revocation of the marketing authorisation are made for a medicinal product authorised by the Member States pursuant to this Directive, the Member States represented within the coordination group shall agree a position on the matter taking into account the recommendation referred to in paragraph 1 and including a timetable for the implementation of the agreed position.

   If, within the coordination group, the Member States represented reach agreement on the action to be taken by consensus, the chairman shall record the agreement and send it to the marketing authorisation holder and the Member States. The Member States shall adopt necessary measures to vary, suspend or revoke the marketing authorisation concerned in accordance with the implementation timetable determined in the agreement.

   In the event that a variation is agreed upon, the marketing authorisation holder shall submit to the national competent authorities an appropriate application for a variation, including an updated summary of product characteristics and package leaflet within the determined timetable for implementation.

   The agreement shall be made public on the European medicines web-portal established in accordance with Article 26 of Regulation (EC) No 726/2004.

   If an agreement by consensus cannot be reached, the position of the majority of the Member States

represented within the coordination group shall be forwarded to the Commission, which shall apply the procedure laid down in Articles 33 and 34.

Where the agreement reached by the Member States represented within the coordination group or the position of the majority of Member States differs from the recommendation of the Pharmacovigilance Risk Assessment Committee, the coordination group shall attach to the agreement or majority position a detailed explanation of the scientific grounds for the differences together with the recommendation.

CHAPTER 5 - Implementation, Delegation and Guidance

Article 108

In order to harmonise the performance of the pharmacovigilance activities provided for in this Directive, the Commission shall adopt implementing measures in the following areas for which pharmacovigilance activities are provided for in Article 8(3), and in Articles 101, 104, 104a, 107, 107a, 107b, 107h, 107n and 107p:

(a) the content and maintenance of the pharmacovigilance system master file kept by the marketing authorisation holder;

(b) the minimum requirements for the quality system for the performance of pharmacovigilance activities by the national competent authorities and the marketing authorisation holder;

(c) the use of internationally agreed terminology, formats and standards for the performance of pharmacovigilance activities;

(d) the minimum requirements for the monitoring of data in the Eudravigilance database to determine whether there are new risks or whether risks have changed;

(e) the format and content of the electronic transmission of suspected adverse reactions by Member States and the marketing authorisation holder;

(f) the format and content of electronic periodic safety update reports and risk management plans;

(g) the format of protocols, abstracts and final study reports for the post-authorisation safety studies.

Those measures shall take account of the work on international harmonisation carried out in the area of pharmacovigilance and shall, where necessary, be revised to take account of technical and scientific progress. Those measures shall be adopted in accordance with the regulatory procedure referred to in Article 121(2).

Article 108a

In order to facilitate the performance of pharmacovigilance activities within the Union, the Agency shall, in cooperation with competent authorities and other interested parties, draw up:

(a) guidance on good pharmacovigilance practices for both competent authorities and marketing authorisation holders;

(b) scientific guidance on post-authorisation efficacy studies.

Article 108b

The Commission shall make public a report on the performance of pharmacovigilance tasks by the Member States on 21 July 2015 at the latest and then every 3 years thereafter.

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/EC 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, in cooperation with the Agency, ensure that the legal requirements governing medicinal products are complied with, by means of inspections, if necessary unannounced, and, where appropriate, by asking an Official Medicines Control Laboratory or a laboratory designated for that purpose to carry out tests on samples. This cooperation shall consist in sharing information with the Agency on both inspections that are planned and that have been conducted. Member States and the Agency shall cooperate in the coordination of inspections in third countries. The inspections shall include but not be limited to the ones mentioned in paragraphs 1a to 1f.

a. Manufacturers, located in the Union or in third countries, and wholesale distributors of medicinal products shall be subject to repeated inspections.

b. The competent authority of the Member State concerned shall have a system of supervision including by inspections at an appropriate frequency based on risk, at the premises of the manufacturers, importers, or distributors of active substances, located on its territory, and effective follow-up thereof.

Whenever it considers that there are grounds for suspecting non-compliance with the legal requirements laid down in this Directive, including the principles and guidelines of good manufacturing practice and good distribution practices referred to in point (f) of Article 46 and in Article 47, the competent authority may carry out inspections at the premises of:

or distributors of active substances located in third countries;

manufacturers or importers of excipients.

c. Inspections referred to in paragraphs 1a and 1b may also be carried out in the Union and in third countries at the request of a Member State, the Commission or the Agency.

d. Inspections may also take place at the premises of marketing authorisation holders and of brokers of medicinal products.

e. In order to verify whether the data submitted in order to obtain a conformity certificate comply with the monographs of the European Pharmacopoeia, the standardisation body of the nomenclatures and the quality norms within the meaning of the Convention relating to the elaboration of the European Pharmacopoeia (the European Directorate for the Quality of Medicines and Healthcare) 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.

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

g. Inspections shall be carried out by officials representing the competent authority who shall be empowered to:

inspect the manufacturing or commercial establishments of manufacturers of medicinal products, of active substances or of excipients, and any laboratories employed by the holder of the manufacturing authorisation to carry out checks pursuant to Article 20;

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;

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;

inspect the premises, records, documents and pharmacovigilance system master file of the marketing authorisation holder or any firms employed by the marketing authorisation holder to perform the activities described in Title IX.

h. Inspections shall be carried out in accordance with the guidelines referred to in Article 111a.

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.

3. After every inspection as referred to in paragraph 1, the competent authority shall report on whether the inspected entity complies with the principles and guidelines of good manufacturing practice and good distribution practices referred to in Articles 47 and 84, as applicable, or on whether the marketing authorisation holder complies with the requirements laid down in Title IX.

The competent authority which carried out the inspection shall communicate the content of those

reports to the inspected entity.

Before adopting the report, the competent authority shall give the inspected entity concerned the opportunity to submit comments.

4. Without prejudice to any arrangements which may have been concluded between the Union 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 this Article.
5. Within 90 days of an inspection as referred to in paragraph 1, a certificate of good manufacturing practice or good distribution practices shall, when applicable, be issued to the inspected entity if the outcome of the inspection shows that it complies with the principles and guidelines of good manufacturing practice or good distribution practices as provided for by Union 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 and good distribution practices which they issue in a Union database managed by the Agency on behalf of the Union. Pursuant to Article 52a(7), Member States shall also enter information in that database regarding the registration of importers, manufacturers and distributors of active substances. The database shall be publicly accessible.
7. If the outcome of the inspection as referred to in points (a), (b) and (c) of >1 paragraph 1g < or the outcome of an inspection of a distributor of medicinal products or active substances or a manufacturer of excipients>1 --- < is that the inspected entity does not comply with the legal requirements and/or the principles and guidelines of good manufacturing practice or good distribution practices as provided for by Union law, the information shall be entered in the Union database as provided for in paragraph 6.
8. If the outcome of the inspection referred to in >1 point (d) of paragraph 1g < is that the marketing authorisation holder does not comply with the pharmacovigilance system as described in the pharmacovigilance system master file and with Title IX, the competent authority of the Member State concerned shall bring the deficiencies to the attention of the marketing authorisation holder and give him the opportunity to submit comments.

   In such case the Member State concerned shall inform the other Member States, the Agency and the Commission.

   Where appropriate, the Member State concerned shall take the necessary measures to ensure that a marketing authorisation holder is subject to effective, proportionate and dissuasive penalties.

Article 111a

The Commission shall adopt detailed guidelines laying down the principles applicable to inspections referred to in Article 111.

Member States shall, in cooperation with the Agency, establish the form and content of the authorisation referred to in Articles 40(1) and 77(1), of the reports referred to in Article 111(3), of the certificates of good manufacturing practice and of the certificates of good distribution practices referred to in Article 111(5).

Article 111b

1. At the request of a third country, the Commission shall assess whether that country's regulatory framework applicable to active substances exported to the Union and the respective control and enforcement activities ensure a level of protection of public health equivalent to that of the Union. If the assessment confirms such equivalence, the Commission shall adopt a decision to include the third country in a list. The assessment shall take the form of a review of relevant documentation and, unless arrangements as referred to in Article 51(2) of this Directive are in place that cover this area of activity, that assessment shall include an on-site review of the third country's regulatory system and, if necessary, an observed inspection of one or more of the third country's manufacturing sites for active substances. In the assessment particular account shall be taken of:
    (a) the country's rules for good manufacturing practice;
    (b) the regularity of inspections to verify compliance with good manufacturing practice;
    (c) the effectiveness of enforcement of good manufacturing practice;
    (d) the regularity and rapidity of information provided by the third country relating to non-compliant producers of active substances.
2. The Commission shall adopt the necessary implementing acts to apply the requirements set out in points (a) to (d) of paragraph 1 of this Article. Those implementing acts shall be adopted in accordance with the procedure referred to in Article 121(2).
3. The Commission shall verify regularly whether the conditions laid down in paragraph 1 are fulfilled. The first verification shall take place no later than 3 years after the country has been included in the list referred to in paragraph 1.
4. The Commission shall perform the assessment and verification referred to in paragraphs 1 and 3 in cooperation with the Agency and the competent authorities of the Member States.

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[1] 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[1] 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 or vary a marketing authorisation if the view is taken that the medicinal product is harmful or that it lacks therapeutic efficacy, or that the risk-benefit balance is not favourable, or that its qualitative and quantitative composition is not as declared. Therapeutic efficacy shall be considered to be lacking when it is concluded that therapeutic results cannot be obtained from the medicinal product.

A marketing authorisation may also be suspended, revoked or varied where the particulars supporting the application as provided for in Articles 8, 10, 10a, 10b, 10c or 11 are incorrect or have not been amended in accordance with Article 23, or where any conditions referred to in Articles 21a, 22 or 22a have not been fulfilled or where the controls referred to in Article 112 have not been carried out.

The second paragraph of this Article also applies in cases where the manufacture of the medicinal product is not carried out in compliance with the particulars provided pursuant to point (d) of Article 8(3), or where controls are not carried out in compliance with the control methods described pursuant to point (h) of Article 8(3).

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; or
    (b) it lacks therapeutic efficacy; or
    (c) the risk-benefit balance is not favourable; or
    (d) its qualitative and quantitative composition is not as declared; orthe 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.
3. The competent authority may, for a medicinal product for which the supply has been prohibited or which has been withdrawn from the market in accordance with paragraphs 1 and 2, in exceptional circumstances during a transitional period allow the supply of the medicinal product to patients who are already being treated with the medicinal product.

Article 117a

1. Member States shall have a system in place which aims at preventing medicinal products that are suspected to present a danger to health from reaching the patient.
2. The system referred to in paragraph 1 shall cover the receipt and handling of notifications of suspected falsified medicinal products as well as of suspected quality defects of medicinal products. The system shall also cover recalls of medicinal products by marketing authorisation holders or withdrawals of medicinal products from the market ordered by national competent authorities from all relevant actors in the supply chain both during and outside normal working hours. The system shall also make it possible to recall, where necessary with the assistance of health professionals, medicinal products from patients who received such products.
3. If the medicinal product in question is suspected of presenting a serious risk to public health, the competent authority of the Member State in which that product was first identified shall, without any delay, transmit a rapid alert notification to all Member States and all actors in the supply chain in that

Member State. In the event of such medicinal products being deemed to have reached patients, urgent public announcements shall be issued within 24 hours in order to recall those medicinal products from the patients. Those announcements shall contain sufficient information on the suspected quality defect or falsification and the risks involved.

4. Member States shall by 22 July 2013 notify the Commission of the details of their respective national systems referred to in this Article.

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 118a

1. The Member States shall lay down the rules on penalties applicable to infringements of the national provisions adopted pursuant to this Directive and shall take all necessary measures to ensure that those penalties are implemented. The penalties must be effective, proportionate and dissuasive.

   Those penalties shall not be inferior to those applicable to infringements of national law of similar nature and importance.

   The rules referred to in paragraph 1 shall address, inter alia, the following:

   (a) the manufacturing, distribution, brokering, import and export of falsified medicinal products, as well as the sale of falsified medicinal products at a distance to the public by means of information society services;

   (b) non-compliance with the provisions laid down in this Directive on manufacturing, distribution, import and export of active substances;

   (c) non-compliance with the provisions laid down in this Directive on the use of excipients.

2. Where relevant, the penalties shall take into account the risk to public health presented by the falsification of medicinal products.
3. The Member States shall notify the national provisions adopted pursuant to this Article to the Commission by 2 January 2013 and shall notify any subsequent amendment of those provisions without delay.

   By 2 January 2018, the Commission shall submit a report to the European Parliament and to the Council giving an overview of the transposition measures of Member States as regards this Article, together with an evaluation of the effectiveness of those measures.

Article 118b

Member States shall organise meetings involving patients 'and consumers' organisations and, as necessary, Member States' enforcement officers, in order to communicate public information about the actions undertaken in the area of prevention and enforcement to combat the falsification of medicinal products.

Article 118c

Member States, in applying this Directive, shall take the necessary measures to ensure cooperation between competent authorities for medicinal products and customs authorities.

Article 119

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

TITLE XII - STANDING COMMITTEE

Article 120

The Commission shall adopt any changes which are necessary in order to adapt Annex I to take account of scientific and technical progress. Those measures, designed to amend non-essential elements of this Directive, shall be adopted in accordance with the regulatory procedure with scrutiny referred to in Article 121(2a).

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.
   Where reference is made to this paragraph, Article 5a(1) to (4) and Article 7 of Decision 1999/468/EC shall apply, having regard to the provisions of Article 8 thereof.
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 rules of procedure of the Standing Committee shall be made public.

Article 121a

1. The power to adopt the delegated acts referred to in$_1$ Articles 22b, 47, 52b and 54a shall be conferred on the Commission for a period of 5 years from 20 January 2011. The Commission shall draw up a report in respect of the delegated powers not later than 6 months before the end of the 5 year period. The delegation of powers shall be automatically extended for periods of an identical duration, unless the European Parliament or the Council revokes it in accordance with Article 121b.
2. As soon as it adopts a delegated act, the Commission shall notify it simultaneously to the European Parliament and to the Council.

3. The power to adopt delegated acts is conferred on the Commission subject to the conditions laid down in Articles 121b and 121c.

Article 121b

1. The delegation of powers referred to in$_2$ Articles 22b, 47, 52b and 54a may be revoked at any time by the European Parliament or by the Council.
2. The institution which has commenced an internal procedure for deciding whether to revoke the delegation of powers shall endeavour to inform the other institution and the Commission within a reasonable time before the final decision is taken, indicating the delegated powers which could be subject to revocation and possible reasons for a revocation.
3. The decision of revocation shall put an end to the delegation of the powers specified in that decision. It shall take effect immediately or at a later date specified therein. It shall not affect the validity of the delegated acts already in force. It shall be published in the Official Journal of the European Union.

Article 121c

1. The European Parliament or the Council may object to a delegated act within a period of 2 months from the date of notification.
   At the initiative of the European Parliament or the Council that period shall be extended by 2 months.
2. If, on expiry of the period referred to in paragraph 1, neither the European Parliament nor the Council has objected to the delegated act, it shall be published in the Official Journal of the European Union and shall enter into force on the date stated therein.
   The delegated act may be published in the Official Journal of the European Union and enter into force before the expiry of that period if the European Parliament and the Council have both informed the Commission of their intention not to raise objections.
3. If either the European Parliament or the Council objects to the delegated act within the period referred to in paragraph 1, it shall not enter into force. The institution which objects shall state the reasons for objecting to the delegated act.

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 send electronically the reports referred to in Article 111(3) to the competent authorities of another Member State or to the Agency.
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 authorisation holder shall be obliged to notify the Member States concerned forthwith of any action taken by the holder to suspend the marketing of a medicinal product, to withdraw a medicinal product from the market, to request the withdrawal of a marketing authorisation or not to apply for the renewal of a marketing authorisation, together with the reasons for such action. The marketing authorisation holder shall in particular declare if such action is based on any of the grounds set out in Article 116 or Article 117(1).

a. The marketing authorisation holder shall also make the notification pursuant to paragraph 2 of this Article in cases where the action is taken in a third country and where such action is based on any of the grounds set out in Article 116 or Article 117(1).

b. The marketing authorisation holder shall furthermore notify the Agency where the action referred to in paragraph 2 or 2a of this Article is based on any of the grounds referred to in Article 116 or Article 117(1).

c. The Agency shall forward notifications received in accordance with paragraph 2b to all Member States without undue delay.

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. Each year, the Agency shall make public a list of the medicinal products for which marketing authorisations have been refused, revoked or suspended in the Union, whose supply has been prohibited or which have been withdrawn from the market, including the reasons for such action.

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. Member States may decide that Article 63(1) and (2) shall not apply to medicinal products authorised under paragraph 1.
3. Before granting such a marketing authorisation, a Member State:
    (a) shall notify the marketing authorisation holder, in the Member State in which the medicinal product concerned is authorised, of the proposal to grant a marketing authorisation under this Article in respect of the medicinal product concerned.
    (b) may request the competent authority in that Member State to submit copies of the assessment report referred to in Article 21(4) and of the marketing authorisation in force in respect of the medicinal product concerned. If so requested, the competent authority in that Member State shall supply, within 30 days of receipt of the request, a copy of the assessment report and the marketing authorisation in respect of the medicinal product concerned.
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 opinion

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 Committee for Medicinal Products for Human Use in its opinion refers to recommended conditions or restrictions as provided for in points (c), (ca), (cb) or (cc) of Article 9(4) thereof, the Commission may adopt a decision addressed to the Member States, in accordance with 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. marketing authorization is available.

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.

ANNEX I - ANALYTICAL, PHARMACOTOXICOLOGICAL AND CLINICAL STANDARDS AND PROTOCOLS IN RESPECT OF THE TESTING OF MEDICINAL PRODUCTS

TABLE OF CONTENTS

2.7. Clinical Summary

3. Module 3: Chemical, pharmaceutical and biological information for medicinal products containing chemical and/or biological active substances
   - 3.1. Format and presentation
   - 3.2. Content: basic principles and requirements
     - 3.2.1.Active substance(s)
       - 3.2.1.1.General information and information related to the starting and raw materials
       - 3.2.1.2.Manufacturing process of the active substance(s)
       - 3.2.1.3.Characterisation of the active substance(s)
       - 3.2.1.4.Control of active substance(s)
       - 3.2.1.5.Reference standards or materials
       - 3.2.1.6.Container and closure system of the active substance
       - 3.2.1.7.Stability of the active substance(s)
     - 3.2.2.Finished medicinal product
       - 3.2.2.1.Description and composition of the finished medicinal product
       - 3.2.2.2.Pharmaceutical development
       - 3.2.2.3.Manufacturing process of the finished medicinal product
       - 3.2.2.4.Control of excipients
       - 3.2.2.5.Control of the finished medicinal product
       - 3.2.2.6.Reference standards or materials
       - 3.2.2.7.Container and closure of the finished medicinal product
       - 3.2.2.8.Stability of the finished medicinal product
4. Module 4: Non-clinical reports
   - 4.1. Format and Presentation
   - 4.2. Content: basic principles and requirements
     - 4.2.1.Pharmacology ?M2 2001L0083 ó EN ó 16.11.2012 ó 011.001 ó 120
     - 4.2.2.Pharmaco-kinetics
     - 4.2.3.Toxicology
5. Module 5: Clinical study reports
   - 5.1. Format and Presentation
   - 5.2. Content: basic principles and requirements
     - 5.2.1.Reports of bio-pharmaceutics studies
     - 5.2.2.Reports of studies pertinent to pharmaco-kinetics using human bio-materials
     - 5.2.3.Reports of human pharmaco-kinetic studies
     - 5.2.4.Reports of human pharmaco-dynamic studies
     - 5.2.5.Reports of efficacy and safety studies
       - 5.2.5.1.Study Reports of Controlled Clinical Studies Pertinent to the Claimed Indication
       - 5.2.5.2.Study reports of uncontrolled clinical studies reports of analyses of data from more than one study and other clinical study reports
     - 5.2.6.Reports of post-marketing experience

5.2.7.Case reports forms and individual patient listings

Part II: Specific marketing authorisation dossiers and requirements

1. Well-established medicinal use
2. Essentially similar medicinal products
3. Additional data required in specific situations
4. Similar biological medicinal products
5. Fixed combination medicinal products
6. Documentation for applications in exceptional circumstances
7. Mixed marketing authorisation applications

Part III: Particular medicinal products

1. Biological medicinal products
   1.1. Plasma-derived medicinal product
   1.2. Vaccines
2. Radio-pharmaceuticals and precursors
   2.1. Radio-pharmaceuticals
   2.2. Radio-pharmaceutical precursors for radio-labelling purposes
3. Homeopathic medicinal products
4. Herbal medicinal products
5. Orphan Medicinal Products

Part IV: Advanced therapy medicinal products

1. Introduction
2. Definitions
   2.1. Gene therapy medicinal product
   2.2. Somatic cell therapy medicinal product
3. Specific requirements regarding Module 3
   3.1. Specific requirements for all advanced therapy medicinal products
   3.2. Specific requirements for gene therapy medicinal products
      3.2.1.Introduction: finished product, active substance and starting materials
         3.2.1.1.Gene therapy medicinal product containing recombinant nucleic acid sequence(s) or genetically modified microorganism(s) or virus(es)
         3.2.1.2.Gene therapy medicinal product containing genetically modified cells
         3.2.1.3..
         3.2.1.4..
         3.2.1.5..
      3.2.2. Specific requirements
   3.3. Specific requirements for somatic cell therapy medicinal products and tissue engineered products
      3.3.1.Introduction: finished product, active substance and starting materials
      3.3.2.Specific requirements
         3.3.2.1.Starting materials
         3.3.2.2.Manufacturing process

Introduction and general principles

(1) The particulars and documents accompanying an application for marketing authorisation pursuant to Articles 8 and 10 (1) shall be presented in accordance with the requirements set out in this Annex and shall follow the

guidance published by the Commission in The rules governing medicinal products in the European Community, Volume 2 B, Notice to applicants, Medicinal products for human use, Presentation and content of the dossier, Common Technical Document (CTD).

(2) The particulars and documents shall be presented as five modules: Module 1 provides European Community specific administrative data; Module 2 provides quality, non-clinical and clinical summaries, Module 3 provides chemical, pharmaceutical and biological information, Module 4 provides non-clinical reports and Module 5 provides clinical study reports. This presentation implements a common format for all ICH[30] regions (European Community, United States of America, Japan). These five Modules shall be presented in strict accordance with the format, content and numbering system delineated in details in Volume 2 B of the Notice to Applicants referred to above.

(3) The European Community-CTD-presentation is applicable for all types of marketing authorisation applications irrespective of the procedure to be applied (i.e. centralised, mutual recognition or national) and of whether they are based on a full or abridged application. It is also applicable for all types of products including new chemical entities (NCE), radio-pharmaceuticals, plasma derivatives, vaccines, herbal medicinal products, etc.

(4) In assembling the dossier for application for marketing authorisation, applicants shall also take into account the scientific guidelines relating to the quality, safety and efficacy of medicinal products for human use as adopted by the Committee for Proprietary Medicinal Products (CPMP) and published by the European Medicine Evaluation Agency (EMEA) and the other pharmaceutical Community guidelines published by the Commission in the different volumes of The rules governing medicinal products in the European Community.

(5) With respect to the quality part (chemical, pharmaceutical and biological) of the dossier, all monographs including general monographs and general chapters of the European Pharmacopoeia are applicable.

(6) The manufacturing process shall comply with the requirements of Commission Directive 91/356/EEC laying down the principles and guidelines of Good Manufacturing Practice (GMP) for medicinal products for human use[31] and with the principles and guidelines on GMP, published by the Commission in The rules governing medicinal products in the European Community, Volume 4.

(7) ll information, which is relevant to the evaluation of the medicinal product concerned, shall be included in the application, whether favourable or unfavourable to the product. In particular, all relevant details shall be given of any incomplete or abandoned pharmaco-toxicological or clinical test or trial relating to the medicinal product and/or completed trials concerning therapeutic indications not covered by the application.

(8) All clinical trials, conducted within the European Community, must comply with the requirements of Directive 2001/20/EC of the European Parliament and of the Council 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 use[32]. To be taken into account during the assessment of an application, clinical trials, conducted outside the European Community, which relate to medicinal products intended to be used in the European Community, shall be designed, implemented and

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

31 OJ L 193, 17.7.1991, p. 30.

32 OJ L 121, 1.5.2001, p. 34.

reported on what good clinical practice and ethical principles are concerned, on the basis of principles, which are equivalent to the provisions of Directive 2001/20/EC. They shall be carried out in accordance with the ethical principles that are reflected, for example, in the Declaration of Helsinki.

(9) Non-clinical (pharmaco-toxicological) studies shall be carried out in conformity with the provisions related to Good Laboratory Practice laid down in Council Directives 87/18/EEC on the harmonisation of regulations and administrative provisions relating to the application of the principles of good laboratory practice and the verification of their application for tests in chemical substances[33] and 88/320/EEC on the inspection and verification of good laboratory practice (GLP)[34].

(10) Member States shall also ensure that all tests on animals are conducted in accordance with Council Directive 86/609/EEC of 24 November 1986 on the approximation of laws, regulation and administrative provisions of the Member States regarding the protection of animals for experimental and other scientific purposes.

(11) In order to monitor the benefit/risk assessment, any new information not in the original application and all pharmaco-vigilance information shall be submitted to the competent authority. After marketing authorisation has been granted, any change to the data in the dossier shall be submitted to the competent authorities in accordance with the requirements of Commission Regulations (EC) No 1084/2003[35] and (EC) No 1085/2003[36] of the Commission or, if relevant, in accordance with national provisions, as well as the requirements in Volume 9 of Commission publication The rules governing medicinal products in the European Community.

This Annex is divided in four different parts:

- Part I describes the application format, the summary of product characteristics, the labelling, the leaflet and presentation requirements for standard applications (Modules 1 to 5).
- Part II provides derogation for 'Specific applications', i.e. well-established medicinal use, essentially similar products, fixed combinations, similar biological products, exceptional circumstances and mixed applications (part bibliographic and part own studies).
- Part III deals with 'Particular application requirements' for biological medicinal products (Plasma Master File; Vaccine Antigen Master File), radio-pharmaceuticals, homeopathic medicinal products, herbal medicinal products and orphan medicinal products.
- Part IV deals with 'Advanced therapy medicinal products' and concerns specific requirements for gene therapy medicinal products (using human autologous or allogeneic system, or xenogeneic system) and cell therapy medicinal products both of human or animal origin and xenogeneic transplantation medicinal products.

PART I - STANDARDISED MARKETING AUTHORISATION DOSSIER REQUIREMENTS

1. MODULE 1: ADMINISTRATIVE INFORMATION

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33 OJ L 15, 17.1.1987, p. 29.

34 OJ L 145, 11.6.1988, p. 35.

35 See p. 1 of this Official Journal.

36 See p. 24 of this Official Journal.

1.1. Table of contents

A comprehensive table of contents of Modules 1 to 5 of the dossier submitted for marketing authorisation application shall be presented.

1.2. Application form

The medicinal product, which is the subject of the application, shall be identified by name and name of the active substance(s), together with the pharmaceutical form, the route of administration, the strength and the final presentation, including packaging.

The name and address of the applicant shall be given, together with the name and address of the manufacturers and the sites involved in the different stages of the manufacture (including the manufacturer of the finished product and the manufacturer(s) of the active substance(s)), and where relevant the name and address of the importer.

The applicant shall identify the type of application and indicate what samples, if any, are also provided.

Annexed to the administrative data shall be copies of the manufacturing authorisation as defined in Article 40, together with a list of countries in which authorisation has been granted, copies of all the summaries of product characteristics in accordance with Article 11 as approved by Member States and a list of countries in which an application has been submitted.

As outlined in the application form, the applicants shall provide, inter alia, details of the medicinal product subject of the application, the legal basis of the application, the proposed marketing authorisation holder and manufacture(s), information on orphan medicinal product status, scientific advice and paediatric development program.

1.3. Summary of product characteristics, labelling and package leaflet

1.3.1. Summary of product characteristics

The applicant shall propose a summary of the product characteristics, in accordance with Article 11.

1.3.2. Labelling and package leaflet

A proposed labelling text for immediate and outer packaging as well as for the package leaflet shall be provided. These shall be in accordance with all mandatory items listed in Title V on the labelling of medicinal products for human use (Article 63) and on package leaflet (Article 59).

1.3.3. Mock-ups and specimens

The applicant shall provide specimen and/or mock-ups of the immediate and outer packaging, labels and package leaflets for the medicinal product concerned.

1.3.4. Summaries of product characteristics already approved in the Member States

Annexed to the administrative data of the application form shall be copies of all the summaries of product characteristics in accordance with Articles 11 and 21 as approved by Member States, where applicable and a list of countries in which an application has been submitted.

1.4. Information about the experts

In accordance with Article 12 (2) experts must provide detailed reports of their observations on the documents and particulars which constitute the marketing authorisation dossier and in particular on Modules 3, 4 and 5 (chemical, pharmaceutical and biological documentation, non-clinical

documentation and clinical documentation, respectively). The experts are required to address the critical points related to the quality of the medicinal product and of the investigations carried out on animals and human beings and bring out all the data relevant for evaluation.

These requirements shall be met by providing a quality overall summary, a non-clinical overview (data from studies carried out in animals) and a clinical overview that shall be located in Module 2 of the marketing authorisation application dossier. A declaration signed by the experts together with brief information on their educational background, training and occupational experience shall be presented in Module 1. The experts shall have suitable technical or professional qualifications. The professional relationship of the expert to the applicant shall be declared.

1.5. Specific requirements for different types of applications

Specific requirements for different types of applications are addressed in Part II of the present Annex.

1.6. 1.6. Environmental risk assessment

Where applicable, applications for marketing authorisations shall include a risk assessment overview evaluating possible risks to the environment due to the use and/or disposal of the medicinal product and make proposals for appropriate labelling provisions. Environmental risk connected with the release of medicinal products containing or consisting of GMOs (Genetically Modified Organisms) within the meaning of Article 2 of Directive 2001/18/EC of the European Parliament and of the Council of 12 March 2001 on the deliberate release into the environment of modified organisms and repealing Council Directive 90/220/EEC[37] shall be addressed.

Information pertaining to the environmental risk shall appear as an appendix to Module 1.

The information shall be presented in accordance with the provisions of Directive 2001/18/EC, taking into account any guidance documents published by the Commission in connection with the implementation of the said Directive.

The information shall consist of:

- an introduction;
- a copy of any written consent or consents to the deliberate release into the environment of the GMO(s) for research and development purposes according to Part B of Directive 2001/18/EC;
- the information requested in Annexes II to IV of the Directive 2001/18/EC, including detection and identification methods as well as unique code of the GMO, plus any additional information on the GMO or the product of relevance to evaluating the environmental risk;
- an environment risk assessment (ERA) report prepared on basis of the information specified in Annexes III and IV of Directive 2001/18/EC and in accordance with Annex II of Directive 2001/18/EC;
- taking into account the above information and the ERA, a conclusion which proposes an appropriate risk management strategy which includes, as relevant to the GMO and product in question, a post-market monitoring plan and the identification of any special particulars which need to appear in the Summary of Product Characteristics, labelling and package leaflet;

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37 OJ L 106, 17.4.2001, p. 1.

- appropriate measures in order to inform the public.

  A dated signature of the author, information on the author's educational, training and occupational experience, and a statement of the author's relationship with the applicant, shall be included.

2. MODULE 2: SUMMARIES

This Module aims to summarise the chemical, pharmaceutical and biological data, the non-clinical data and the clinical data presented in Modules 3, 4 and 5 of the dossier for marketing authorisation, and to provide the reports/overviews described in Article 12 of this Directive.

Critical points shall be addressed and analysed. Factual summaries including tabular formats shall be provided. Those reports shall provide cross-references to tabular formats or to the information contained in the main documentation presented in Module 3 (chemical, pharmaceutical and biological documentation), Module 4 (non-clinical documentation) and Module 5 (clinical documentation).

Information contained in Module 2 shall be presented in accordance with the format, content and numbering system delineated in the Volume 2 of the Notice to Applicants. The overviews and summaries shall comply with the basic principles and requirements as laid down herewith:

2.1. Overall table of contents

Module 2 shall contain a table of contents for the scientific documentation submitted in Modules 2 to 5.

2.2. Introduction

Information on the pharmacological class, mode of action and proposed clinical use of the medicinal product for which a marketing authorisation is requested shall be supplied.

2.3. Quality overall summary

A review of the information related to the chemical, pharmaceutical and biological data shall be provided in a quality overall summary.

Key critical parameters and issues related to quality aspects shall be emphasised as well as justification in cases where the relevant guidelines are not followed. This document shall follow the scope and outline of the corresponding detailed data presented in Module 3.

2.4. Non-clinical overview

An integrated and critical assessment of the non-clinical evaluation of the medicinal product in animals/in vitro shall be required. Discussion and justification of the testing strategy and of deviation from the relevant guidelines shall be included.

Except for biological medicinal products, an assessment of the impurities and degradation products shall be included along with their potential pharmacological and toxicological effects. The implications of any differences in the chirality, chemical form, and impurity profile between the compound used in the non-clinical studies and the product to be marketed shall be discussed.

For biological medicinal products, comparability of material used in non-clinical studies, clinical studies, and the medicinal product for marketing shall be assessed.

Any novel excipient shall be the subject of a specific safety assessment.

The characteristics of the medicinal product, as demonstrated by the non-clinical studies shall be

defined and the implications of the findings for the safety of the medicinal product for the intended clinical use in human shall be discussed.

2.5. Clinical overview

The clinical overview is intended to provide a critical analysis of the clinical data included in the clinical summary and Module 5. The approach to the clinical development of the medicinal product, including critical study design, decisions related to and performance of the studies shall be provided.

A brief overview of the clinical findings, including important limitations as well as an evaluation of benefits and risks based on the conclusions of the clinical studies shall be provided. An interpretation of the way the efficacy and safety findings support the proposed dose and target indications and an evaluation of how the summary of product characteristics and other approaches will optimise the benefits and manage the risks is required.

Efficacy or safety issues encountered in development and unresolved issues shall be explained.

2.6. Non-clinical summary

The results of pharmacology, pharmaco-kinetics and toxicology studies carried out in animals/in vitro shall be provided as factual written and tabulated summaries which shall be presented in the following order:

- Introduction
- Pharmacology Written Summary
- Pharmacology Tabulated Summary
- Pharmaco-kinetics Written Summary
- Pharmaco-kinetics Tabulated Summary
- Toxicology Written Summary
- Toxicology Tabulated Summary.

2.7. Clinical Summary

A detailed, factual summary of the clinical information on the medicinal product included in Module 5 shall be provided. This shall include the results of all bio-pharmaceutics studies, of clinical pharmacology studies, and of clinical efficacy and safety studies. A synopsis of the individual studies is required.

Summarised clinical information shall be presented in the following order:

- Summary of Bio-pharmaceutics and Associated Analytical Methods
- Summary of Clinical Pharmacology Studies
- Summary of Clinical Efficacy
- Summary of Clinical Safety
- Synopses of Individual Studies

3. MODULE 3: CHEMICAL, PHARMACEUTICAL AND BIOLOGICAL INFORMATION FOR MEDICINAL PRODUCTS CONTAINING CHEMICAL AND/OR BIOLOGICAL ACTIVE SUBSTANCES

3.1. Format and presentation

The general outline of Module 3 is as follows:

- Table of contents

- Body of data
  - *Active substance*
  - *General Information*
    - Nomenclature
    - Structure
    - General Properties
  - *Manufacture*
    - Manufacturer(s)
    - Description of Manufacturing Process and Process Controls
    - Control of Materials
    - Controls of Critical Steps and Intermediates
    - Process Validation and/or Evaluation
    - Manufacturing Process Development
  - *Characterisation*
    - Elucidation of Structure and other Characteristics
    - Impurities
  - *Control of Active Substance*
    - Specification
    - Analytical Procedures
    - Validation of Analytical Procedures
    - Batch Analyses
    - Justification of Specification
  - *Reference Standards or Materials*
  - *Container Closure System*
  - *Stability*
    - Stability Summary and Conclusions
    - Post-approval Stability Protocol and Stability Commitment
    - Stability Data
- *Finished Medicinal Product*
  - *Description and Composition of the Medicinal Product*
  - *Pharmaceutical Development*
    - Components of the Medicinal Product
      - Active Substance
      - Excipients
    - Medicinal Product
      - Formulation Development
      - Overages
      - Physicochemical and Biological Properties
    - Manufacturing Process Development
    - Container Closure System
    - Microbiological Attributes

        - Compatibility
    - *Manufacture*
        - Manufacturer(s)
        - Batch Formula
        - Description of Manufacturing Process and Process Controls
        - Controls of Critical Steps and Intermediates
        - Process Validation and/or Evaluation
    - *Control of Excipients*
        - Specifications
        - Analytical Procedures
        - Validation of Analytical Procedures
        - Justification of Specifications
        - Excipients of Human or Animal Origin
        - Novel Excipients
    - *Control of Finished Medicinal Product*
        - Specification(s)
        - Analytical Procedures
        - Validation of Analytical Procedures
        - Batch Analyses
        - Characterisation of Impurities
        - Justification of Specification(s)
    - *Reference Standards or Materials*
    - *Container Closure System*
    - *Stability*
        - Stability Summary and Conclusion
        - Post-approval Stability Protocol and Stability Commitment
        - Stability Data
- *Appendices*
    - Facilities and Equipment (Biological Medicinal Products only)
    - Adventitious Agents Safety Evaluation
    - Excipients
- *European Community Additional Information*
    - Process Validation Scheme for the Medicinal Product
    - Medical Device
    - Certificate(s) of Suitability
    - Medicinal products containing or using in the manufacturing process materials of animal and/or human origin (TSE procedure)
- Literature References

3.2. Content: basic principles and requirements

(1) The chemical, pharmaceutical and biological data that shall be provided shall include for the active substance(s) and for the finished medicinal product all of

relevant information on: the development, the manufacturing process, the characterisation and properties, the quality control operations and requirements, the stability as well as a description of the composition and presentation of the finished medicinal product.

(2) Two main sets of information shall be provided, dealing with the active substance(s) and with the finished medicinal product, respectively.

(3) This Module shall in addition supply detailed information on the starting and raw materials used during the manufacturing operations of the active substance(s) and on the excipients incorporated in the formulation of the finished medicinal product.

(4) All the procedures and methods used for manufacturing and controlling the active substance and the finished medicinal product shall be described in sufficient details to enable them to be repeated in control tests, carried out at the request of the competent authority. All test procedures shall correspond to the state of scientific progress at the time and shall be validated. Results of the validation studies shall be provided. In the case of test procedures included in the European Pharmacopoeia, this description shall be replaced by the appropriate detailed reference to the monograph(s) and general chapter(s).

(5) The monographs of the European Pharmacopoeia shall be applicable to all substances, preparations and pharmaceutical forms appearing in it. In respect of other substances, each Member State may require observance of its own national pharmacopoeia.

However, where a material in the European Pharmacopoeia or in the pharmacopoeia of a Member State has been prepared by a method liable to leave impurities not controlled in the pharmacopoeia monograph, these impurities and their maximum tolerance limits must be declared and a suitable test procedure must be described. In cases where a specification contained in a monograph of the European Pharmacopoeia or in the national pharmacopoeia of a Member State might be insufficient to ensure the quality of the substance, the competent authorities may request more appropriate specifications from the marketing authorisation holder. The competent authorities shall inform the authorities responsible for the pharmacopoeia in question. The marketing authorisation holder shall provide the authorities of that pharmacopoeia with the details of the alleged insufficiency and the additional specifications applied.

In the case of analytical procedures included in the European Pharmacopoeia, this description shall be replaced in each relevant section by the appropriate detailed reference to the monograph(s) and general chapter(s).

(6) In case where starting and raw materials, active substance(s) or excipient(s) are described neither in the European Pharmacopoeia nor in the pharmacopoeia of a Member State, compliance with the monograph of a third

country pharmacopoeia can be accepted. In such cases, the applicant shall submit a copy of the monograph accompanied by the validation of the analytical procedures contained in the monograph and by a translation where appropriate.

(7) Where the active substance and/or a raw and starting material or excipient(s) are the subject of a monograph of the European Pharmacopoeia, the applicant can apply for a certificate of suitability that, where granted by the European Directorate for the Quality of Medicines, shall be presented in the relevant section of this Module. Those certificates of suitability of the monograph of the European Pharmacopoeia are deemed to replace the relevant data of the corresponding sections described in this Module. The manufacturer shall give the assurance in writing to the applicant that the manufacturing process has not been modified since the granting of the certificate of suitability by the European Directorate for the Quality of Medicines.

(8) For a well-defined active substance, the active substance manufacturer or the applicant may arrange for the
- detailed description of the manufacturing process
- quality control during manufacture, and
- process validation

to be supplied in a separate document directly to the competent authorities by the manufacturer of the active substance as an Active Substance Master File.
In this case, the manufacturer shall, however, provide the applicant with all of the data, which may be necessary for the latter to take responsibility for the medicinal product. The manufacturer shall confirm in writing to the applicant that he shall ensure batch to batch consistency and not modify the manufacturing process or specifications without informing the applicant. Documents and particulars supporting the application for such a change shall be supplied to the competent authorities; these documents and particulars will be also supplied to the applicant when they concern the open part of the active substance master file.

(9) Specific measures concerning the prevention of the transmission of animal spongiform encephalopathies (materials from ruminant origin): at each step of the manufacturing process, the applicant must demonstrate the compliance of the materials used with the Note for Guidance on Minimising the Risk of Transmitting Animal Spongiform Encephalopathy Agents via Medicinal Products and its updates, published by the Commission in the Official Journal of the European Union. Demonstration of compliance with the said Note for Guidance can be done by submitting either, preferably a certificate of suitability to the relevant monograph of the European Pharmacopoeia that has been granted by

the European Directorate for the Quality of Medicines or by the supply of scientific data to substantiate this compliance.

(10) For adventitious agents, information assessing the risk with respect to potential contamination with adventitious agents, whether they are non-viral or viral, as laid down in relevant guidelines as well as in relevant general monograph and general chapter of the European Pharmacopoeia, shall be provided.

(11) Any special apparatus and equipment, which may be used at any stage of the manufacturing process and control operations of the medicinal product, shall be described in adequate details.

(12) Where applicable and if needed, a CE marking which is required by Community legislation on medical devices shall be provided.

Special attention shall be paid to the following selected elements.

3.2.1. Active substance(s)

3.2.1.1. General information and information related to the starting and raw materials

a) Information on the nomenclature of the active substance shall be provided, including recommended International Non-proprietary Name (INN), European Pharmacopoeia name if relevant, chemical name(s).

The structural formula, including relative and absolute stereo-chemistry, the molecular formula, and the relative molecular mass shall be provided. For biotechnological medicinal products if appropriate, the schematic amino acid sequence and relative molecular mass shall be provided.

A list shall be provided of physicochemical and other relevant properties of the active substance, including biological activity for biological medicinal products.

b) For the purposes of this Annex, starting materials shall mean all the materials from which the active substance is manufactured or extracted.

For biological medicinal products, starting materials shall mean any substance of biological origin such as micro-organisms, organs and tissues of either plant or animal origin, cells or fluids (including blood or plasma) of human or animal origin, and biotechnological cell constructs (cell substrates, whether they are recombinant or not, including primary cells).

A biological medicinal product is a product, the active substance of which is a biological substance. A biological substance is a substance that is produced by or extracted from a biological source and that needs for its characterisation and the determination of its quality a combination of physico-chemical-biological testing, together with the production process and its control. The following shall be considered as biological medicinal products: immunological medicinal products and medicinal products derived from human blood and human plasma as defined, respectively in paragraphs (4) and (10) of Article 1; medicinal products falling within the scope of Part A of the Annex to Regulation (EEC) No 2309/93; advanced therapy medicinal products

as defined in Part IV of this Annex.

Any other substances used for manufacturing or extracting the active substance(s) but from which this active substance is not directly derived, such as reagents, culture media, foetal calf serum, additives, and buffers involved in chromatography, etc. are known as raw materials.

3.2.1.2.Manufacturing process of the active substance(s)

a) The description of the active substance manufacturing process represents the applicant's commitment for the manufacture of the active substance. To adequately describe the manufacturing process and process controls, appropriate information as laid down in guidelines published by the Agency shall be provided.

b) All materials needed in order to manufacture the active substance(s) shall be listed, identifying where each material is used in the process. Information on the quality and control of these materials shall be provided. Information demonstrating that materials meet standards appropriate for their intended use shall be provided.

Raw materials shall be listed and their quality and controls shall also be documented.

The name, address, and responsibility of each manufacturer, including contractors, and each proposed production site or facility involved in manufacturing and testing shall be provided.

c) For biological medicinal products, the following additional requirements shall apply.

The origin and history of starting materials shall be described and documented.

Regarding the specific measures for the prevention of the Transmission of animal Spongiform Encephalopathies, the applicant must demonstrate that the active substance complies with the Note for Guidance on Minimising the Risk of Transmitting Animal Spongiform Encephalopathy Agents via Medicinal Products and its updates, published by the Commission in the Official Journal of the European Union.

When cell banks are used, the cell characteristics shall be shown to have remained unchanged at the passage level used for the production and beyond.

Seed materials, cell banks, pools of serum or plasma and other materials of biological origin and, whenever possible, the materials from which they are derived shall be tested for adventitious agents.

If the presence of potentially pathogenic adventitious agents is inevitable, the corresponding material shall be used only when further processing ensures their elimination and/or inactivation, and this shall be validated.

Whenever possible, vaccine production shall be based on a seed lot system and on established cell banks. For bacterial and viral vaccines, the characteristics of the infectious agent shall be demonstrated on the seed. In addition, for live vaccines, the stability of the attenuation characteristics shall be demonstrated on the seed; if this proof is not sufficient, the attenuation characteristics shall also be demonstrated at the production stage.

For medicinal products derived from human blood or plasma, the origin and the criteria

and procedures for collection, transportation and storage of the starting material shall be described and documented in accordance with provisions laid down in Part III of this Annex.

The manufacturing facilities and equipment shall be described.

d) Tests and acceptance criteria carried out at every critical step, information on the quality and control of intermediates and process validation and/or evaluation studies shall be provided as appropriate.

e) If the presence of potentially pathogenic adventitious agents is inevitable, the correspondent material shall be used only when further processing ensures their elimination and/or inactivation and this shall be validated in the section dealing with viral safety evaluation.

f) A description and discussion of the significant changes made to the manufacturing process during development and/or manufacturing site of the active substance shall be provided.

3.2.1.3.Characterisation of the active substance(s)

Data highlighting the structure and other characteristics of the active substance(s) shall be provided.

Confirmation of the structure of the active substance(s) based on any physico-chemical and/or immuno-chemical and/or biological methods, as well as information on impurities shall be provided.

3.2.1.4.Control of active substance(s)

Detailed information on the specifications used for routine control of active substance(s), justification for the choice of these specifications, methods of analysis and their validation shall be provided.

The results of control carried out on individual batches manufactured during development shall be presented.

3.2.1.5.Reference standards or materials

Reference preparations and standards shall be identified and described in detail. Where relevant, chemical and biological reference material of the European Pharmacopoeia shall be used.

3.2.1.6.Container and closure system of the active substance

A description of the container and the closure system(s) and their specifications shall be provided.

3.2.1.7.Stability of the active substance (s)

a) The types of studies conducted, protocols used, and the results of the studies shall be summarized

b) Detailed results of the stability studies, including information on the analytical procedures used to generate the data and validation of these procedures shall be presented in an appropriate format

c) The post authorisation stability protocol and stability commitment shall be provided

3.2.2.Finished medicinal product

3.2.2.1.Description and composition of the finished medicinal product

A description of the finished medicinal product and its composition shall be provided. The information shall include the description of the pharmaceutical form and composition with all the constituents of the finished medicinal product, their amount on a per-unit basis, the function of the constituents of:

- the active substance(s),
- the constituent(s) of the excipients, whatever their nature or the quantity used, including colouring matter, preservatives, adjuvants, stabilisers, thickeners, emulsifiers, flavouring and aromatic substances, etc.,
- the constituents, intended to be ingested or otherwise administered to the patient, of the outer covering of the medicinal products (hard capsules, soft capsules, rectal capsules, coated tablets, films-coated tablets, etc.),
- these particulars shall be supplemented by any relevant data concerning the type of container and, where appropriate, its manner of closure, together with details of devices with which the medicinal product will be used or administered and which will be delivered with the medicinal product.

The 'usual terminology', to be used in describing the constituents of medicinal products, shall mean, notwithstanding the application of the other provisions in Article 8 (3) ©:

- in respect of substances which appear in the European Pharmacopoeia or, failing this, in the national pharmacopoeia of one of the Member States, the main title at the head of the monograph in question, with reference to the pharmacopoeia concerned,
- in respect of other substances, the international non-proprietary name (INN) recommended by the World Health Organisation, or, failing this, the exact scientific designation; substances not having an international non-proprietary name or an exact scientific designation shall be described by a statement of how and from what they were prepared, supplemented, where appropriate, by any other relevant details,
- in respect of colouring matter, designation by the 'E' code assigned to them in Council Directive 78/25/EEC of 12 December 1977 on the approximation of the rules of the Member States concerning the colouring matters authorised for use in medicinal products[38] and/or European Parliament and Council Directive 94/36/EC of 30 June 1994 on colours for use in foodstuffs[39].

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38 OJ L 11, 14.1.1978, p. 18.

39 OJ L 237, 10.9.1994, p. 13.

In order to give the 'quantitative composition' of the active substance(s) of the finished medicinal products, it is necessary, depending on the pharmaceutical form concerned, to specify the mass, or the number of units of biological activity, either per dosage-unit or per unit of mass or volume, of each active substance.

Active substances present in the form of compounds or derivatives shall be designated quantitatively by their total mass, and if necessary or relevant, by the mass of active entity or entities of the molecule.

For medicinal products containing an active substance, which is the subject of an application for marketing authorisation in any Member State for the first time, the quantitative statement of an active substance, which is a salt or hydrate shall be systematically expressed in terms of the mass of the active entity or entities in the molecule. All subsequently authorised medicinal products in the Member States shall have their quantitative composition stated in the same way for the same active substance.

Units of biological activity shall be used for substances, which cannot be defined molecularly. Where an International Unit of biological activity has been defined by the World Health Organisation, this shall be used. Where no International Unit has been defined, the units of biological activity shall be expressed in such a way as to provide unambiguous information on the activity of the substances by using where applicable the European Pharmacopoeia Units.

3.2.2.2.Pharmaceutical development

This chapter shall be devoted to information on the development studies conducted to establish that the dosage form, the formulation, manufacturing process, container closure system, microbiological attributes and usage instructions are appropriate for the intended use specified in the marketing authorisation application dossier.

The studies described in this chapter are distinct from routine control tests conducted according to specifications. Critical parameters of the formulation and process attributes that can influence batch reproducibility, medicinal product performance and medicinal product quality shall be identified and described. Additional supportive data, where appropriate, shall be referenced to the relevant chapters of Module 4 (Non Clinical Study Reports) and Module 5 (Clinical Study Reports) of the marketing authorisation application dossier.

a) The compatibility of the active substance with excipients as well as key physicochemical characteristics of the active substance that can influence the performance of the finished product or the compatibility of different active substances with each other in the case of combination products, shall be documented.
b) The choice of excipients, in particular relative to their respective functions and concentration shall be documented.

c) A description of the development of the finished product shall be provided, taking into consideration the proposed route of administration and usage.
d) Any overages in the formulation(s) shall be warranted.
e) As far as the physiochemical and biological properties are concerned, any parameter relevant to the performance of finished product shall be addressed and documented.
f) The selection and optimisation of the manufacturing process as well as differences between the manufacturing process(es) used to produce pivotal clinical batches and the process used for manufacturing the proposed finished medicinal product shall be provided.
g) The suitability of the container and closure system used for the storage, shipping and use of the finished product shall be documented. A possible interaction between medicinal product and container may need to be considered.
h) The microbiological attributes of the dosage form in relation with non-sterile and sterile products shall be in accordance with and documented as prescribed in the European Pharmacopoeia.
i) In order to provide appropriate and supportive information for the labelling the compatibility of the finished product with reconstitution diluent(s) or dosage devices shall be documented.

3.2.2.3. Manufacturing process of the finished medicinal product

a) The description of the manufacturing method accompanying the application for Marketing Authorisation pursuant to Article 8 (3) (d), shall be drafted in such a way as to give an adequate synopsis of the nature of the operations employed. For this purpose it shall include at least:
    - mention of the various stages of manufacture including process controls and corresponding acceptance criteria, so that an assessment can be made of whether the processes employed in producing the pharmaceutical form might have produced an adverse change in the constituents,
    - in the case of continuous manufacture, full details concerning precautions taken to ensure the homogeneity of the finished product,
    - experimental studies validating the manufacturing process, where a non-standard method of manufacture is used or where it is critical for the product,
    - for sterile medicinal products, details of the sterilisation processes and/ or aseptic procedures used,
    - a detailed batch formula.

The name, address, and responsibility of each manufacturer, including contractors, and each proposed production site or facility involved in manufacturing and testing shall be provided.

b) Particulars relating to the product control tests that may be carried out at an intermediate stage of the manufacturing process, with a view to ensuring the consistency of the production process shall be included.

These tests are essential for checking the conformity of the medicinal product with the formula when, exceptionally, an applicant proposes an analytical method for testing the finished product which does not include the assay of all the active substances (or of all the excipient constituents subject to the same requirements as the active substances).

The same applies where the quality control of the finished product depends on in-process control tests, particularly if the medicinal product is essentially defined by its method of preparation.

c) Description, documentation, and results of the validation studies for critical steps or critical assays used in the manufacturing process shall be provided.

3.2.2.4. Control of excipients

a) All the materials needed in order to manufacture the excipient(s) shall be listed identifying where each material is used in the process. Information on the quality and control of these materials shall be provided. Information demonstrating that materials meet standards appropriate for their intended use shall be provided.

Colouring matter shall, in all cases, satisfy the requirements of Directives 78/25/EEC and/or 94/36/EC. In addition, colouring matter shall meet purity criteria as laid down in Directive 95/45/EC, as amended.

b) For each excipient, the specifications and their justifications shall be detailed. The analytical procedures shall be described and duly validated.

c) Specific attention shall be paid to excipients of human or animal origin.

Regarding the specific measures for the prevention of the Transmission of animal Spongiform Encephalopathies, the applicant must demonstrate also for excipients that the medicinal product is manufactured in accordance with the Note for Guidance on Minimising the Risk of Transmitting Animal Spongiform Encephalopathy Agents via Medicinal Products and its updates, published by the Commission in the Official Journal of the European Union.

Demonstration of compliance with the aforementioned Note for Guidance can be done by submitting either preferably a certificate of suitability to the relevant monograph on Transmissible Spongiform Encephalopathies of the European Pharmacopoeia, or by the supply of scientific data to substantiate this compliance.

d) Novel excipients:

For excipient(s) used for the first time in a medicinal product or by a new route of administration, full details of manufacture, characterisation, and controls, with cross

references to supporting safety data, both non-clinical and clinical, shall be provided according to the active substance format previously described.

A document containing the detailed chemical, pharmaceutical and biological information shall be presented. This information shall be formatted in the same order as the chapter devoted to Active Substance(s) of Module 3.

Information on novel excipient(s) may be presented as a stand-alone document following the format described in the former paragraphs. Where the applicant differs from the novel excipient manufacturer the said stand-alone document shall be made available to the applicant for submission to the competent authority.

Additional information on toxicity studies with the novel excipient shall be provided in Module 4 of the dossier.

Clinical studies shall be provided in Module 5.

3.2.2.5. Control of the finished medicinal product

For the control of the finished medicinal product, a batch of a medicinal product is an entity which comprises all the units of a pharmaceutical form which are made from the same initial quantity of material and have undergone the same series of manufacturing and/or sterilisation operations or, in the case of a continuous production process, all the units manufactured in a given period of time.

Unless there is appropriate justification, the maximum acceptable deviation in the active substance content of the finished product shall not exceed ± 5 % at the time of manufacture.

Detailed information on the specifications, (release and shelf life) justification for their choice, methods of analysis and their validation shall be provided.

3.2.2.6.Reference standards or materials

Reference preparations and standards used for testing of the finished medicinal product shall be identified and described in detail, if not previously provided in the section related to the active substance.

3.2.2.7. Container and closure of the finished medicinal product

A description of the container and the closure system(s) including the identity of each immediate packaging material and their specifications shall be provided. The specifications shall include description and identification. Non-pharmacopoeial methods (with validation) shall be included where appropriate.

For non-functional outer packaging materials only a brief description shall be provided.

For functional outer packaging materials additional information shall be provided.

3.2.2.8. Stability of the finished medicinal product

a) The types of studies conducted, protocols used, and the results of the studies shall be summarised;
b) Detailed results of the stability studies, including information on the analytical procedures used to generate the data and validation of these procedures shall

be presented in an appropriate format; in case of vaccines, information on cumulative stability shall be provided where appropriate;

c) The post authorisation stability protocol and stability commitment shall be provided.

4. MODULE 4: NON-CLINICAL REPORTS

4.1. Format and Presentation

The general outline of Module 4 is as follows:

Table of contents

- Study reports
  - *Pharmacology*
    - Primary Pharmaco-dynamics
    - Secondary Pharmaco-dynamics
    - Safety Pharmacology
    - Pharmaco-dynamic Interactions
  - *Pharmaco-kinetics*
    - Analytical Methods and Validation Reports
    - Absorption
    - Distribution
    - Metabolism
    - Excretion
    - Pharmaco-kinetic Interactions (non-clinical)
    - Other Pharmaco-kinetic Studies
  - *Toxicology*
    - Single-Dose Toxicity
    - Repeat-Dose Toxicity
    - Genotoxicity
      - In vitro
      - In vivo (including supportive toxico-kinetics evaluations)
    - Carcinogenicity
      - Long-term studies
      - Short- or medium-term studies
      - Other studies
    - Reproductive and Developmental Toxicity
      - Fertility and early embryonic development
      - Embryo-fetal development
      - Prenatal and postnatal development
      - Studies in which the offspring (juvenile animals) are dosed and/or further evaluated
    - Local Tolerance

- *Other Toxicity Studies*
    - Antigenicity
    - Immuno-toxicity
    - Mechanistic studies
    - Dependence
    - Metabolites
    - Impurities
    - Other
- Literature references

4.2. Content: basic principles and requirements

Special attention shall be paid to the following selected elements.

(1) The pharmacological and toxicological tests must show:

a) the potential toxicity of the product and any dangerous or undesirable toxic effects that may occur under the proposed conditions of use in human beings; these should be evaluated in relation to the pathological condition concerned;

b) the pharmacological properties of the product, in both qualitative and quantitative relationship to the proposed use in human beings. All results must be reliable and of general applicability. Whenever appropriate, mathematical and statistical procedures shall be used in designing the experimental methods and in evaluating the results.

Additionally, it is necessary for clinicians to be given information about the therapeutic and toxicological potential of the product.

(2) For biological medicinal products such as immunological medicinal products and medicinal products derived from human blood or plasma, the requirements of this Module may have to be adapted for individual products; therefore the testing program carried out shall be justified by the applicant.

In establishing the testing program, the following shall be taken into consideration:

all tests requiring repeated administration of the product shall be designed to take account of the possible induction of, and interference by, antibodies;

examination of reproductive function, of embryo/foetal and peri-natal toxicity, of mutagenic potential and of carcinogenic potential shall be considered. Where constituents other than the active substance(s) are incriminated, validation of their removal may replace the study.

(3) The toxicology and pharmaco-kinetics of an excipient used for the first time in the pharmaceutical field shall be investigated.

(4) Where there is a possibility of significant degradation during storage of the medicinal product, the toxicology of degradation products must be considered.

4.2.1.Pharmacology

Pharmacology study shall follow two distinct lines of approach.

- Firstly, the actions relating to the proposed therapeutic use shall be adequately investigated and described. Where possible, recognised and validated assays, both in vivo and in vitro, shall be used. Novel experimental techniques must be described in such detail as to allow them to be reproduced. The results shall be expressed in quantitative terms using, for example, dose-effect curves, time-effect curves, etc. Wherever possible, comparisons shall be made with data relating to a substance or substances with a similar therapeutic action.
- Secondly, the applicant shall investigate the potential undesirable pharmaco-dynamic effects of the substance on physiological functions. These investigations shall be performed at exposures in the anticipated therapeutic range and above. The experimental techniques, unless they are standard procedures, must be described in such detail as to allow them to be reproduced, and the investigator must establish their validity. Any suspected modification of responses resulting from repeated administration of the substance shall be investigated.
  For the pharmaco-dynamic medicinal product interaction, tests on combinations of active substances may be prompted either by pharmacological premises or by indications of therapeutic effect. In the first case, the pharmaco-dynamic study shall demonstrate those interactions, which might make the combination of value in therapeutic use. In the second case, where scientific justification for the combination is sought through therapeutic experimentation, the investigation shall determine whether the effects expected from the combination can be demonstrated in animals, and the importance of any collateral effects shall at least be investigated.

4.2.2.Pharmaco-kinetics

Pharmaco-kinetics means the study of the fate of the active substance, and its metabolites, within the organism, and covers the study of the absorption, distribution, metabolism (bio-transformation) and excretion of these substances.

The study of these different phases may be carried mainly by means of physical, chemical or possibly by biological methods, and by observation of the actual pharmaco-dynamic activity of the substance itself.

Information on distribution and elimination shall be necessary in all cases where such data are indispensable to determine the dosage for humans, and in respect of chemo-therapeutic substances (antibiotics, etc.) and substances whose use depends on their non-pharmaco-dynamic effects (e.g. numerous diagnostic agents, etc.).

In vitro studies also can be carried out with the advantage of using human material for comparison with animal material (i.e. protein binding, metabolism, drug-drug interaction).
Pharmaco-kinetic investigation of all pharmacologically active substances is necessary. In the

case of new combinations of known substances, which have been investigated in accordance with the provisions of this Directive, pharmaco-kinetic studies may not be required, if the toxicity tests and therapeutic experimentation justify their omission.

The pharmaco-kinetic program shall be design to allow comparison and extrapolation between animal and human.

4.2.3.Toxicology

a) Single-dose toxicity

A single-dose toxicity test shall mean a qualitative and quantitative study of the toxic reactions, which may result from a single administration of the active substance or substances contained in the medicinal product, in the proportions and physico-chemical state in which they are present in the actual product.
The single-dose toxicity test must be carried out in accordance with the relevant guidelines published by the Agency.

b) Repeat-dose toxicity

Repeated dose toxicity tests are intended to reveal any physiological and/or anatomo-pathological changes induced by repeated administration of the active substance or combination of active substances under examination, and to determine how these changes are related to dosage.
Generally, it is desirable that two tests be performed: one short term, lasting two to four weeks, the other long-term. The duration of the latter shall depend on the conditions of clinical use. Its purpose is to describe potential adverse effects to which attention should be paid in clinical studies. The duration is defined in the relevant guidelines published by the Agency.

c) Geno-toxicity

The purposes of the study of mutagenic and clastogenic potential is to reveal the changes which a substance may cause in the genetic material of individuals or cells. Mutagenic substances may present a hazard to health since exposure to a mutagen carries the risk of inducing germ-line mutation, with the possibility of inherited disorders, and the risk of somatic mutations including those leading to cancer. These studies are obligatory for any new substance.

d) Carcino-genicity

Tests to reveal carcinogenic effects shall normally be required:

1. These studies shall be performed for any medicinal product whose expected clinical use is for a prolonged period of a patient's life, either continuously or repeatedly in an intermittent manner.
2. These studies are recommended for some medicinal products if there is concern about their carcinogenic potential, e.g. from product of the same class or similar structure, or from evidence in repeated dose toxicity studies.
3. Studies with unequivocally geno-toxic compounds are not needed, as they are presumed to be trans-species carcinogens, implying a hazard to humans. If such a medicinal product is intended to be administered chronically to humans a chronic study may be necessary to detect early tumorigenic effects.

e) Reproductive and developmental toxicity

Investigation of possible impairment of male or female reproductive function as well as harmful effects on progeny shall be performed by appropriate tests.

These tests comprise studies of effect on adult male or female reproductive function, studies of the toxic and teratogenic effects at all stages of development from conception to sexual maturity as well as latent effects, when the medicinal product under investigation has been administered to the female during pregnancy.

Omission of these tests must be adequately justified.

Depending on the indicated use of the medicinal product, additional studies addressing development when administering the medicinal product of the offspring may be warranted.

Embryo/foetal toxicity studies shall normally be conducted on two mammalian species, one of which shall be other than a rodent. Peri- and postnatal studies shall be conducted in at least one species. If the metabolism of a medicinal product in particular species is known to be similar to that in man, it is desirable to include this species. It is also desirable that one of the species is the same as in the repeated dose toxicity studies.

The state of scientific knowledge at the time when the application is lodged shall be taken into account when determining the study design.

f) Local tolerance

The purpose of local tolerance studies is to ascertain whether medicinal products (both active substances and excipients) are tolerated at sites in the body, which may come into contact with the medicinal product as a result of its administration in clinical use. The testing strategy shall be such that any mechanical effects of administration or purely physico-chemical actions

of the product can be distinguished from toxicological or pharmaco-dynamic ones.

Local tolerance testing shall be conducted with the preparation being developed for human use, using the vehicle and/or excipients in treating the control group(s). Positive controls/ reference substances shall be included where necessary.
The design of local tolerance tests (choice of species, duration, frequency and route of administration, doses) will depend upon the problem to be investigated and the proposed conditions of administration in clinical use. Reversibility of local lesions shall be performed where relevant.

Studies in animals can be substituted by validated in vitro tests provided that the test results are of comparable quality and usefulness for the purpose of safety evaluation.
For chemicals applied to the skin (e.g. dermal, rectal, vaginal) the sensitising potential shall be evaluated in at least one of the test systems currently available (the guinea pig assay or the local lymph node assay).

5. MODULE 5: CLINICAL STUDY REPORTS

5.1. Format and Presentation

The general outline of Module 5 is as follows:

- Table of contents for clinical study reports
- Tabular listing of all clinical studies
- Clinical study reports
    - *Reports of Bio-pharmaceutical Studies*
        - Bio-availability Study Reports
        - Comparative Bio-availability and Bio-equivalence Study Reports
        - In vitro — In vivo Correlation Study Report
        - Reports of Bio-analytical and Analytical Methods
    - *Reports of Studies Pertinent to Pharmaco-kinetics Using Human Bio-materials*
        - Plasma Protein Binding Study Reports
        - Reports of Hepatic Metabolism and Interaction Studies
        - Reports of Studies Using Other Human Bio-materials
    - *Reports of Human Pharmaco-kinetic Studies*
        - Healthy subjects Pharmaco-kinetics and Initial Tolerability Study Reports
        - Patient Pharmaco-kinetics and Initial Tolerability Study Reports
        - Intrinsic Factor Pharmaco-kinetics Study Reports
        - Extrinsic Factor Pharmaco-kinetics Study Reports
        - Population Pharmaco-kinetics Study Reports
    - *Reports of Human Pharmaco-dynamic Studies*
        - Healthy Subject Pharmaco-dynamic and Pharmaco-kinetics/Pharmaco-dynamic Study Reports
        - Patient Pharmaco-dynamic and Pharmaco-kinetics/Pharmaco-dynamic Studies Study Reports

- *Reports of Efficacy and Safety Studies*
  - Study Reports of Controlled Clinical Studies Pertinent to the Claimed Indication
  - Study Reports of Uncontrolled Clinical Studies
  - Reports of Analyses of Data from More than One Study including any formal integrated analyses, meta-analyses and bridging analyses
  - Other Study Reports
- *Reports of Post-marketing Experience*

- Literature references

5.2. Content: basic principles and requirements

Special attention shall be paid to the following selected elements.

a) The clinical particulars to be provided pursuant to Articles 8 (3) (i) and 10 (1) must enable a sufficiently well-founded and scientifically valid opinion to be formed as to whether the medicinal product satisfies the criteria governing the granting of a marketing authorisation. Consequently, an essential requirement is that the results of all clinical trials should be communicated, both favourable and unfavourable.

b) Clinical trials must always be preceded by adequate pharmacological and toxicological tests, carried out on animals in accordance with the requirements of Module 4 of this Annex. The investigator must acquaint himself with the conclusions drawn from the pharmacological and toxicological studies and hence the applicant must provide him at least with the investigator's brochure, consisting of all the relevant information known prior to the onset of a clinical trial including chemical, pharmaceutical and biological data, toxicological, pharmaco-kinetic and pharmaco-dynamic data in animals and the results of earlier clinical trials, with adequate data to justify the nature, scale and duration of the proposed trial; the complete pharmacological and toxicological reports shall be provided on request. For materials of human or animal origin, all available means shall be employed to ensure safety from transmission of infectious agents prior to the commencement of the trial.

c) Marketing authorisation holders must arrange for essential clinical trial documents (including case report forms) other than subject's medical files, to be kept by the owners of the data:
- for at least 15 years after completion or discontinuation of the trial,
- or for at least two years after the granting of the last marketing authorisation in the European Community and when there are no pending or contemplated marketing applications in the European Community,
- or for at least two years after formal discontinuation of clinical development of the investigational product.

Subject's medical files should be retained in accordance with applicable legislation and in accordance with the maximum period of time permitted by the hospital, institution or private practice.

The documents can be retained for a longer period, however, if required by the applicable regulatory requirements or by agreement with the sponsor. It is the responsibility of the sponsor to inform the hospital, institution or practice as to when these documents no longer need to be retained.

The sponsor or other owner of the data shall retain all other documentation pertaining to the trial as long as the product is authorised. This documentation shall include: the protocol including the rationale, objectives and statistical design and methodology of the trial, with conditions under which it is performed and managed, and details of the investigational product, the reference medicinal product and/or the placebo used; standard operating procedures; all written opinions on the protocol and procedures; the investigator's brochure; case report forms on each trial subject; final report; audit certificate(s), if available. The final report shall be retained by the sponsor or subsequent owner, for five years after the medicinal product is no longer authorised.

In addition for trials conducted within the European Community, the marketing authorisation holder shall make any additional arrangements for archiving of documentation in accordance with the provisions of Directive 2001/20/EC and implementing detailed guidelines.

Any change of ownership of the data shall be documented.

All data and documents shall be made available if requested by relevant authorities.

d) The particulars of each clinical trial must contain sufficient detail to allow an objective judgement to be made:

- the protocol, including the rationale, objectives and statistical design and methodology of the trial, with conditions under which it is performed and managed, and details of the investigational medicinal product used
- audit certificate(s), if available
- the list of investigator(s), and each investigator shall give his name, address, appointments, qualifications and clinical duties, state where the trial was carried out and assemble the information in respect of each patient individually, including case report forms on each trial subject
- final report signed by the investigator and for multi-centre trials, by all the investigators or the co-ordinating (principal) investigator.

e) The particulars of clinical trials referred to above shall be forwarded to the competent authorities. However, in agreement with the competent authorities, the applicant may omit part of this information. Complete documentation shall be provided forthwith upon request.

The investigator shall, in his conclusions on the experimental evidence, express an opinion on the safety of the product under normal conditions of use, its tolerance, its efficacy and any useful information relating to indications and contra-indications, dosage and average duration of treatment as well as any special precautions to be taken during treatment and the clinical symptoms of over dosage. In reporting the results of a multi-centre study, the principal

investigator shall, in his conclusions, express an opinion on the safety and efficacy of the investigational medicinal product on behalf of all centres.

f) The clinical observations shall be summarised for each trial indicating:
    1) the number and sex of subjects treated;
    2) the selection and age-distribution of the groups of patients being investigated and the comparative tests;
    3) the number of patients withdrawn prematurely from the trials and the reasons for such withdrawal;
    4) where controlled trials were carried out under the above conditions, whether the control group:
        - received no treatment
        - received a placebo
        - received another medicinal product of known effect
        - received treatment other than therapy using medicinal products
    5) the frequency of observed adverse reactions;
    6) details concerning patients who may be at increased risk, e.g. elderly people, children, women during pregnancy or menstruation, or whose physiological or pathological condition requires special consideration;
    7) parameters or evaluation criteria of efficacy and the results in terms of these parameters;
    8) a statistical evaluation of the results when this is called for by the design of the trials and the variable factors involved.
g) In addition, the investigator shall always indicate his observations on:
    1) any signs of habituation, addiction or difficulty in weaning patients from the medicinal product;
    2) any interactions that have been observed with other medicinal products administered concomitantly;
    3) the criteria determining exclusion of certain patients from the trials;
    4) any deaths which occurred during the trial or within the follow-up period.
h) Particulars concerning a new combination of medicinal substances must be identical to those required for new medicinal products and must substantiate the safety and efficacy of the combination.
i) Total or partial omission of data must be explained. Should unexpected results occur during the course of the trials, further pre clinical toxicological and pharmacological tests must be undertaken and reviewed.
j) If the medicinal product is intended for long-term administration, particulars shall be given of any modification of the pharmacological action following repeated administration, as well as the establishment of long-term dosage.

5.2.1 Reports of bio-pharmaceutics studies

Bio-availability study reports, comparative bio-availability, bio-equivalence study reports, reports on in vitro and in vivo correlation study, and bio-analytical and analytical methods shall be provided.

In addition, an assessment of bio-availability shall be undertaken where necessary to demonstrate bio-equivalence for the medicinal products referred to in Article 10 (1) (a).

5.2.2 Reports of studies pertinent to pharmaco-kinetics using human bio-materials

For the purposes of this Annex, human bio-materials shall mean any proteins, cells, tissues and related materials derived from human sources that are used in vitro or ex vivo to assess pharmaco-kinetics properties of drug substances.

In this respect, reports of plasma protein binding study, hepatic metabolism and active substance interaction studies and studies using other human bio-materials shall be provided.

5.2.3. Reports of human pharmaco-kinetic studies

a) The following pharmaco-kinetic characteristics shall be described:
   - absorption (rate and extent),
   - distribution,
   - metabolism,
   - excretion.

   Clinically significant features including the implication of the kinetic data for the dosage regimen especially for patients at risk, and differences between man and animal species used in the pre clinical studies, shall be described.

   In addition to standard multiple-sample pharmaco-kinetics studies, population pharmaco-kinetics analyses based on sparse sampling during clinical studies can also address questions about the contributions of intrinsic and extrinsic factors to the variability in the dose- pharmaco-kinetics response relationship. Reports of pharmaco-kinetic and initial tolerability studies in healthy subjects and in patients, reports of pharmaco-kinetic studies to assess effects of intrinsic and extrinsic factors, and reports of population pharmaco-kinetic studies shall be provided.

b) If the medicinal product is normally to be administered concomitantly with other medicinal products, particulars shall be given of joint administration tests performed to demonstrate possible modification of the pharmacological action.

   Pharmaco-kinetic interactions between the active substance and other medicinal products or substances shall be investigated.

5.2.4. Reports of human pharmaco-dynamic studies

a) The pharmaco-dynamic action correlated to the efficacy shall be demonstrated including:
   - the dose-response relationship and its time course,
   - justification for the dosage and conditions of administration,
   _ the mode of action, if possible.

The pharmaco-dynamic action not related to efficacy shall be described.

The demonstration of pharmaco-dynamic effects in human beings shall not in itself be sufficient to justify conclusions regarding any particular potential therapeutic effect.

b) If the medicinal product is normally to be administered concomitantly with other medicinal products, particulars shall be given of joint administration tests performed to demonstrate possible modification of the pharmacological action.

Pharmaco-dynamic interactions between the active substance and other medicinal products or substances shall be investigated.

5.2.5. Reports of efficacy and safety studies

5.2.5.1. Study Reports of Controlled Clinical Studies Pertinent to the Claimed Indication

In general, clinical trials shall be done as 'controlled clinical trials' if possible, randomised and as appropriate versus placebo and versus an established medicinal product of proven therapeutic value; any other design shall be justified. The treatment of the control groups will vary from case to case and also will depend on ethical considerations and therapeutic area; thus it may, in some instances, be more pertinent to compare the efficacy of a new medicinal product with that of an established medicinal product of proven therapeutic value rather than with the effect of a placebo.

(1) As far as possible, and particularly in trials where the effect of the product cannot be objectively measured, steps shall be taken to avoid bias, including methods of randomisation and blinding.

(2) The protocol of the trial must include a thorough description of the statistical methods to be employed, the number and reasons for inclusion of patients (including calculations of the power of the trial), the level of significance to be used and a description of the statistical unit. Measures taken to avoid bias, particularly methods of randomisation, shall be documented. Inclusion of a large number of subjects in a trial must not be regarded as an adequate substitute for a properly controlled trial.

The safety data shall be reviewed taking into account guidelines published by the Commission, with particular attention to events resulting in changes of dose or need for concomitant medication, serious adverse events, events resulting in withdrawal, and deaths. Any patients or patient groups at increased risk shall be identified and particular attention paid to potentially vulnerable patients who may be present in small numbers, e.g., children, pregnant women, frail elderly, people with marked abnormalities of metabolism or excretion etc. The implication of the safety evaluation for the possible uses of the medicinal product shall be described.

5.2.5.2. Study reports of uncontrolled clinical studies reports of analyses of data from more than one study and other clinical study reports

These reports shall be provided.

5.2.6. Reports of post-marketing experience

If the medicinal product is already authorised in third countries, information shall be given in respect of adverse reactions of the medicinal product concerned and medicinal products containing the same active

substance(s), in relation to the usage rates if possible.

5.2.7. Case reports forms and individual patient listings

When submitted in accordance with the relevant Guideline published by the Agency, case report forms and individual patient data listings shall be provided and presented in the same order as the clinical study reports and indexed by study.

PART II - SPECIFIC MARKETING AUTHORISATION DOSSIERS AND REQUIREMENTS

Some medicinal products present specific features which are such that all the requirements of the marketing authorisation application dossier as laid down in Part I of this Annex need to be adapted. To take account of these particular situations, an appropriate and adapted presentation of the dossier shall be followed by applicants.

1. WELL-ESTABLISHED MEDICINAL USE

For medicinal products the active substance(s) of which has/have a 'well-established medicinal use' as referred to Article 10(1)(a)(ii), with recognised efficacy and an acceptable level of safety, the following specific rules shall apply.

The applicant shall submit Modules 1, 2 and 3 as described in part I of this Annex.

For Modules 4 and 5, a detailed scientific bibliography shall address non-clinical and clinical characteristics.

The following specific rules shall apply in order to demonstrate the well-established medicinal use:

a) Factors which have to be taken into account in order to establish a well-established medicinal use of constituents of medicinal products are:
   - the time over which a substance has been used,
   - quantitative aspects of the use of the substance,
   - the degree of scientific interest in the use of the substance (reflected in the published scientific literature) and
   - the coherence of scientific assessments.

   Therefore different periods of time may be necessary for establishing well-established use of different substances. In any case, however, the period of time required for establishing a well established medicinal use of a constituent of a medicinal product must not be less than one decade from the first systematic and documented use of that substance as a medicinal product in the Community.

b) The documentation submitted by the applicant should cover all aspects of the safety and/or efficacy assessment and must include or refer to a review of the relevant literature, taking into account pre- and post-marketing studies and published scientific literature concerning experience in the form of epidemiological studies and in particular of comparative epidemiological studies. All documentation, both favourable and unfavourable, must be communicated. With respect to the provisions on 'well-established medicinal use' it is in particular necessary to clarify that 'bibliographic reference' to other

sources of evidence (post marketing studies, epidemiological studies, etc.) and not just data related to tests and trials may serve as a valid proof of safety and efficacy of a product if an application explains and justifies the use of these sources of information satisfactorily.

c) Particular attention must be paid to any missing information and justification must be given why demonstration of an acceptable level of safety and/or efficacy can be supported although some studies are lacking.

d) The non-clinical and/or clinical overviews must explain the relevance of any data submitted which concern a product different from the product intended for marketing. A judgement must be made whether the product studied can be considered as similar to the product, for which application for a marketing authorisation has been made in spite of the existing differences.

e) Post-marketing experience with other products containing the same constituents is of particular importance and applicants should put a special emphasis on this issue.

2. ESSENTIALLY SIMILAR MEDICINAL PRODUCTS

a) Applications based upon Article 10(1) (a) (i) (essentially similar products) shall contain the data described in Modules 1, 2 and 3 of Part I of this Annex provided the applicant has been granted the consent of the holder of the original marketing authorisation to cross refer to the content of his Modules 4 and 5.

b) Applications based upon Article 10(1) (a) (iii) (essentially similar products i.e. generics) shall contain the data described in Modules 1, 2 and 3 of Part I of this Annex together with data showing bio-availability and bio-equivalence with the original medicinal product provided the latter is not a biological medicinal product (see Part II, 4 Similar biological medicinal products).

   For these products the non-clinical/clinical overviews/summaries shall particularly focus on the following elements:

   - the grounds for claiming essential similarity;
   - a summary of impurities present in batches of the active substance(s) as well as those of the finished medicinal product (and where relevant decomposition products arising during storage) as proposed for use in the product to be marketed together with an evaluation of these impurities;
   - an evaluation of the bio-equivalence studies or a justification why studies were not performed with respect to the guideline on 'Investigation of Bio-availability and Bio-equivalence';
   - an update of published literature relevant to the substance and the present application. It may be acceptable for articles in 'peer review' journals to be annotated for this purpose;
   - every claim in the summary of product characteristics not known from or inferred from the properties of the medicinal product and/or its therapeutic group should be discussed in the non clinical/clinical overviews/summaries and substantiated by published literature and/or additional studies.

– if applicable, additional data in order to demonstrate evidence on the equivalence of safety and efficacy properties of different salts, esters or derivatives of an authorised active substance should be provided by the applicant when he claims essential similarity.

3. ADDITIONAL DATA REQUIRED IN SPECIFIC SITUATIONS

Where the active substance of an essentially similar medicinal product contains the same therapeutic moiety as the original authorised product associated with a different salt/ester complex/derivative evidence that there is no change in the pharmaco-kinetics of the moiety, pharmaco-dynamics and/or in toxicity which could change the safety/efficacy profile shall be demonstrated. Should this not be the case, this association shall be considered as a new active substance.

Where a medicinal product is intended for a different therapeutic use or presented in a different pharmaceutical form or to be administered by different routes or in different doses or with a different posology, the results of appropriate toxicological and pharmacological tests and/or of clinical trials shall be provided.

4. SIMILAR BIOLOGICAL MEDICINAL PRODUCTS

The provisions of Article 10(1)(a) (iii) may not be sufficient in the case of biological medicinal products. If the information required in the case of essentially similar products (generics) does not permit the demonstration of the similar nature of two biological medicinal products, additional data, in particular, the toxicological and clinical profile shall be provided.

When a biological medicinal product as defined in Part I, paragraph 3.2 of this Annex, which refers to an original medicinal product having been granted a marketing authorisation in the Community, is submitted for a marketing authorisation by an independent applicant after the expiry of data protection period, the following approach shall be applied.

– Information to be supplied shall not be limited to Modules 1, 2 and 3 (pharmaceutical, chemical and biological data), supplemented with bio-equivalence and bio-availability data. The type and amount of additional data (i.e. toxicological and other non-clinical and appropriate clinical data) shall be determined on a case by case basis in accordance with relevant scientific guidelines.
– Due to the diversity of biological medicinal products, the need for identified studies foreseen in Modules 4 and 5, shall be required by the competent authority, taking into account the specific characteristic of each individual medicinal product.

The general principles to be applied are addressed in a guideline taking into account the characteristics of the concerned biological medicinal product published by the Agency. In case the originally authorised medicinal product has more than one indication, the efficacy and safety of the medicinal product claimed to be similar has to be justified or, if necessary, demonstrated separately for each of the claimed indications.

5. FIXED COMBINATION MEDICINAL PRODUCTS

Applications based upon Article 10 (1) (b) shall relate to new medicinal products made of at least two active substances not previously authorised as a fixed combination medicinal product.

For those applications a full dossier (Modules 1 to 5) shall be provided for the fixed combination medicinal product. Where applicable, information regarding the manufacturing sites and the adventitious agents, safety evaluation shall be provided.

6. DOCUMENTATION FOR APPLICATIONS IN EXCEPTIONAL CIRCUMSTANCES

When, as provided for in Article 22, the applicant can show that he is unable to provide comprehensive data on the efficacy and safety under normal conditions of use, because:

- the indications for which the product in question is intended are encountered so rarely that the applicant cannot reasonably be expected to provide comprehensive evidence, or
- in the present state of scientific knowledge, comprehensive information cannot be provided, or
- it would be contrary to generally accepted principles of medical ethics to collect such information,

marketing authorisation may be granted subject to certain specific obligations.

These obligations may include the following:

- the applicant shall complete an identified programme of studies within a time period specified by the competent authority, the results of which shall form the basis of a reassessment of the benefit/risk profile,
- the medicinal product in question may be supplied on medical prescription only and may in certain cases be administered only under strict medical supervision, possibly in a hospital and in the case of a radio-pharmaceutical, by an authorised person,
- the package leaflet and any medical information shall draw the attention of the medical practitioner to the fact that the particulars available concerning the medicinal product in question are as yet inadequate in certain specified respects.

7. MIXED MARKETING AUTHORISATION APPLICATIONS

Mixed marketing-authorisation applications shall mean marketing-authorisation application dossiers where Module 4 and/or 5 consists of a combination of reports of limited non-clinical and/or clinical studies carried out by the applicant and of bibliographical references. All other Module(s) are in accordance with the structure described in Part I of this Annex. The competent authority shall accept the proposed format presented by the applicant on a case by case basis.

PART III - PARTICULAR MEDICINAL PRODUCTS

This Part lays down specific requirements related to the nature of identified medicinal products.

1. BIOLOGICAL MEDICINAL PRODUCTS

1.1. Plasma-derived medicinal product

For medicinal products derived from human blood or plasma and by derogation from the provisions of Module 3, the dossier requirements mentioned in 'Information related to the starting and raw materials', for starting materials made of human blood/plasma may be replaced by a Plasma Master File certified in accordance with this Part.

a) Principles

For the purposes of this Annex:

- Plasma Master File shall mean a stand-alone documentation, which is separate from the dossier for marketing authorisation which provides all relevant detailed information on the characteristics of the entire human plasma used as a starting material and/or a raw material for the manufacture of sub/ intermediate fractions, constituents of the excipient and active substance(s), which are part of medicinal products or medical devices referred to in Directive 2000/70/EC of the European Parliament and of the Council of 16 November 2000 amending Council Directive 93/42/EC as regards medical devices incorporating stable derivatives of human blood or human plasma[40].
- Every centre or establishment for fractionation/processing of human plasma shall prepare and keep updated the set of detailed relevant information referred to in the Plasma Master File.
- The Plasma Master File shall be submitted to the Agency or to the competent authority by the applicant for a marketing authorisation or the holder of the marketing authorisation. Where the applicant for a marketing authorisation or the marketing authorisation holder differs from the holder of the Plasma Master File, the Plasma Master File shall be made available to the applicant or marketing authorisation holder for submission to the competent authority. In any case, the applicant or marketing authorisation holder shall take responsibility for the medicinal product.
- The competent authority that is evaluating the marketing authorisation shall await for the Agency to issue the certificate before deciding on the application.
- Any marketing authorisation dossier containing a human plasma-derived constituent shall refer to the Plasma Master File corresponding to the plasma used as a starting/raw material.

b) Content

In accordance with the provisions of Article 109, as amended by Directive 2002/98/EC, which refers to the requirements for donors and the testing of donations, the Plasma Master File shall include information on the plasma used as starting/raw material, in particular:

(1) Plasma origin

i) information on centres or establishments in which blood/plasma collection is carried out, including inspection and approval, and epidemiological data on blood transmissible infections.

ii) information on centres or establishments in which testing of donations and plasma pools is carried out, including inspection and approval status.

iii) selection/exclusion criteria for blood/plasma donors.

iv) system in place which enables the path taken by each donation to be traced from the blood/plasma collection establishment through to finished products and vice versa.

(2) Plasma quality and safety

i) compliance with European Pharmacopoeia Monographs.

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40 OJ L 313, 13.12.2000, p. 22.

ii) testing of blood/plasma donations and pools for infectious agents, including information on test methods and, in the case of plasma pools, validation data on the tests used.

iii) technical characteristics of bags for blood and plasma collection, including information on anticoagulants solutions used.

iv) conditions of storage and transport of plasma.

v) procedures for any inventory hold and/or quarantine period.

vi) characterisation of the plasma pool.

(3) System in place between the plasma-derived medicinal product manufacturer and/or plasma fractionator/processor on the one hand, and blood/plasma collection and testing centres or establishments on the other hand, which defines the conditions of their interaction and their agreed specifications.

In addition, the Plasma Master File shall provide a list of the medicinal products for which the Plasma Master File is valid, whether the medicinal products have been granted a marketing authorisation or are in the process of being granted such an authorisation, including medicinal products referred to in Article 2 of Directive 2001/20/EC of the European Parliament and of the Council relating to the implementation of good clinical practice in the conduct of clinical trials on medicinal products for human use.

c) Evaluation and Certification

- For medicinal products not yet authorised, the marketing authorisation applicant shall submit a full dossier to a competent authority, which shall be accompanied by a separate Plasma Master File where one does not already exist.
- The Plasma Master File is subject to a scientific and technical evaluation carried out by the Agency. A positive evaluation shall result in a certificate of compliance with Community legislation for the Plasma Master File, which shall be accompanied by the evaluation report. The certificate issued shall apply throughout the Community.
- The Plasma Master File shall be updated and re-certified on an annual basis.
- Changes subsequently introduced to the terms of a Plasma Master File must follow evaluation procedure laid down by Commission Regulation (EC) No 542/95[41] concerning the examination of variations to the terms of a marketing authorisation falling within the scope of Council regulation (EEC) No 2309/93 of 22 July 1993 laying down Community procedures for the authorisation and supervision of medicinal products for human and veterinary use and establishing a European Agency for the Evaluation of Medicinal Products[42]. Conditions for the assessment of these changes are laid down by Regulation (EC) No 1085/2003.
- As a second step to the provisions in the first, second, third and fourth indents, the competent authority that will grant or has granted the marketing authorisation shall take into account the

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41 OJ L 55, 11.3.1995, p. 15.

42 OJ L 214, 24.8.1993, p. 1.

certification, re-certification or variation of the Plasma Master File on the concerned medicinal product(s).

- By derogation from the provisions of the second indent of the present point (evaluation and certification), where a Plasma Master File corresponds only to blood/plasma-derived medicinal products the marketing authorisation of which is restricted to a single Member State, the scientific and technical evaluation of the said Plasma Master File shall be carried out by the national competent authority of that Member State.

1.2. Vaccines

For vaccines for human use and by derogation from the provisions of Module 3 on 'Active substance(s)', the following requirements when based on the use of a Vaccine Antigen Master File system shall apply.
The marketing authorisation application dossier of a vaccine other than human influenza vaccine, shall be required to include a Vaccine Antigen Master File for every vaccine antigen that is an active substance of this vaccine.

a) Principles

For the purposes of this Annex:

- Vaccine Antigen Master File shall mean a stand-alone part of the marketing authorisation application dossier for a vaccine, which contains all relevant information of biological, pharmaceutical and chemical nature concerning each of the active substances, which are part of this medicinal product. The stand-alone part may be common to one or more monovalent and/or combined vaccines presented by the same applicant or marketing authorisation holder.
- A vaccine may contain one or several distinct vaccine antigens. There are as many active substance(s) as vaccine antigen(s) present in a vaccine.
- A combined vaccine contains at least two distinct vaccine antigens aimed at preventing a single or several infectious diseases.
- A monovalent vaccine is a vaccine, which contains one vaccine antigen aimed at preventing a single infectious disease.

b) Content

The Vaccine Antigen Master File shall contain the following information extracted from the relevant part (Active substance) of Module 3 on 'Quality Data' as delineated in Part I of this Annex:
Active Substance

1. General Information, including compliance with the relevant monograph(s) of the European Pharmacopoeia.
2. Information on the manufacture of the active substance: this heading must cover the manufacturing process, information on the starting and raw materials, specific measures on TSEs and adventitious agents safety evaluation and facilities and equipment.
3. Characterisation of the active substance
4. Quality control of the active substance

5. Reference standard and materials
6. Container and closure system of the active substance
7. Stability of the active substance.

c) Evaluation and Certification

– For novel vaccines, which contain a novel vaccine antigen, the applicant shall submit to a competent authority a full marketing-authorisation application dossier including all the Vaccine Antigen Master Files corresponding to each single vaccine antigen that is part of the novel vaccine where no master file already exists for the single vaccine antigen. A scientific and technical evaluation of each Vaccine Antigen Master File shall be carried out by the Agency. A positive evaluation shall result in a certificate of compliance to the European legislation for each Vaccine Antigen Master File, which shall be accompanied by the evaluation report. The certificate shall apply throughout the Community.
– The provisions of the first indent shall also apply to every vaccine, which consists of a novel combination of vaccine antigens, irrespective of whether or not one or more of these vaccine antigens are part of vaccines already authorised in the Community.
– Changes to the content of a Vaccine Antigen Master File for a vaccine authorised in the Community shall be subject to a scientific and technical evaluation carried out by the Agency in accordance with the procedure laid down in Commission Regulation (EC) No 1085/2003. In the case of a positive evaluation the Agency shall issue a certificate of compliance with Community legislation for the Vaccine Antigen Master File. The certificate issued shall apply throughout the Community.
– By derogation from the provisions of the first, second and third indents of the present point (evaluation and certification), where a Vaccine Antigen Master File corresponds only to a vaccine which is the subject of a marketing authorisation which has not been/will not be granted according to a Community procedure, and, provided the authorised vaccine includes vaccine antigens which have not been evaluated through a Community procedure, the scientific and technical evaluation of the said Vaccine Antigen Master File and its subsequent changes, shall be carried out by the national competent authority that has granted the marketing authorisation.
– As a second step to the provisions in the first, second, third and fourth indents, the competent authority that will grant or has granted the marketing authorisation shall take into account the certification, re-certification or variation of the Vaccine Antigen Master File on the concerned medicinal product(s).

2. RADIO-PHARMACEUTICALS AND PRECURSORS

2.1. Radio-pharmaceuticals

For the purposes of this chapter, applications based upon Articles 6 (2) and 9 shall provide a full dossier in which the following specific details shall be included:

Module 3

a) In the context of a radio-pharmaceutical kit, which is to be radio-labelled after supply by the manufacturer, the active substance is considered to be that part of the formulation which is intended

to carry or bind the radio-nuclide. The description of the manufacturing method of radio-pharmaceutical kits shall include details of the manufacture of the kit and details of its recommended final processing to produce the radioactive medicinal product. The necessary specifications of the radio-nuclide shall be described in accordance, where relevant, with the general monograph or specific monographs of the European Pharmacopoeia. In addition, any compounds essential for the radio-labelling shall be described. The structure of the radio-labelled compound shall also be described.

For radio-nuclides, the nuclear reactions involved shall be discussed.

In a generator, both mother and daughter radio-nuclides shall be considered as active substances.

b) Details of the nature of the radio-nuclide, the identity of the isotope, likely impurities, the carrier, the use and the specific activity shall be provided.
c) Starting materials include irradiation target materials.
d) Considerations on chemical/radiochemical purity and its relationship to bio-distribution shall be provided.
e) Radio-nuclide purity, radiochemical purity and specific activity shall be described.
f) For generators, details on the testing for mother and daughter radio-nuclides are required. For generator-eluates, tests for mother radio-nuclides and for other constituents of the generator system shall be provided.
g) The requirement to express the content of active substances in terms of the mass of active entities shall onlyapply to radio-pharmaceutical kits. For radio-nuclides, radioactivity shall be expressed in Becquerels at a given date and, if necessary, time with reference to time zone. The type of radiation shall be indicated.
h) For kits, the specifications of the finished product shall include tests on performance of products after radio-labelling. Appropriate controls on radiochemical and radio-nuclidic purity of the radio-labelled compound shall be included. Any material essential for radio-labelling shall be identified and assayed.
i) Information on stability shall be given for radio-nuclide generators, radio-nuclide kits and radio-labelled products. The stability during use of radio-pharmaceuticals in multi-dose vials shall be documented.

Module 4

It is appreciated that toxicity may be associated with a radiation dose. In diagnosis, this is a consequence of the use of radio-pharmaceuticals; in therapy, it is the property desired. The evaluation of safety and efficacy of radio-pharmaceuticals shall, therefore, address requirements for medicinal products and radiation dosimetry aspects. Organ/tissue exposure to radiation shall be documented. Absorbed radiation dose estimates shall be calculated according to a specified, internationally recognised system by a particular route of administration.

Module 5

The results of clinical trials shall be provided where applicable otherwise justified in the clinical overviews.

2.2. Radio-pharmaceutical precursors for radio-labelling purposes

In the specific case of a radio-pharmaceutical precursor intended solely for radio-labelling purposes, the primary objective shall be to present information which would address the possible consequences of poor radio-labeling efficiency or in vivo dissociation of the radio-labeled conjugate, i.e. questions related to the effects produced in the patient by free radio-nuclide. In addition, it is also necessary to present relevant information relating to occupational hazards, i.e. radiation exposure to hospital staff and to the environment.
In particular, the following information where applicable shall be provided:

Module 3

The provisions of Module 3 shall apply to the registration of radio-pharmaceutical precursors as define above (indents a) to i)), where applicable.

Module 4

Concerning single dose and repeat dose toxicity, the results of studies carried out in conformity with the provisions related to good laboratory practice laid down in Council Directives 87/18/EEC and 88/320/EEC shall be provided, unless otherwise justified.
Mutagenicity studies on the radio-nuclide are not considered to be useful in this particular case.
Information relating to the chemical toxicity and disposition of the relevant 'cold' nuclide shall be presented.

Module 5

Clinical information generated from clinical studies using on the precursor itself is not considered to be relevant in the specific case of a radio-pharmaceutical precursor intended solely for radio-labelling purposes.
However, information demonstrating the clinical utility of the radio-pharmaceutical precursor when attached to relevant carrier molecules shall be presented.

3. HOMEOPATHIC MEDICINAL PRODUCTS

This section sets out specific provisions on the application of Modules 3 and 4 to homeopathic medicinal products as defined in Article 1(5).

Module 3

The provisions of Module 3 shall apply to the documents submitted in accordance with Article 15 in the simplified registration of homeopathic medicinal products referred to in Article 14(1) as well as to the documents for authorisation of other homeopathic medicinal products referred to in Article 16(1) with the following modifications.

a) Terminology

The Latin name of the homeopathic stock described in the marketing authorisation application dossier must be in accordance with the Latin title of the European Pharmacopoeia or, in absence thereof, by an

official pharmacopoeia of a Member State. Where relevant the traditional name(s) used in each Member State shall be provided.

b) Control of starting materials

The particulars and documents on the starting materials, i.e. all of the materials used including raw materials and intermediates up to the final dilution to be incorporated into the finished medicinal product, accompanying the application shall be supplemented by additional data on the homeopathic stock.

The general quality requirements shall apply to all of the starting and raw materials as well as intermediate steps of the manufacturing process up to the final dilution to be incorporated into the finished medicinal product. If possible, an assay is required if toxic components are present and if the quality cannot be controlled on final dilution to be incorporated because of the high dilution degree. Every step of the manufacturing process from the starting materials up to the final dilution to be incorporated into the finished medicinal product must be fully described.

In case dilutions are involved, these dilution steps should be done in accordance with the homeopathicmanufacturing methods laid down in the relevant monograph of the European Pharmacopoeia or, in absence thereof, by an official pharmacopoeia of a Member State.

c) Control tests on the finished medicinal product

The general quality requirements shall apply to the homeopathic finished medicinal products, any exception needs to be duly justified by the applicant.

Identification and assay of all the toxicologically relevant constituents shall be carried out. If it can be justified that an identification and/or an assay on all the toxicologically relevant constituents is not possible e.g. due to their dilution in the finished medicinal product the quality shall be demonstrated by complete validation of the manufacturing and dilution process.

d) Stability tests

The stability of the finished medicinal product must be demonstrated. Stability data from the homeopathic stocks are generally transferable to dilutions/triturations obtained thereof. If no identification or assay of the active substance is possible due to the degree of dilution, stability data of the pharmaceutical form may be considered.

Module 4

The provisions of Module 4 shall apply to the simplified registration of homeopathic medicinal products referred to in Article 14(1) with the following specifications.

Any missing information must be justified, e.g., justification must be given why demonstration of an acceptable level of safety can be supported although some studies are lacking.

4. HERBAL MEDICINAL PRODUCTS

Applications for herbal medicinal products shall provide a full dossier in which the following specific details shall be included.

Module 3

The provisions of Module 3, including compliance with monograph(s) of the European Pharmacopoeia, shall apply to the authorisation of herbal medicinal products. The state of scientific knowledge at the time when the application is lodged shall be taken into account.
The following aspects specific to herbal medicinal products shall be considered:

(1) Herbal substances and herbal preparations

For the purposes of this Annex the terms 'herbal substances and preparations' shall be considered equivalent to the terms 'herbal drugs and herbal drug preparations', as defined in the European Pharmacopoeia.

With respect to the nomencRlature of the herbal substance, the binomial scientific name of plant (genus, species, variety and author), and chemotype (where applicable), the parts of the plants, the definition of the herbal substance, the other names (synonyms mentioned in other Pharmacopoeias) and the laboratory code shall be provided.

With respect to the nomenclature of the herbal preparation, the binomial scientific name of plant (genus, species, variety and author), and chemotype (where applicable), the parts of the plants, the definition of the herbal preparation, the ratio of the herbal substance to the herbal preparation, the extraction solvent(s), the other names (synonyms mentioned in other Pharmacopoeias) and the laboratory code shall be provided.

To document the section of the structure for herbal substance(s) and herbal preparation(s) where applicable, the physical form, the description of the constituents with known therapeutic activity or markers (molecular formula, relative molecular mass, structural formula, including relative and absolute stereo-chemistry, the molecular formula, and the relative molecular mass) as well as other constituent(s) shall be provided.

To document the section on the manufacturer of the herbal substance, the name, address, and responsibility of each supplier, including contractors, and each proposed site or facility involved in production/collection and testing of the herbal substance shall be provided, where appropriate.

To document the section on the manufacturer of the herbal preparation, the name, address, and responsibility of each manufacturer, including contractors, and each proposed manufacturing site or facility involved in manufacturing and testing of the herbal preparation shall be provided, where appropriate.

With respect to the description of manufacturing process and process controls for the herbal substance, information shall be provided to adequately describe the plant production and plant collection, including the geographical source of the medicinal plant and cultivation, harvesting, drying and storage conditions.

With respect to the description of manufacturing process and process controls for the herbal preparation, information shall be provided to adequately describe the manufacturing process of the

herbal preparation, including description of the processing, solvents and reagents, purification stages and standardisation.

With respect to the manufacturing process development, a brief summary describing the development of the herbal substance(s) and herbal preparation(s) where applicable shall be provided, taking into consideration the proposed route of administration and usage. Results comparing the phyto-chemical composition of the herbal substance(s) and herbal preparation(s) where applicable used in supporting bibliographic data and the herbal substance(s) and herbal preparation(s), where applicable, contained as active substance(s) in the herbal medicinal product applied for shall be discussed, where appropriate.

With respect to the elucidation of the structure and other characteristics of the herbal substance, information on the botanical, macroscopical, microscopical, phyto-chemical characterisation, and biological activity if necessary, shall be provided.

With respect to the elucidation of the structure and other characteristics of the herbal preparation, information on the phyto- and physicochemical characterisation, and biological activity if necessary, shall be provided.

The specifications for the herbal substance(s) and herbal preparation(s) where applicable shall be provided.

The analytical procedures used for testing the herbal substance(s) and herbal preparation(s) where applicable shall be provided.

With respect to the validation of analytical procedures, analytical validation information, including experimental data for the analytical procedures used for testing the herbal substance(s) and herbal preparation(s) where applicable shall be provided.

With respect to batch analyses, description of batches and results of batch analyses for the herbal substance(s) and herbal preparation(s) where applicable shall be provided, including those for pharmacopoeial substances.

Justification for the specifications of the herbal substance(s) and herbal preparation(s) where applicable shall be provided.

Information on the reference standards or reference materials used for testing of the herbal substance(s) and herbal preparation(s) where applicable shall be provided.

Where the herbal substance or the herbal preparation is the subject of a monograph, the applicant can apply for a certificate of suitability that was granted by the European Directorate for the Quality of Medicines.

(2) Herbal Medicinal Products

With respect to the formulation development, a brief summary describing the development of the herbal medicinal product should be provided, taking into consideration the proposed route of administration and usage. Results comparing the phyto-chemical composition of the products used in supporting bibliographic data and the herbal medicinal product applied for shall be discussed, where appropriate.

5. ORPHAN MEDICINAL PRODUCTS

- In the case of an orphan medicinal product in the meaning of Regulation (EC) No 141/2000, general provisions of Part II-6 (exceptional circumstances) can be applied. The applicant shall then justify in the non-clinical and clinical summaries the reasons for which it is not possible to provide the complete information and shall provide a justification of the benefit/risk balance for the orphan medicinal product concerned.
- When an applicant for an marketing authorisation for an orphan medicinal product invokes the provisions of Article 10 (1)(a)(ii) and Part II-1 of this Annex (well-established medicinal use), the systematic and documented use of the concerned substance can refer — as way of derogation — to the use of that substance in accordance with the provisions of Article 5 of this Directive.

PART IV - ADVANCED THERAPY MEDICINAL PRODUCTS

1. INTRODUCTION

Marketing authorisation applications for advanced therapy medicinal products, as defined in point (a) of Article 2(1) of Regulation (EC) No 1394/2007, shall follow the format requirements (Modules 1, 2, 3, 4 and 5) described in Part I of this Annex.

The technical requirements for Modules 3, 4 and 5 for biological medicinal products, as described in Part I of this Annex, shall apply. The specific requirements for advanced therapy medicinal products described in sections 3, 4 and 5 of this part explain how the requirements in Part I apply to advanced therapy medicinal products. In addition, where appropriate and taking into account the specificities of advanced therapy medicinal products, additional requirements have been set.

Due to the specific nature of advanced therapy medicinal products, a risk-based approach may be applied to determine the extent of quality, non-clinical and clinical data to be included in the marketing authorisation application, in accordance with the scientific guidelines relating to the quality, safety and efficacy of medicinal products referred to in point 4 of the 'Introduction and general principles'.

The risk analysis may cover the entire development. Risk factors that may be considered include: the origin of the cells (autologous, allogeneic, xenogeneic), the ability to proliferate and/or differentiate and to initiate an immune response, the level of cell manipulation, the combination of cells with bioactive molecules or structural materials, the nature of the gene therapy medicinal products, the extent of replication competence of viruses or micro-organisms used *in vivo*, the level of integration of nucleic acids sequences or genes into the genome, the long time functionality, the risk of oncogenicity and the mode of administration or use.

Relevant available non-clinical and clinical data or experience with other, related advanced therapy medicinal products may also be considered in the risk analysis.

Any deviation from the requirements of this Annex shall be scientifically justified in Module 2 of the application dossier. The risk analysis described above, when applied, shall also be included and described in Module 2. In this case, the methodology followed, the nature of the identified risks and the implications of the risk based approach for the development and evaluation program shall be discussed and any deviations from the requirements of this Annex resulting from the risk analysis shall be described.

2. DEFINITIONS

For the purposes of this Annex, in addition to the definitions laid down in Regulation (EC) No 1394/2007, the definitions set out in sections 2.1 and 2.2 shall apply.

2.1. Gene therapy medicinal product

Gene therapy medicinal product means a biological medicinal product which has the following characteristics:

a) it contains an active substance which contains or consists of a recombinant nucleic acid used in or administered to human beings with a view to regulating, repairing, replacing, adding or deleting a genetic sequence;

b) its therapeutic, prophylactic or diagnostic effect relates directly to the recombinant nucleic acid sequence it contains, or to the product of genetic expression of this sequence.

Gene therapy medicinal products shall not include vaccines against infectious diseases.

2.2. Somatic cell therapy medicinal product

Somatic cell therapy medicinal product means a biological medicinal product which has the following characteristics:

a) contains or consists of cells or tissues that have been subject to substantial manipulation so that biological characteristics, physiological functions or structural properties relevant for the intended clinical use have been altered, or of cells or tissues that are not intended to be used for the same essential function(s) in the recipient and the donor;

b) is presented as having properties for, or is used in or administered to human beings with a view to treating, preventing or diagnosing a disease through the pharmacological, immunological or metabolic action of its cells or tissues.

For the purposes of point (a), the manipulations listed in Annex I to Regulation (EC) No 1394/2007, in particular, shall not be considered as substantial manipulations.

3. SPECIFIC REQUIREMENTS REGARDING MODULE 3

3.1. Specific requirements for all advanced therapy medicinal products

A description of the traceability system that the marketing authorisation holder intends to establish and maintain to ensure that the individual product and its starting and raw materials, including all substances

coming into contact with the cells or tissues it may contain, can be traced through the sourcing, manufacturing, packaging, storage, transport and delivery to the hospital, institution or private practice where the product is used, shall be provided.
The traceability system shall be complementary to, and compatible with, the requirements established in Directive 2004/23/EC of the European Parliament and of the Council[43], as regards human cells and tissues other than blood cells, and Directive 2002/98/EC, as regards human blood cells.

3.2. Specific requirements for gene therapy medicinal products

3.2.1.Introduction: finished product, active substance and starting materials

3.2.1.1. Gene therapy medicinal product containing recombinant nucleic acid sequence(s) or genetically modified microorganism(s) or virus(es)

The finished medicinal product shall consist of nucleic acid sequence(s) or genetically modified microorganism(s) or virus(es) formulated in their final immediate container for the intended medical use. The finished medicinal product may be combined with a medical device or active implantable medical device.
The active substance shall consist of nucleic acid sequence(s) or genetically modified microorganism(s) or virus(es).

3.2.1.2. Gene therapy medicinal product containing genetically modified cells

The finished medicinal product shall consist of genetically modified cells formulated in the final immediate container for the intended medical use. The finished medicinal product may be combined with a medical device or active implantable medical device.
The active substance shall consist of cells genetically modified by one of the products described in section 3.2.1.1 above.

3.2.1.3. In the case of products consisting of viruses or viral vectors, the starting materials shall be the components from which the viral vector is obtained, i.e. the master virus vector seed or the plasmids used to transfect the packaging cells and the master cell bank of the packaging cell line.

3.2.1.4. In the case of products consisting of plasmids, non-viral vectors and genetically modified microorganism(s) other than viruses or viral vectors, the starting materials shall be the components used to generate the producing cell, i.e. the plasmid, the host bacteria and the master cell bank of recombinant microbial cells.

3.2.1.5. In the case of genetically modified cells, the starting materials shall be the components used to obtain the genetically modified cells, i.e. the starting materials to produce the vector, the vector and the human or animal cells. The principles of good manufacturing practice shall apply from the bank system

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43 OJ L 102, 7.4.2004, p. 48.

used to produce the vector onwards.

3.2.2.Specific requirements

In addition to the requirements set out in sections 3.2.1 and 3.2.2 of Part I of this Annex, the following requirements shall apply:

a) information shall be provided on all the starting materials used for the manufacture of the active substance, including the products necessary for the genetic modification of human or animal cells and, as applicable, subsequent culture and preservation of the genetically modified cells, taking into consideration the possible absence of purification steps;
b) for products containing a microorganism or a virus, data on the genetic modification, sequence analysis, attenuation of virulence, tropism for specific tissues and cell types, cell cycle dependence of the microorganism or virus, pathogenicity and characteristics of the parental strain shall be provided;
c) process-related impurities and product-related impurities shall be described in the relevant sections of the dossier, and in particular replication competent virus contaminants if the vector is designed to be replication incompetent;
d) for plasmids, quantification of the different plasmid forms shall be undertaken throughout the shelf life of the product;
e) for genetically modified cells, the characteristics of the cells before and after the genetic modification, as well as before and after any subsequent freezing/storage procedures, shall be tested.
   For genetically modified cells, in addition to the specific requirements for gene therapy medicinal products, the quality requirements for somatic cell therapy medicinal products and tissue engineered products (see section 3.3) shall apply.

3.3. Specific requirements for somatic cell therapy medicinal products and tissue engineered products

3.3.1.Introduction: finished product, active substance and starting materials

The finished medicinal product shall consist of the active substance formulated in its immediate container for the intended medical use, and in its final combination for combined advanced therapy medicinal products.

The active substance shall be composed of the engineered cells and/or tissues.

Additional substances (e.g. scaffolds, matrices, devices, biomaterials, biomolecules and/or other components) which are combined with manipulated cells of which they form an integral part shall be considered as starting materials, even if not of biological origin.

Materials used during the manufacture of the active substance (e.g. culture media, growth factors) and that are not intended to form part of the active substance shall be considered as raw materials.

3.3.2.Specific requirements

In addition to the requirements set out in sections 3.2.1 and 3.2.2 of Part I of this Annex, the

following requirements shall apply:

3.3.2.1.Starting materials

a) Summary information shall be provided on donation, procurement and testing of the human tissue and cells used as starting materials and made in accordance with Directive 2004/23/EC. If non-healthy cells or tissues (e.g. cancer tissue) are used as starting materials, their use shall be justified.
b) If allogeneic cell populations are being pooled, the pooling strategies and measures to ensure traceability shall be described.
c) The potential variability introduced through the human or animal tissues and cells shall be addressed as part of the validation of the manufacturing process, characterisation of the active substance and the finished product, development of assays, setting of specifications and stability.
d) For xenogeneic cell-based products, information on the source of animals (such as geographical origin, animal husbandry, age), specific acceptance criteria, measures to prevent and monitor infections in the source/donor animals, testing of the animals for infectious agents, including vertically transmitted micro-organisms and viruses, and evidence of the suitability of the animal facilities shall be provided.
e) For cell-based products derived from genetically modified animals, the specific characteristics of the cells related to the genetic modification shall be described. A detailed description of the method of creation and the characterisation of the transgenic animal shall be provided.
f) For the genetic modification of the cells, the technical requirements specified in section 3.2 shall apply.
g) The testing regimen of any additional substance (scaffolds, matrices, devices, biomaterials, biomolecules or other components), which are combined with engineered cells of which they form an integral part, shall be described and justified.
h) For scaffolds, matrices and devices that fall under the definition of a medical device or active implantable medical device, the information required under section 3.4 for the evaluation of the combined advanced therapy medicinal product shall be provided.

3.3.2.2.Manufacturing process

a) The manufacturing process shall be validated to ensure batch and process consistency, functional integrity of the cells throughout manufacturing and transport up to the moment of application or administration, and proper differentiation state.
b) If cells are grown directly inside or on a matrix, scaffold or device, information shall be provided on the validation of the cell culture process with respect to cell-growth, function and integrity of the combination.

3.3.2.3.Characterisation and control strategy

a) Relevant information shall be provided on the characterisation of the cell population or cell mixture in terms of identity, purity (e.g. adventitious microbial agents and cellular

contaminants), viability, potency, karyology, tumourigenicity and suitability for the intended medicinal use. The genetic stability of the cells shall be demonstrated.

b) Qualitative and, where possible, quantitative information on product- and process-related impurities, as well as on any material capable of introducing degradation products during production, shall be provided. The extent of the determination of impurities shall be justified.

c) If certain release tests cannot be performed on the active substance or finished product, but only on key intermediates and/or as in-process testing, this shall be justified.

d) Where biologically active molecules (such as growth factors, cytokines) are present as components of the cell-based product, their impact and interaction with other components of the active substance shall be characterised.

e) Where a three-dimensional structure is part of the intended function, the differentiation state, structural and functional organisation of the cells and, where applicable, the extracellular matrix generated shall be part of the characterisation for these cell-based products. Where needed, non-clinical investigations shall complement the physicochemical characterisation.

3.3.2.4.Excipients

For excipient(s) used in cell or tissue-based medicinal products (e.g. the components of the transport medium), the requirements for novel excipients, as laid down in Part I of this Annex, shall apply, unless data exists on the interactions between the cells or tissues and the excipients.

3.3.2.5.Developmental studies

The description of the development program shall address the choice of materials and processes. In particular, the integrity of the cell population as in the final formulation shall be discussed.

3.3.2.6.Reference materials

A reference standard, relevant and specific for the active substance and/or the finished product, shall be documented and characterised.

3.4. Specific requirements for advanced therapy medicinal products containing devices

3.4.1.Advanced therapy medicinal product containing devices as referred to in Article 7 of Regulation (EC) No 1394/2007

A description of the physical characteristics and performance of the product and a description of the product design methods shall be provided.

The interaction and compatibility between genes, cells and/or tissues and the structural components shall be described.

3.4.2.Combined advanced therapy medicinal products as defined in Article 2(1)(d) of Regulation (EC) No 1394/2007

For the cellular or tissue part of the combined advanced therapy medicinal product, the specific requirements for somatic cell therapy medicinal products and tissue engineered products set out in section 3.3 shall apply and, in the case of genetically modified cells, the specific requirements for gene therapy medicinal products set out in section 3.2 shall apply.

The medical device or the active implantable medical device may be an integral part of the active substance. Where the medical device or active implantable medical device is combined with the cells at the time of the manufacture or application or administration of the finished products, they shall be considered as an integral part of the finished product.

Information related to the medical device or the active implantable medical device (which is an integral part of the active substance or of the finished product) which is relevant for the evaluation of the combined advanced therapy medicinal product shall be provided. This information shall include:

a) information on the choice and intended function of the medical device or implantable medical device and demonstration of compatibility of the device with other components of the product;

b) evidence of conformity of the medical device part with the essential requirements laid down in Annex I to Council Directive 93/42/EEC44, or of conformity of the active implantable device part with the essential requirements laid down in Annex 1 to Council Directive 90/385/EEC45;

c) where applicable, evidence of compliance of the medical device or implantable medical device with the BSE/TSE requirements laid down in Commission Directive 2003/32/EC46;

d) where available, the results of any assessment of the medical device part or the active implantable medical device part by a notified body in accordance with Directive 93/42/EEC or Directive 90/385/EEC.

The notified body which has carried out the assessment referred to in point (d) of this section shall make available on request of the competent authority assessing the application, any information related to the results of the assessment in accordance with Directive 93/42/EEC or Directive 90/385/EEC. This may include information and documents contained in the conformity assessment application concerned, where necessary for the evaluation of the combined advanced therapy medicinal product as a whole.

4. SPECIFIC REQUIREMENTS REGARDING MODULE 4

4.1. Specific requirements for all advanced therapy medicinal products

The requirements of Part I, Module 4 of this Annex on the pharmacological and toxicological testing of medicinal products may not always be appropriate due to unique and diverse structural and biological properties of advanced therapy medicinal products. The technical requirements in sections 4.1, 4.2 and 4.3

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44 OJ L 169, 12.7.1993, p. 1.

45 OJ L 189, 20.7.1990, p. 17.

46 OJ L 105, 26.4.2003, p. 18.

below explain how the requirements in Part I of this Annex apply to advanced therapy medicinal products. Where appropriate and taking into account the specificities of advanced therapy medicinal products, additional requirements have been set.

The rationale for the non-clinical development and the criteria used to choose the relevant species and models (*in vitro* and *in vivo*) shall be discussed and justified in the non-clinical overview. The chosen animal model(s) may include immuno-compromised, knockout, humanised or transgenic animals. The use of homologous models (e.g. mouse cells analysed in mice) or disease mimicking models shall be considered, especially for immunogenicity and immunotoxicity studies.

In addition to the requirements of Part I, the safety, suitability and biocompatibility of all structural components (such as matrices, scaffolds and devices) and any additional substances (such as cellular products, biomolecules, biomaterials, and chemical substances), which are present in the finished product, shall be provided. Their physical, mechanical, chemical and biological properties shall be taken into account.

4.2. Specific requirements for gene therapy medicinal products

In order to determine the extent and type of non-clinical studies necessary to determine the appropriate level of non-clinical safety data, the design and type of the gene therapy medicinal product shall be taken into account.

4.2.1.Pharmacology

(a) In vitro and in vivo studies of actions relating to the proposed therapeutic use (i.e. pharmacodynamic 'proof of concept' studies) shall be provided using models and relevant animal species designed to show that the nucleic acid sequence reaches its intended target (target organ or cells) and provides its intended function (level of expression and functional activity). The duration of the nucleic acid sequence function and the proposed dosing regimen in the clinical studies shall be provided.

(b) Target selectivity: When the gene therapy medicinal product is intended to have a selective or target-restricted functionality, studies to confirm the specificity and duration of functionality and activity in target cells and tissues shall be provided.

4.2.2.Pharmacokinetics

(a) Biodistribution studies shall include investigations on persistence, clearance and mobilisation. Biodistribution studies shall additionally address the risk of germline transmission.

(b) Investigations of shedding and risk of transmission to third parties shall be provided with the environmental risk assessment, unless otherwise duly justified in the application on the basis of the type of product concerned.

4.2.3. Toxicology

(a) Toxicity of the finished gene therapy medicinal product shall be assessed. In addition, depending on the type of product, individual testing of active substance and excipients shall be taken into consideration, the in vivo effect of expressed nucleic acid sequence-related products which are not intended for the physiological function shall be evaluated.

(b) Single-dose toxicity studies may be combined with safety pharmacology and pharmacokinetic studies, e.g. to investigate persistence.

(c) Repeated dose toxicity studies shall be provided when multiple dosing of human subjects is intended. The mode and scheme of administration shall closely reflect the planned clinical dosing. For those cases where single dosing may result in prolonged functionality of the nucleic acid sequence in humans, repeated toxicity studies shall be considered. The duration of the studies may be longer than in standard toxicity studies depending on the persistence of the gene therapy medicinal product and the anticipated potential risks. A justification for the duration shall be provided.

(d) Genotoxicity shall be studied. However, standard genotoxicity studies shall only be conducted when they are necessary for testing a specific impurity or a component of the delivery system.

(e) Carcinogenicity shall be studied. Standard lifetime rodent carcinogenicity studies shall not be required. However, depending on the type of product, the tumourigenic potential shall be evaluated in relevant in vivo/in vitro models.

(f) Reproductive and developmental toxicity: Studies on the effects on fertility and general reproductive function shall be provided. Embryo-foetal and perinatal toxicity studies and germline transmission studies shall be provided, unless otherwise duly justified in the application on the basis of the type of product concerned.

(g) Additional toxicity studies

- Integration studies: integration studies shall be provided for any gene therapy medicinal product, unless the lack of these studies is scientifically justified, e.g. because nucleic acid sequences will not enter into the cell nucleus. For gene therapy medicinal products not expected to be capable of integration, integration studies shall be performed, if biodistribution data indicate a risk for germline transmission.
- Immunogenicity and immunotoxicity: potential immunogenic and immunotoxic effects shall be studied.

4.3. Specific requirements for somatic cell therapy medicinal products and tissue engineered products

4.3.1.Pharmacology

(a) The primary pharmacological studies shall be adequate to demonstrate the proof of concept. The interaction of the cell-based products with the surrounding tissue shall be studied.

(b) The amount of product needed to achieve the desired effect/the effective dose, and, depending on the type of product, the frequency of dosing shall be determined.

(c) Secondary pharmacological studies shall be taken into account to evaluate potential physiological effects that are not related to the desired therapeutic effect of the somatic cell therapy medicinal product, of the tissue engineered product or of additional substances, as biologically active molecules besides the protein(s) of interest might be secreted or the protein(s) of interest could have unwanted target sites.

4.3.2.Pharmacokinetics

(a) Conventional pharmacokinetic studies to investigate absorption, distribution, metabolism and excretion shall not be required. However, parameters such as viability, longevity, distribution, growth, differentiation and migration shall be investigated, unless otherwise duly justified in the application on the basis of the type of product concerned.

(b) For somatic cell therapy medicinal products and tissue engineered products, producing systemically active biomolecules, the distribution, duration and amount of expression of these molecules shall be studied.

4.3.3.Toxicology

(a) The toxicity of the finished product shall be assessed. Individual testing of active substance(s), excipients, additional substances and any process-related impurities shall be taken into consideration.

(b) The duration of observations may be longer than in standard toxicity studies and the anticipated lifespan of the medicinal product, together with its pharmacodynamic and pharmacokinetic profile, shall be taken into consideration. A justification of the duration shall be provided.

(c) Conventional carcinogenicity and genotoxicity studies shall not be required, except with regard to the tumourigenic potential of the product.

(d) Potential immunogenic and immunotoxic effects shall be studied.

(e) In the case of cell-based products containing animal cells, the associated specific safety concerns such as transmission to humans of xenogeneic pathogens shall be addressed.

5. SPECIFIC REQUIREMENTS REGARDING MODULE 5

5.1. Specific requirements for all advanced therapy medicinal products

5.1.1.The specific requirements in this section of Part IV are additional requirements to those set in Module 5 in Part I of this Annex.

5.1.2.Where the clinical application of advanced therapy medicinal products requires specific concomitant therapy and involve surgical procedures, the therapeutic procedure as a whole shall be investigated and described. Information on the standardisation and optimisation of those procedures during clinical development shall be provided.

Where medical devices used during the surgical procedures for application, implantation or administration of the advanced therapy medicinal product may have an impact on the efficacy or safety of the advanced therapy product, information on these devices shall be provided.

Specific expertise required to carry out the application, implantation, administration or follow-up activities shall be defined. Where necessary, the training plan of health care professionals on the use, application, implantation or administration procedures of these products shall be provided.

5.1.3. Given that, due to the nature of advanced therapy medicinal products, their manufacturing process may change during clinical development, additional studies to demonstrate comparability may be required.

5.1.4. During clinical development, risks arising from potential infectious agents or the use of material derived from animal sources and measures taken to reduce such risk shall be addressed.

5.1.5. Dose selection and schedule of use shall be defined by dose-finding studies.

5.1.6. The efficacy of the proposed indications shall be supported by relevant results from clinical studies using clinically meaningful endpoints for the intended use. In certain clinical conditions, evidence of long-term efficacy may be required. The strategy to evaluate long-term efficacy shall be provided.

5.1.7. A strategy for the long-term follow-up of safety and efficacy shall be included in the risk management plan.

5.1.8. For combined advanced therapy medicinal products, the safety and efficacy studies shall be designed for and performed on the combined product as a whole.

5.2. Specific requirements for gene therapy medicinal products

5.2.1. Human pharmacokinetic studies

Human pharmacokinetic studies shall include the following aspects:

(a) shedding studies to address the excretion of the gene therapy medicinal products;
(b) biodistribution studies;
(c) pharmacokinetic studies of the medicinal product and the gene expression moieties (e.g. expressed proteins or genomic signatures).

5.2.2. Human pharmacodynamic studies

Human pharmacodynamic studies shall address the expression and function of the nucleic acid sequence following administration of the gene therapy medicinal product.

5.2.3. Safety studies

Safety studies shall address the following aspects:

(a) emergence of replication competent vector;
(b) emergence of new strains;
(c) reassortment of existing genomic sequences;
(d) neoplastic proliferation due to insertional mutagenicity.

5.3. Specific requirements for somatic cell therapy medicinal products

5.3.1. Somatic cell therapy medicinal products where the mode of action is based on the production of defined active biomolecule(s)

For somatic cell therapy medicinal products where the mode of action is based on the production of defined active biomolecule(s), the pharmacokinetic profile (in particular distribution, duration and amount of expression) of those molecules shall be addressed, if feasible.

5.3.2. Biodistribution, persistence and long-term engraftment of the somatic cell therapy medicinal product components

The biodistribution, persistence and long-term engraftment of the somatic cell therapy medicinal product components shall be addressed during the clinical development

5.3.3. Safety studies

Safety studies shall address the following aspects:

(a) distribution and engrafting following administration;

(b) ectopic engraftment;

(c) oncogenic transformation and cell/tissue lineage fidelity.

5.4. Specific requirements for tissue engineered products

5.4.1. Pharmacokinetic studies

Where conventional pharmacokinetic studies are not relevant for tissue engineered products, the biodistribution, persistence and degradation of the tissue engineered product components shall be addressed during the clinical development.

5.4.2. Pharmacodynamic studies

Pharmacodynamic studies shall be designed and tailored to the specificities of tissue engineered products. The evidence for the 'proof of concept' and the kinetics of the product to obtain the intended regeneration, repairing or replacement shall be provided. Suitable pharmacodynamic markers, related to the intended function(s) and structure shall be taken into account.

5.4.3. Safety studies

Section 5.3.3 shall apply.

ANNEX II

PART A

Repealed Directives, with their successive amendments (referred to by Article 128)

Council Directive 65/65/EEC (OJ 22, 9.2.1965, p. 369/65)

Council Directive 66/454/EEC (OJ 144, 5.8.1966, p. 2658/66)
Council Directive 75/319/EEC (OJ L 147, 9.6.1975, p. 13)
Council Directive 83/570/EEC (OJ L 332, 28.11.1983, p. 1)
Council Directive 87/21/EEC (OJ L 15, 17.1.1987, p. 36)
Council Directive 89/341/EEC (OJ L 142, 25.5.1989, p. 11)
Council Directive 92/27/EEC (OJ L 113, 30.4.1992, p. 8)
Council Directive 93/39/EEC (OJ L 214, 24.8.1993, p. 22)

Council Directive 75/318/EEC (OJ L 147, 9.6.1975, p. 1)
Council Directive 83/570/EEC
Council Directive 87/19/EEC (OJ L 15, 17.1.1987, p. 31)
Council Directive 89/341/EEC
Commission Directive 91/507/EEC (OJ L 270, 26.9.1991, p. 32)
Council Directive 93/39/EEC
Commission Directive 1999/82/EC (OJ L 243, 15.9.1999, p. 7)
Commission Directive 1999/83/EC (OJ L 243, 15.9.1999, p. 9)

Council Directive 75/319/EEC
Council Directive 78/420/EEC (OJ L 123, 11.5.1978, p. 26)
Council Directive 83/570/EEC
Council Directive 89/341/EEC
Council Directive 92/27/EEC
Council Directive 93/39/EEC
Commission Directive 2000/38/EC (OJ L 139, 10.6.2000, p. 28

Council Directive 89/342/EEC (OJ L 142, 25.5.1989, p. 14)
Council Directive 89/343/EEC (OJ L 142, 25.5.1989, p. 16)
Council Directive 89/381/EEC (OJ L 181, 28.6.1989, p. 44)
Council Directive 92/25/EEC (OJ L 113, 30.4.1992, p. 1)
Council Directive 92/26/EEC (OJ L 113, 30.4.1992, p. 5)
Council Directive 92/27/EEC
Council Directive 92/28/EEC (OJ L 113, 30.4.1992, p. 13)
Council Directive 92/73/EEC (OJ L 297, 13.10.1992, p. 8)

PART B

Time-limits for transposition into national law (referred to by Article 128)

Directive	Deadline for transposition
Directive 65/65/EEC	31 December 1966
Directive 66/454/EEC	—
Directive 75/318/EEC	21 November 1976
Directive 75/319/EEC	21 November 1976
Directive 78/420/EEC	—
Directive 83/570/EEC	31 October 1985
Directive 87/19/EEC	1 July 1987
Directive 87/21/EEC	1 July 1987 1 January 1992
Directive 89/341/EEC	1 January 1992
Directive 89/342/EEC	1 January 1992
Directive 89/343/EEC	1 January 1992
Directive 89/381/EEC	1 January 1992
Directive 91/507/EEC	1 January 1992 1 January 1995
Directive 92/25/EEC	1 January 1993
Directive 92/26/EEC	1 January 1993
Directive 92/27/EEC	1 January 1993
Directive 92/28/EEC	1 January 1993
Directive 92/73/EEC	31 December 1993
Directive 93/39/EEC	1 January 1995 1 January 1998
Directive 1999/82/EC	1 January 2000
Directive 1999/83/EC	1 March 2000
Directive 2000/38/EC	5 December 2001

ANNEX III - CORRELATION TABLE

This Dir.	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	92/73/ EEC
Art. 1(1) to (3)	Art. 1(1) to (3)										
Art. 1(4)			Annex	Art. 1(1) and (2)							
Art. 1(5)											Art. 1
Art. 1(6) to (9)					Art. 1(2)						
Art. 1(10)						Art. 1(1)					
Art. 1(11) to (16)			Art. 29b, 1st paragraph								
Art. 1(17) and (18)							Art. 1(2)				
Art. 1(19)								Art. 1(2), 2nd sentence			
Art. 1(20) to (26)									Art. 1(2)		
Art. 1(27)			Art. 8(1)								
Art. 1(28)			Art. 10(1)								
Art. 2	Art. 2(1)										
Art. 3(1) and (2)	Art. 1(4) and (5) Art 2(3), 1st indent										
Art. 3(3) and (4)	Art.2(3), 2nd and 3rd indents										
Art. 3(5)					Art. 1(1)						
Art. 3(6)						Art. 1(2)					
Art. 4(1)					Art. 1(3)						
Art. 4(2)						Art. 1(3)					

Art. 4(3)	Art. 3, 2nd subparagraph										
Art. 4(4)	Art. 6										
Art. 5	Art. 2(4)										
Art. 6(1)	Art. 3(1)										
Art. 6(2)					Art. 2, 1st sentence						
Art. 7					Art. 2, 2nd sentence						
Art. 8(1) and (2)	Art. 4(1) and (2)										
Art. 8(3) (a) to (e)	Art. 4, 3rd para., points 1 to 5	Art. 1, 1st paragraph									
Art. 8(3) (f) to (i)	Art. 4, 3rd para., points 6 to 8.1										
Art. 8(3) (j) to (l)	Art. 4, 3rd para., points 9 to 11										
Art. 9					Art. 3						
Art. 10(1)	Art. 4, 3rd paragraph, point 8.2										
Art. 10(2)		Art. 1, 2nd paragraph									
Art. 11, points 1 to 5.3	Art. 4a, points 1 to 5.3										
Art. 11, point 5.4	Art. 4a, point 5.4			Art. 3							

Art. 11, points 5.5 to 6.4	Art. 4a, points 5.5 to 6.4										
Art. 11, point 6.5	Art. 4a, point 6.6										
Art. 11, point 7	Art. 4a, point 6.5										
Art. 11, points 8 to 9					Art. 4						
Art. 12(1)			Art. 1								
Art. 12(2) and (3)			Art. 2								
Art. 13											Art. 6(1) and (2)
Art. 14(1) and (2)											Art. 7(1) and (4)
Art. 14(3)											Art. 4, 2nd paragraph
Art. 15											Art. 8
Art. 16											Art. 9
Art. 17	Art. 7										
Art. 18	Art. 7a										
Art. 19			Art. 4								
Art. 20			Art. 5								
Art. 21	Art. 4b										
Art. 22	Art. 10(2)										
Art. 23	Art. 9a										
Art. 24	Art. 10(1)										
Art. 25	Art. 9										
Art. 26	Art. 5										
Art. 27			Art. 8								
Art. 28(1)			Art. 9(3)								

Art. 28(2)			Art. 9(1)								
Art. 28(3)			Art. 9(2)								
Art. 28(4)			Art. 9(4)								
Art. 29			Art. 10								
Art. 30			Art. 11								
Art. 31			Art. 12								
Art. 32			Art. 13								
Art. 33			Art. 14(1)								
Art. 34			Art. 14(2) to (4)								
Art. 35			Art. 15								
Art. 36			Art. 15a								
Art. 37			Art. 15b								
Art. 38			Art. 15c								
Art. 39			Art. 14(5)								
Art. 40			Art. 16								
Art. 41			Art. 17								
Art. 42			Art. 18								
Art. 43			Art. 20(1)								
Art. 44			Art. 20(2)								
Art. 45			Art. 20(3)								
Art. 46			Art. 19								
Art. 47			Art. 19a								
Art. 48			Art. 21								
Art. 49			Art. 23								
Art. 50			Art. 24								
Art. 51(1) and (2)			Art. 22(1)								
Art. 51(3)			Art. 22(2)								

Art. 52			Art. 25								
Art. 53											Art. 3
Art. 54									Art. 2(1)		
Art. 55									Art. 3		
Art. 56									Art. 4(1)		
Art. 57									Art. 5(2)		
Art. 58									Art. 6		
Art. 59									Art. 7(1) and (2)		
Art. 60									Art. 5(1) and Art. 9		
Art. 61									Art. 10(1) to (4)		
Art. 62									Art. 2(2) and Art. 7(3)		
Art. 63(1)									Art. 4(2)		
Art. 63(2)									Art. 8		
Art. 63(3)									Art. 10(5)		
Art. 64									Art. 11(1)		
Art. 65									Art. 12		
Art. 66					Art. 5						
Art. 67					Art. 6(1)						
Art. 68											Art. 2(2)
Art. 69											Art. 7(2) and (3)
Art. 70								Art. 2			
Art. 71								Art. 3			
Art. 72								Art. 4			

Art. 73								Art. 5(1)			
Art. 74								Art. 5(2)			
Art. 75								Art. 6(2)			
Art. 76							Art. 2				
Art. 77							Art. 3				
Art. 78							Art. 4(1)				
Art. 79							Art. 5				
Art. 80							Art. 6				
Art. 81							Art. 7				
Art. 82							Art. 8				
Art. 83							Art. 9				
Art. 84							Art. 10				
Art. 85											Art. 9
Art. 86										Art. 1(3) and (4)	
Art. 87										Art. 2	
Art. 88										Art. 3(1) to (6)	
Art. 89										Art. 4	
Art. 90										Art. 5	
Art. 91										Art. 6	
Art. 92										Art. 7	
Art. 93										Art. 8	
Art. 94										Art. 9	
Art. 95										Art. 10	
Art. 96										Art. 11	
Art. 97(1) to (4)										Art. 12(1) and (2)	
Art. 97(5)										Art. 12(4)	
Art. 98										Art. 13	
Art. 99										Art. 14	
Art. 100											Art. 6(3)
Art. 101			Art. 29e								
Art. 102			Art. 29a								

Art. 103			Art. 29c								
Art. 104			Art. 29d								
Art. 105			Art. 29f								
Art. 106(1)			Art. 29g								
Art. 106(2)			Art. 29b, 2nd paragraph								
Art. 107			Art. 29h								
Art. 108			Art. 29i								
Art. 109						Art. 3(1) to (3)					
Art. 110						Art. 3(4)					
Art. 111(1)			Art. 26, 1st and 2nd paragraph								
Art. 111(2)				Art. 4(1)							
Art. 111(3)			Art. 26, 3rd paragraph								
Art. 112	Art. 8		Art. 27								
Art. 113				Art. 4(2)		Art. 4(2)					
Art. 114(1)				Art. 4(3)							
Art. 114(2)						Art. 4(3)					
Art. 115						Art. 4(1)					
Art. 116	Art. 11										
Art. 117			Art. 28								
Art. 118			Art. 29								
Art. 119											Art. 4(1)
Art. 120		Art. 2a, 1st paragraph									
Art. 121		Art. 2b	Art. 37a								

Art. 122			Art. 30								
Art. 123			Art. 33								
Art. 124											Art. 5
Art. 125	Art. 12		Art. 31				Art. 4(2)		Art. 11(2)	Art. 12(3)	
Art. 126, 1st paragraph	Art. 21										
Art. 126, 2nd paragraph			Art. 32								
Art. 127			Art. 28a								
Art. 128	—	—	—	—	—	—	—	—	—	—	—
Art. 129	—	—	—	—	—	—	—	—	—	—	—
Art. 130	—	—	—	—	—	—	—	—	—	—	—
Annex I		Annex									
Annex II	—	—	—	—	—	—	—	—	—	—	—
Annex III	—	—	—	—	—	—	—	—	—	—	—

Regulation (EC) No 726/2004 - European Medicines Agency

REGULATION (EC) NO 726/2004 OF THE EUROPEAN PARLIAMENT AND THE COUNCIL OF 31 MARCH 2004 LAYING DOWN COMMUNITY PROCEDURES FOR THE AUTHORISATION AND SUPERVISION OF MEDICINAL PRODUCTS FOR HUMAN AND VETERINARY USE AND ESTABLISHING A EUROPEAN MEDICINES AGENCY

(Text with EEA relevance)

THE EUROPEAN PARLIAMENT AND THE COUNCIL OF THE EUROPEAN UNION,

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

Having regard to the proposal from the Commission,

Having regard to the Opinion of the European Economic and Social Committee,

After consulting the Committee of the Regions,

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

Whereas:

(1) Article 71 of Council Regulation (EEC) No 2309/93 of 22 July 1993 laying down Community procedures for the authorisation and supervision of medicinal products for human and veterinary use and establishing a European Agency for the Evaluation of Medicinal Products provides that, within six years of the entry into force of the Regulation, the Commission is to publish a general report on the experience acquired as a result of the operation of the procedures laid down in the Regulation.

(2) In the light of the Commission's report on the experience gained, it has proved necessary to improve the operation of the authorisation procedures for the placing of medicinal products on the market in the Community and to amend certain administrative aspects of the European Agency for the Evaluation of Medicinal Products. In addition, the name of that Agency should be simplified and changed to the European Medicines Agency, (hereinafter referred to as the 'Agency').

(3) It emerges from the conclusions of that report that the amendments to be made to the centralised procedure set up by Regulation (EEC) No 2309/93 consist of corrections to some of the operating procedures and adaptations to take account of the probable development of science and technology and the future enlargement of the European Union. It also emerges from the report that the general principles previously established which govern the centralised procedure should be maintained.

(4) Moreover, since the European Parliament and the Council have adopted Directive 2001/83/EC of 6 November 2001 on the Community code relating to medicinal products for human use and Directive 2001/82/EC of 6 November 2001 on the Community code relating to veterinary medicinal products, all the references to the codified Directives in Regulation (EEC) No 2309/93 should be updated.

(5) For the sake of clarity, it is necessary to replace the said Regulation with a new Regulation.

(6) It is appropriate to preserve the Community mechanism set up by the repealed Community legislation for concertation prior to any national decision relating to a high-technology medicinal product.

(7) Experience gained since the adoption of Council Directive 87/22/EEC of 22 December 1986 on the approximation of national measures relating to the placing on the market of high-technology medicinal products, particularly those derived from biotechnology has shown that it is necessary to create a centralised authorisation procedure that is compulsory for high-technology medicinal products, particularly those resulting from biotechnical processes, in order to maintain the high level of scientific evaluation of these medicinal products in the European Union and thus to preserve the confidence of patients and the medical professions in the evaluation. This is particularly important in the context of the emergence of new therapies, such as gene therapy and associated cell therapies, and xenogenic somatic therapy. This approach should be maintained, particularly with a view to ensuring the effective operation of the internal market in the pharmaceutical sector.

(8) With a view to harmonising the internal market for new medicinal products, this procedure should also be made compulsory for orphan medicinal products and any medicinal product for human use containing an entirely new active substance, i.e. one that has not yet been authorised in the Community, 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 this Regulation, the procedure should also become compulsory for medicinal products for human use containing a new active substance, and for which the therapeutic indication is for the treatment of auto-immune diseases and other immune dysfunctions and viral diseases. It should be possible to review the provisions in point 3 of the Annex via a simplified decision-making procedure not earlier than four years after the entry into force of this Regulation.

(9) As regards medicinal products for human use, optional access to the centralised procedure should also be provided for in cases where use of a single procedure produces added value for the patient. This procedure should remain optional for medicinal products which, although not belonging to the abovementioned categories, are nevertheless therapeutically innovative. It is also appropriate to allow access to this procedure for medicinal products which, although not innovative, may be of benefit to society or to patients if they are authorised from the outset at Community level, such as certain medicinal products which can be supplied without a medical prescription. This option may be extended to generic medicinal products authorised by the Community, provided that this in no way undermines either the harmonisation achieved when the reference medicinal product was evaluated or the results of that evaluation.

(10) In the field of veterinary medicinal products, administrative measures should be laid down in order to take account of the specific features of this field, particularly those due to the regional distribution of certain diseases. It should be possible to use the centralised procedure for the authorisation of veterinary medicinal products used within the framework of Community provisions regarding prophylactic measures for epizootic diseases. Optional access to the centralised procedure should be maintained for veterinary medicinal products containing a new active substance.

(11) For medicinal products for human use, the period for protection of data relating to pre-clinical tests and clinical trials should be the same as that provided for in Directive 2001/83/EC. For medicinal products for veterinary use, the period for protection of data relating to pre-clinical tests and clinical trials as well as safety and residue tests should be the same as that provided for in Directive 2001/82/EC.

(12) In order to reduce the cost for small and medium-sized enterprises of marketing medicinal products authorised via the centralised procedure, provisions should be adopted to allow for a reduction of fees, deferring the

payment of fees, taking over responsibility for translations and offering administrative assistance in respect of these enterprises.

(13) In the interest of public health, authorisation decisions under the centralised procedure should be taken on the basis of the objective scientific criteria of quality, safety and efficacy of the medicinal product concerned, to the exclusion of economic and other considerations. However, Member States should be able exceptionally to prohibit the use in their territory of medicinal products for human use which infringe objectively defined concepts of public policy and public morality. Moreover, a veterinary medicinal product is not to be authorised by the Community if its use would contravene the rules laid down within the framework of the Common Agricultural Policy or if presented for a use prohibited under other Community provisions, inter alia Directive 96/22/EC.

(14) Provision should be made for the quality, safety and efficacy criteria in Directives 2001/83/EC and 2001/82/EC to apply to medicinal products authorised by the Community and it should be possible to assess the risk-benefit balance of all medicinal products when they are placed on the market, at the time of the renewal of the authorisation and at any other time the competent authority deems appropriate.

(15) The Community is required, pursuant to Article 178 of the Treaty, to take account of the development policy aspects of any measure and to promote the creation of conditions fit for human beings worldwide. Pharmaceutical law should continue to ensure that only efficacious, safe and top-quality medicinal products are exported, and the Commission should consider creating further incentives to carry out research into medicinal products against widespread tropical diseases.

(16) There is also a need to provide for the ethical requirements of Directive 2001/20/EC of 4 April 2001 of the European Parliament and of the Council 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 use to apply to medicinal products authorised by the Community. In particular, with respect to clinical trials conducted outside the Community on medicinal products destined to be authorised within the Community, at the time of the evaluation of the application for authorisation, it should be verified that these trials were conducted in accordance with the principles of good clinical practice and the ethical requirements equivalent to the provisions of the said Directive.

(17) The Community should have the means to carry out a scientific assessment of the medicinal products presented in accordance with the decentralised Community authorisation procedures. Moreover, with a view to ensuring the effective harmonisation of administrative decisions taken by Member States with regard to medicinal products presented in accordance with decentralised authorisation procedures, it is necessary to endow the Community with the means to resolve disagreements between Member States concerning the quality, safety and efficacy of medicinal products.

(18) The structure and operation of the various bodies making up the Agency should be designed in such a way as to take into account the need constantly to renew scientific expertise, the need for cooperation between Community and national bodies, the need for adequate involvement of civil society, and the future enlargement of the European Union. The various bodies of the Agency should establish and develop appropriate contacts with the parties concerned, in particular representatives of patients and health-care professionals.

(19) The chief task of the Agency should be to provide Community institutions and Member States with the best possible scientific opinions so as to enable them to exercise the powers regarding the authorisation and supervision of medicinal products conferred on them by Community legislation in the field of medicinal products. Only after a single scientific evaluation procedure addressing the quality, safety and efficacy of high-technology medicinal products has been conducted by the Agency, applying the highest possible standards, should marketing authorisation be granted by the Community, and this should be done by means of a rapid procedure ensuring close cooperation between the Commission and Member States.

(20) In order to ensure close cooperation between the Agency and scientists operating in Member States, the composition of the Management Board should be such as to guarantee that the competent authorities of the Member States are closely involved in the overall management of the Community system for authorising medicinal products.

(21) The Agency's budget should be composed of fees paid by the private sector and contributions paid out of the Community budget to implement Community policies.

(22) Paragraph 25 of the Interinstitutional Agreement of 6 May 1999 between the European Parliament, the Council and the Commission on budgetary discipline and improvement of budgetary procedure provides for the Financial Perspective to be adjusted in order to cover the new needs resulting from enlargement.

(23) Exclusive responsibility for preparing the Agency's opinions on all questions concerning medicinal products for human use should be vested in a Committee for Medicinal Products for Human Use. As far as veterinary medicinal products are concerned, such responsibility should be vested in a Committee for Medicinal Products for Veterinary Use. As regards orphan medicinal products, the task should fall to the Committee on Orphan Medicinal Products set up under Regulation (EC) No 141/2000 of the European Parliament and of the Council of 16 December 1999 on orphan medicinal products. Lastly, as regards herbal medicinal products, this responsibility should be vested in the Committee on Herbal Medicinal Products set up under Directive 2001/83/EC.

(24) The creation of the Agency will make it possible to reinforce the scientific role and independence of the committees, particularly through the setting-up of a permanent technical and administrative secretariat.

(25) The field of activity of the Scientific Committees should be enlarged and their operating methods and composition modernised. Scientific advice for future applicants seeking marketing authorisation should be provided more generally and in greater depth. Similarly, structures allowing the development of advice for companies, in particular small and medium-sized enterprises, should be put in place. The committees should be able to delegate some of their evaluation duties to standing working parties open to experts from the scientific world appointed for this purpose, whilst retaining total responsibility for the scientific opinions issued. The re-examination procedures should be amended to provide a better guarantee for applicants' rights.

(26) The number of members of the Scientific Committees participating in the centralised procedure should be established with a view to ensuring that the committees remain of an efficient size after the enlargement of the European Union.

(27) It is also necessary to reinforce the role of the Scientific Committees in such a way as to enable the Agency to participate actively in international scientific dialogue and to develop certain activities that will be necessary, in particular regarding international scientific harmonisation and technical cooperation with the World Health Organisation.

(28) Furthermore, in order to create greater legal certainty it is necessary to define the responsibilities regarding the transparency rules for the Agency's work, to set certain conditions for the marketing of medicinal products authorised by the Community, to confer on the Agency powers to monitor the distribution of medicinal products authorised by the Community and to specify the sanctions and the procedures for implementing them in the event of failure to observe the provisions of this Regulation and the conditions contained in the authorisations granted under the procedures it establishes.

(29) It is also necessary to take measures for the supervision of medicinal products authorised by the Community, and in particular for the intensive supervision of undesirable effects of these medicinal products within the framework of Community pharmacovigilance activities, so as to ensure the rapid withdrawal from the market of any medicinal product presenting a negative risk-benefit balance under normal conditions of use.

(30) In order to enhance the efficiency of market surveillance, the Agency should be responsible for coordinating Member States' pharmacovigilance activities. A number of provisions need to be introduced to put in place stringent and efficient pharmacovigilance procedures, to allow the competent authority to take provisional emergency measures, including the introduction of amendments to the marketing authorisation and, finally, to permit a reassessment to be made at any time of the risk-benefit balance of a medicinal product.

(31) It is also appropriate to entrust the Commission, in close cooperation with the Agency and after consultations with the Member States, with the task of coordinating the execution of the various supervisory responsibilities vested in the Member States, and in particular with the tasks of providing information on medicinal products and of checking the observance of good manufacturing, laboratory and clinical practices.

(32) It is necessary to provide for the coordinated implementation of Community procedures for the authorisation of medicinal products, and of the national procedures of Member States which have already been harmonised to a considerable degree by Directives 2001/83/EC and 2001/82/EC. It is appropriate that the operation of the procedures laid down by this Regulation be re-examined by the Commission every ten years on the basis of experience gained.

(33) In order to meet, in particular, the legitimate expectations of patients and to take account of the increasingly rapid progress of science and therapies, accelerated assessment procedures should be set up, reserved for medicinal products of major therapeutic interest, and procedures for obtaining temporary authorisations subject to certain annually reviewable conditions. In the field of medicinal products for human use, a common approach should also be followed, whenever possible, regarding the criteria and conditions for the compassionate use of new medicinal products under Member States' legislation.

(34) Member States have developed an evaluation of the comparative efficacy of medicinal products aimed at positioning a new medicinal product with respect to those that already exist in the same therapeutic class. Similarly, the Council, in its Conclusions on medicinal products and public health, adopted on 29 June 2000, emphasised the importance of identifying medicinal products that presented an added therapeutic value. However this evaluation should not be conducted in the context of the marketing authorisation, for which it is agreed that the fundamental criteria should be retained. It is useful in this respect to allow for the possibility of gathering information on the methods used by the Member States to determine the therapeutic benefit obtained by each new medicinal product.

(35) In line with the current provisions of Directives 2001/83/EC and 2001/82/EC, the term of validity of a Community marketing authorisation should be limited initially to a period of five years, upon the expiry of

which it should be renewed. 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 Community during that period, should be considered invalid, in order, in particular, to avoid the administrative burden of maintaining such authorisations. However, this rule should be subject to exemptions when these are justified on public health grounds.

(36) Environmental risks may arise from medicinal products containing or consisting of genetically modified organisms. It is thus necessary to subject such products to an environmental risk-assessment procedure similar to the procedure under Directive 2001/18/EC of the European Parliament and of the Council of 12 March 2001 on the deliberate release into the environment of genetically modified organisms, to be conducted in parallel with the evaluation, under a single Community procedure, of the quality, safety and efficacy of the product concerned.

(37) The measures necessary for the implementation of this Regulation 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 Commission.

(38) The provisions of Regulation (EC) No 1647/2003 amending Regulation (EC) No 2309/93 as regards the budgetary and financial rules applicable to the Agency and access to the Agency's documents should be fully incorporated into this Regulation,

HAVE ADOPTED THIS REGULATION:

TITLE I - DEFINITIONS AND SCOPE

Article 1

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

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

Article 2

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

The holder of a marketing authorisation for medicinal products covered by this Regulation must be established in the Community. The holder shall be responsible for the placing on the market of those medicinal products, whether he does it himself or via one or more persons designated to that effect.

Article 3

1. No medicinal product appearing in the Annex may be placed on the market within the Community unless a marketing authorisation has been granted by the Community in accordance with the provisions of this Regulation.

2. Any medicinal product not appearing in the Annex may be granted a marketing authorisation by the Community in accordance with the provisions of this Regulation, if:
   (a) the medicinal product contains a new active substance which, on the date of entry into force of this Regulation, was not authorised in the Community; or
   (b) the applicant shows that the medicinal product constitutes a significant therapeutic, scientific or technical innovation or that the granting of authorisation in accordance with this Regulation is in the interests of patients or animal health at Community level.

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

3. A generic medicinal product of a reference medicinal product authorised by the Community may be authorised by the competent authorities of the Member States in accordance with Directive 2001/83/EC and Directive 2001/82/EC under the following conditions:
   (a) the application for authorisation is submitted in accordance with Article 10 of Directive 2001/83/EC or Article 13 of Directive 2001/82/EC;
   (b) the summary of the product characteristics is in all relevant respects consistent with that of the medicinal product authorised by the Community except for those parts of the summary of product characteristics referring to indications or dosage forms which were still covered by patent law at the time when the generic medicine was marketed; and
   (c) the generic medicinal product is authorised under the same name in all the Member States where the application has been made. For the purposes of this provision, all the linguistic versions of the INN (international non-proprietary name) shall be considered to be the same name.

4. After the competent committee of the Agency has been consulted, the Commission may adapt the Annex to technical and scientific progress and may adopt any necessary amendments without extending the scope of the centralised procedure.

   Those measures, designed to amend non-essential elements of this Regulation, shall be adopted in accordance with the regulatory procedure with scrutiny referred to in Article 87(2a).

Article 4

1. Applications for the marketing authorisations referred to in Article 3 shall be submitted to the Agency.
2. The Community shall grant and supervise marketing authorisations for medicinal products for human use in accordance with Title II.
3. The Community shall grant and supervise marketing authorisations for veterinary medicinal products in accordance with Title III.

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

Chapter 1 - Submission and examination of applications — Authorisations

Article 5

1. A Committee for Medicinal Products for Human Use is hereby established. The Committee shall be part of the Agency.
2. Without prejudice to Article 56 or to other tasks which Community law may confer on it, the Committee for Medicinal Products for Human Use shall be responsible for drawing up the opinion of the Agency on any matter concerning the admissibility of the files submitted in accordance with the centralised procedure, the granting, variation, suspension or revocation of an authorisation to place a medicinal product for human use on the market in accordance with the provisions of this Title, and pharmacovigilance. ☢1 For the fulfillment of its pharmacovigilance tasks, including the approval of risk management systems and monitoring their effectiveness provided for under this Regulation, the Committee for Medicinal Products for Human Use shall rely on the scientific assessment and recommendations of the Pharmacovigilance Risk Assessment Committee referred to in Article 56(1)(aa).
3. At the request of the Executive Director of the Agency or the Commission representative, the Committee for Medicinal Products for Human Use shall also draw up an opinion on any scientific matter concerning the evaluation of medicinal products for human use. The Committee shall take due account of any requests by Member States for an opinion. The Committee shall also formulate an opinion whenever there is disagreement in the evaluation of medicinal products through the mutual recognition procedure. The opinion of the Committee shall be made publicly accessible.

Article 6

1. Each application for the authorisation of a medicinal product for human use shall specifically and completely include the particulars and documents as referred to in Articles 8(3), 10, 10a, 10b or 11 of, and Annex I to, Directive 2001/83/EC. The documents must include a statement to the effect that clinical trials carried out outside the European Union meet the ethical requirements of Directive 2001/20/EC. These particulars and documents shall take account of the unique, Community nature of the authorisation requested and, otherwise than in exceptional cases relating to the application of the law on trade marks, shall include the use of a single name for the medicinal product.

   The application shall be accompanied by the fee payable to the Agency for the examination of the application.
2. In the case of a medicinal product for human use containing or consisting of genetically modified organisms within the meaning of Article 2 of Directive 2001/18/EC, the application shall be accompanied by:

(a) a copy of the competent authorities' written consent to the deliberate release into the environment of the genetically modified organisms for research and development purposes where provided for in Part B of Directive 2001/18/EC or in Part B of Council Directive 90/220/EEC of 23 April 1990 on the deliberate release into the environment of genetically modified organisms;
(b) the complete technical dossier supplying the information required by Annexes III and IV to Directive 2001/18/EC;
(c) the environmental risk assessment in accordance with the principles set out in Annex II to Directive 2001/18/EC; and
(d) the results of any investigations performed for the purposes of research or development.

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

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

   The duration of the analysis of the scientific data in the file concerning the application for marketing authorisation must be at least 80 days, except in cases where the rapporteur and co-rapporteur declare that they have completed their assessment before that time.

   On the basis of a duly reasoned request, the said Committee may call for the duration of the analysis of the scientific data in the file concerning the application for marketing authorisation to be extended.

   In the case of a medicinal product for human use containing or consisting of genetically modified organisms, the opinion of the said Committee shall respect the environmental safety requirements laid down by Directive 2001/18/EC. During the process of evaluating applications for marketing authorisations for medicinal products for human use containing or consisting of genetically modified organisms, the rapporteur shall carry out necessary consultations of bodies that the Community or Member States have set up in accordance with Directive 2001/18/EC.
4. The Commission shall, in consultation with the Agency, Member States and interested parties, draw up a detailed guide regarding the form in which applications for authorisation are to be presented.

Article 7

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

(a) shall verify that the particulars and documents submitted in accordance with Article 6 comply with the requirements of Directive 2001/83/EC, and shall examine whether the conditions specified in this Regulation for granting a marketing authorisation are satisfied;
(b) may request that an Official Medicines Control Laboratory or a laboratory that a Member State has designated for that purpose test the medicinal product for human use, its starting materials and, if need be, its intermediate products or other constituent materials in order to ensure that the control methods employed by the manufacturer and described in the application documents are satisfactory;
(c) may request that the applicant supplement the particulars accompanying the application within a specific time period. Where the said Committee avails itself of this option, the time-limit laid down in Article 6(3), first subparagraph, shall be suspended until such time as the supplementary information

requested has been provided. Likewise, this time-limit shall be suspended for the time allowed for the applicant to prepare oral or written explanations.

Article 8

1. Upon receipt of a written request from the Committee for Medicinal Products for Human Use, a Member State shall forward the information showing that the manufacturer of a medicinal product or the importer from a third country is able to manufacture the medicinal product concerned and/or carry out the necessary control tests in accordance with the particulars and documents supplied pursuant to Article 6.
2. Where it considers it necessary in order to complete its examination of an application, the said Committee may require the applicant to undergo a specific inspection of the manufacturing site of the medicinal product concerned. Such inspections may be made unannounced.

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

Article 9

1. The Agency shall forthwith inform the applicant if` the opinion of the Committee for Medicinal Products for Human Use is that:
   (a) the application does not satisfy the criteria for authorisation set out in this Regulation;
   (b) the summary of the product characteristics proposed by the applicant needs to be amended;
   (c) the labelling or package leaflet of the product is not in compliance with Title V of Directive 2001/83/EC;
   (d) the authorisation needs to be granted subject to the conditions provided for in Article 14(7) and (8).
2. Within 15 days after receipt of the opinion referred to in paragraph 1, the applicant may give written notice to the Agency that he wishes to request a re-examination of the opinion. In that case, the applicant 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 said Committee shall re-examine its opinion in accordance with the conditions laid down in the fourth subparagraph of Article 62(1). The reasons for the conclusion reached shall be annexed to the final opinion.
3. Within 15 days after its adoption, the Agency shall send the final opinion of the said Committee to the Commission, to the Member States and to the applicant, together with a report describing the assessment of the medicinal product by the Committee and stating the reasons for its conclusions.
4. If an opinion is favourable to the granting of the relevant authorisation to place the medicinal product concerned on the market, the following documents shall be annexed to the opinion:
   (a) a draft summary of the product characteristics, as referred to in Article 11 of Directive 2001/83/EC;

   1235/2010 Art. 1.2(a)

   (a)(a) a recommendation on the frequency of submission of periodic safety update reports;

(b) details of any conditions or restrictions which should be imposed on the supply or use of the medicinal product concerned, including the conditions under which the medicinal product may be made available to patients, in accordance with the criteria laid down in Title VI of Directive 2001/83/EC;

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

(c)(a) details of any recommended measures for ensuring the safe use of the medicinal product to be included in the risk management system;

(c)(b)if appropriate, details of any recommended obligation to conduct post-authorisation safety studies or to comply with obligations on the recording or reporting of suspected adverse reactions which are stricter than those referred to in Chapter 3;

(c)(c)if appropriate, details of any recommended obligation to conduct post-authorisation efficacy studies where concerns relating to some aspects of the efficacy of the medicinal product are identified and can be resolved only after the medicinal product has been marketed. Such an obligation to conduct such studies shall be based on the delegated acts adopted pursuant to Article 10b while taking into account the scientific guidance referred to in Article 108a of Directive 2001/83/EC;

(d) the draft text of the labelling and package leaflet proposed by the applicant, presented in accordance with Title V of Directive 2001/83/EC;

(e) the assessment report as regards the results of the pharmaceutical and pre-clinical tests and of the clinical trials, and as regards the risk management system and the pharmacovigilance system for the medicinal product concerned.

Article 10

1. Within 15 days after receipt of the opinion referred to in Article 5(2), the Commission shall prepare a draft of the decision to be taken in respect of the application.

   Where a draft decision envisages the granting of a marketing authorisation, it shall include or make reference to the documents mentioned in points (a) to (d) of Article 9(4).

   Where a draft decision envisages the granting of a marketing authorisation subject to the conditions referred to in points (c), (ca), (cb), or (cc) of Article 9(4), it shall lay down deadlines for the fulfillment of the conditions, where necessary.

   Where the draft decision differs from the opinion of the Agency, the Commission shall attach a detailed explanation of the reasons for the differences.

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

2. The Commission shall take a final decision in accordance with, and within 15 days after the end of, the procedure referred to in Article 87(3).
3. The Standing Committee on Medicinal Products for Human Use referred to in Article 87(1) shall adjust its rules of procedure so as to take account of the tasks incumbent upon it under this Regulation.

   The adjustments shall provide that:

(a) the opinion of the said Standing Committee is to 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 may request in writing that the draft decision referred to in paragraph 1 be discussed by a plenary meeting of the said Standing Committee, stating their reasons in detail.

4. Where, in the opinion of the Commission, a Member State's written observations raise important new questions of a scientific or technical nature which the opinion delivered by the Agency has not addressed, the Chairman shall suspend the procedure and refer the application back to the Agency for further consideration.
5. The Commission shall adopt the provisions necessary for the implementation of paragraph 4 in accordance with the procedure referred to in Article 87(2).
6. The Agency shall disseminate the documents referred to in points (a) to (d) of Article 9(4), together with any deadlines laid down pursuant to the third subparagraph of paragraph 1 of this Article.

Article 10a

1. After the granting of a marketing authorisation, the Agency may impose an obligation on the marketing authorisation holder:

   (a) to conduct a post-authorisation safety study if there are concerns about the risks of an authorised medicinal product. If the same concerns apply to more than one medicinal product, the Agency shall, following consultation with the Pharmacovigilance Risk Assessment Committee, encourage the marketing authorisation holders concerned to conduct a joint post-authorisation safety study;

   (b) to conduct a post-authorisation efficacy study when the understanding of the disease or the clinical methodology indicate that previous efficacy evaluations might have to be revised significantly. The obligation to conduct the post-authorisation efficacy study shall be based on the delegated acts adopted pursuant to Article 10b while taking into account the scientific guidance referred to in Article 108a of Directive 2001/83/EC.

   The imposition of such an obligation shall be duly justified, notified in writing, and shall include the objectives and timeframe for submission and conduct of the study.
2. The Agency shall provide the marketing authorisation holder with an opportunity to present written observations in response to the imposition of the obligation within a time limit which it shall specify, if the marketing authorisation holder so requests within 30 days of receipt of the written notification of the obligation.
3. On the basis of the written observations submitted by the marketing authorisation holder, and of the opinion of the Agency, the Commission shall withdraw or confirm the obligation. Where the Commission confirms the obligation, the marketing authorisation shall be varied to include the obligation as a condition of the marketing authorisation and the risk management system shall be updated accordingly.

Article 10b

1. In order to determine the situations in which post-authorisation efficacy studies may be required under point (cc) of Article 9(4) and point (b) of Article 10a(1) of this Regulation, the Commission may adopt, by means of delegated acts in accordance with Article 87b, and subject to the conditions of Articles 87c and 87d, measures supplementing the provisions in point (cc) of Article 9(4) and point (b) of Article 10a(1).
2. When adopting such delegated acts, the Commission shall act in accordance with the provisions of this Regulation.

Article 11

If an applicant withdraws an application for a marketing authorisation submitted to the Agency before an opinion has been given on the application, the applicant shall communicate its reasons for doing so to the Agency. The Agency shall make this information publicly accessible and shall publish the assessment report, if available, after deletion of all information of a commercially confidential nature.

Article 12

1. The marketing authorisation shall be refused if, after verification of the particulars and documents submitted in accordance with Article 6, it appears that the applicant has not properly or sufficiently demonstrated the quality, safety or efficacy of the medicinal product.
   Authorisation shall likewise be refused if particulars or documents provided by the applicant in accordance with Article 6 are incorrect or if the labelling and package leaflet proposed by the applicant are not in accordance with Title V of Directive 2001/83/EC.
2. The refusal of a Community marketing authorisation shall constitute a prohibition on the placing on the market of the medicinal product concerned throughout the Community.
3. Information about all refusals and the reasons for them shall be made publicly accessible.

Article 13

1. Without prejudice to Article 4(4) and (5) of Directive 2001/83/EC, a marketing authorisation which has been granted in accordance with this Regulation shall be valid throughout the Community. It shall confer the same rights and obligations in each of the Member States as a marketing authorisation granted by that Member State in accordance with Article 6 of Directive 2001/83/EC.
   Authorised medicinal products for human use shall be entered in the Community Register of Medicinal Products and shall be given a number, which shall appear on the packaging.
2. Notification of marketing authorisation shall be published in the Official Journal of the European Union, quoting in particular the date of authorisation and the registration number in the Community Register, any International Non-proprietary Name (INN) of the active substance of the medicinal product, its pharmaceutical form, and any Anatomical Therapeutic Chemical Code (ATC).
3. The Agency shall immediately publish the assessment report on the medicinal product for human use drawn up by the Committee for Medicinal Products for Human Use and the reasons for its opinion in favour of granting authorisation, after deletion of any information of a commercially confidential nature.
   The European Public Assessment Report (EPAR) shall include a summary written in a manner that is

understandable to the public. The summary shall contain in particular a section relating to the conditions of use of the medicinal product.

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

   The marketing authorisation holder shall notify the Agency if the product ceases to be placed on the market of a Member State, either temporarily or permanently. Such notification shall, other than in exceptional circumstances, be made no less than two months before the interruption in the placing on the market of the product. The marketing authorisation holder shall inform the Agency of the reasons for such action in accordance with Article 14b.

   Upon request by the Agency, particularly in the context of pharmacovigilance, the marketing authorisation holder shall provide the Agency with all data relating to the volume of sales of the medicinal product at Community level, broken down by Member State, and any data in the holder's possession relating to the volume of prescriptions.

Article 14

1. Without prejudice to paragraphs 4, 5 and 7 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 by the Agency of the risk-benefit balance.

   To this end, the marketing authorisation holder shall provide the Agency with a consolidated version of the file in respect of quality, safety and efficacy, including the evaluation of data contained in suspected adverse reactions reports and periodic safety update reports submitted in accordance with Chapter 3, and information on all variations introduced since the marketing authorisation was granted, at least 9 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 Commission decides, on justified grounds relating to pharmacovigilance, including exposure of an insufficient number of patients to the medicinal product concerned, to proceed with one additional five-year renewal in accordance with paragraph 2.
4. Any authorisation which is not followed by the actual placing of the medicinal product for human use on the Community market within three years after authorisation shall cease to be valid.
5. When an authorised medicinal product previously placed on the market is no longer actually present on the market for three consecutive years, the authorisation shall cease to be valid.
6. In exceptional circumstances and on public health grounds the Commission may grant exemptions from paragraphs 4 and 5. Such exemptions must be duly justified.
7. Following consultation with the applicant, an authorisation may be granted subject to certain specific obligations, to be reviewed annually by the Agency. The list of these obligations shall be made publicly accessible.

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

The Commission shall adopt a Regulation laying down provisions for granting such authorisation. That measure, designed to amend non-essential elements of this Regulation by supplementing it, shall be adopted in accordance with the regulatory procedure with scrutiny referred to in Article 87(2a).

8. In exceptional circumstances and following consultation with the applicant, the marketing authorisation may be granted subject to certain conditions, in particular relating to the safety of the medicinal product, notification to the competent authorities of any incident relating to its use, and action to be taken. The marketing authorisation may be granted only when the applicant can show that he is unable to provide comprehensive data on the efficacy and safety of the medicinal product under normal conditions of use, for objective, verifiable reasons and must be based on one of the grounds set out in Annex I to Directive 2001/83/EC. Continuation of the marketing authorisation shall be linked to the annual reassessment of these conditions.
9. When an application is submitted for a marketing authorisation in respect of medicinal products for human use which are of major interest from the point of view of public health and in particular from the viewpoint of therapeutic innovation, the applicant may request an accelerated assessment procedure. The request shall be duly substantiated.

   If the Committee for Medicinal Products for Human Use accepts the request, the time-limit laid down in Article 6(3), first subparagraph, shall be reduced to 150 days.
10. When adopting its opinion, the Committee for Medicinal Products for Human Use shall include a proposal concerning the criteria for the prescription or use of the medicinal products in accordance with Article 70(1) of Directive 2001/83/EC.
11. Without prejudice to the law on the protection of industrial and commercial property, medicinal products for human use which have been authorised in accordance with the provisions of this Regulation shall benefit from an eight-year period of data protection and a ten-year period of marketing protection, in which connection the latter period shall be extended to a maximum of 11 years if, during the first eight years of those ten years, the marketing authorisation holder obtains an authorisation for one or more new therapeutic indications which, during the scientific evaluation prior to their authorisation, are held to bring a significant clinical benefit in comparison with existing therapies.

Article 14a

The marketing authorisation holder shall incorporate any conditions referred to in points (c), (ca), (cb) and (cc) of Article 9(4) or in Article 10a, or in Article 14(7) and (8) in his risk management system.

Article 14b

1. The marketing authorisation holder shall notify the Agency forthwith of any action the holder takes to suspend the marketing of a medicinal product, to withdraw a medicinal product from the market, to request the withdrawal of a marketing authorisation or not to apply for the renewal of a marketing authorisation, together with the reasons for such action. The marketing authorisation holder shall in particular declare if such action is based on any of the grounds set out in Article 116 or Article 117(1) of Directive 2001/83/EC.

2. The marketing authorisation holder shall also make the notification pursuant to paragraph 1 of this Article if the action is taken in a third country and such action is based on any of the grounds set out in Article 116 or Article 117(1) of Directive 2001/83/EC.
3. In the cases referred to in paragraphs 1 and 2, the Agency shall forward the information to the competent authorities of the Member States without undue delay.

Article 15

The granting of authorisation shall not affect the civil or criminal liability of the manufacturer or of the holder of the marketing authorisation pursuant to the applicable national law in Member States.

Chapter 2 - Supervision and penalties

Article 16

1. After a marketing authorisation has been granted in accordance with this Regulation, the marketing authorisation holder shall, in respect of the methods of manufacture and control provided for in points (d) and (h) of Article 8(3) of Directive 2001/83/EC, take account of 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. He shall apply for approval of corresponding variations in accordance with this Regulation.
2. The marketing authorisation holder shall forthwith provide the Agency, the Commission and the Member States with any new information which might entail the amendment of the particulars or documents referred to in Article 8(3), Article 10, 10a, 10b and 11, or Article 32(5) of Directive 2001/83/EC, in Annex I thereto, or in Article 9(4) of this Regulation.

   In particular, the marketing authorisation holder shall forthwith inform the Agency and the Commission of any prohibition or restriction imposed by the competent authorities of any country in which the medicinal product is marketed and of any other new information which might influence the evaluation of the benefits and risks of the medicinal product concerned. The information shall include both positive and negative results of clinical trials or other studies in all indications and populations, whether or not included in the marketing authorisation, as well as data on the use of the medicinal product where such use is outside the terms of the marketing authorisation.
3. The marketing authorisation holder shall ensure that the product information is kept up to date with the current scientific knowledge including the conclusions of the assessment and recommendations made public by means of the European medicines web-portal established in accordance with Article 26.

   3a. In order to be able to continuously assess the risk-benefit balance, the Agency may at any time ask the marketing authorisation holder to forward data demonstrating that the risk-benefit balance remains favourable. The marketing authorisation holder shall answer fully and promptly any such request.

   The Agency may at any time ask the marketing authorisation holder to submit a copy of the pharmacovigilance system master file. The marketing authorisation holder shall submit the copy at the latest seven days after receipt of the request.

4. The Commission shall, after consulting the Agency, adopt appropriate provisions for the examination of variations to marketing authorisations in the form of a regulation. Those measures, designed to amend non-essential elements of this Regulation by supplementing it, shall be adopted in accordance with the regulatory procedure with scrutiny referred to in Article 87(2a).

Article 17

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

Article 18

1. In the case of medicinal products manufactured within the Union, the supervisory authorities for manufacturing shall be the competent authorities of the Member State or Member States which granted the manufacturing authorisation provided for in Article 40(1) of Directive 2001/83/EC in respect of the medicinal product concerned.
2. In the case of medicinal products imported from third countries, the supervisory authorities for imports shall be the competent authorities of the Member State or Member States that granted the authorisation provided for in Article 40(3) of Directive 2001/83/EC to the importer, unless appropriate agreements have been made between the Union and the exporting country to ensure that those controls are carried out in the exporting country and that the manufacturer applies standards of good manufacturing practice at least equivalent to those laid down by the Union.
   Member State may request assistance from another Member State or from the Agency.
3. The supervisory authority for pharmacovigilance shall be the competent authority of the Member State in which the pharmacovigilance system master file is located.

Article 19

1. The supervisory authorities for manufacturing and imports shall be responsible for verifying on behalf of the Union that the marketing authorisation holder for the medicinal product or the manufacturer or importer established within the Union satisfies the requirements concerning manufacturing and imports laid down in Titles IV and XI of Directive 2001/83/EC.
   The supervisory authorities for pharmacovigilance shall be responsible for verifying on behalf of the Union that the marketing authorisation holder for the medicinal product satisfies the pharmacovigilance requirements laid down in Titles IX and XI of Directive 2001/83/EC. They may, if this is considered necessary, conduct pre-authorisation inspections to verify the accuracy and successful implementation of the pharmacovigilance system as it has been described by the applicant in support of his application.
2. Where, in accordance with Article 122 of Directive 2001/83/EC, the Commission is informed of serious differences of opinion between Member States as to whether the holder of the marketing authorisation for the medicinal product for human use or a manufacturer or importer established within the Community satisfies the requirements referred to in paragraph 1, the Commission may, after consultation with the Member States concerned, request an inspector from the supervisory authority to undertake a new

inspection of the marketing authorisation holder, the manufacturer or the importer; the inspector in question shall be accompanied by two inspectors from Member States which are not party to the dispute or by two experts nominated by the Committee for Medicinal Products for Human Use.

3. Subject to any agreements which may have been concluded between the Community and third countries in accordance with Article 18(2), the Commission may, following a reasoned request from a Member State or from the said Committee, or on its own initiative, require a manufacturer established in a third country to submit to an inspection.

   The inspection shall be undertaken by inspectors from the Member States who possess the appropriate qualifications. They may be accompanied by a rapporteur or expert appointed by the Committee referred to in paragraph 2. The report of the inspectors shall be made available electronically to the Commission, the Member States and the Agency.

Article 20

1. Where the supervisory authorities or the competent authorities of any other Member State are of the opinion that the manufacturer or importer established within the Community territory is no longer fulfilling the obligations laid down in Title IV of Directive 2001/83/EC, they shall forthwith inform the Committee for Medicinal Products for Human Use and the Commission, stating their reasons in detail and indicating the course of action proposed.

   The same shall apply where a Member State or the Commission considers that one of the measures envisaged in Titles IX and XI of Directive 2001/83/EC should be applied in respect of the medicinal product concerned or where the said Committee has delivered an opinion to that effect in accordance with Article 5 of this Regulation.

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

3. Following an opinion by the Agency, the Commission shall adopt the necessary provisional measures, which shall be applied immediately.

   A final decision in respect of the medicinal product concerned shall be adopted within 6 months, in accordance with the regulatory procedure referred to in Article 87(2).

   The Commission may also adopt a decision addressed to the Member States pursuant to Article 127a of Directive 2001/83/EC.

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

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

5. In this case, the Member State shall ensure that health-care professionals are rapidly informed of its action and the reasons for the action. Networks set up by professional associations may be used to this effect. The Member States shall inform the Commission and the Agency of actions taken for this purpose.
6. The suspensive measures referred to in paragraph 4 may be maintained in force until such time as a definitive decision has been reached in accordance with the procedure referred to in Article 87(3).
7. The Agency shall, upon request, inform any person concerned of the final decision and make the decision publicly accessible immediately after it has been taken.
8. Where the procedure is initiated as a result of the evaluation of data relating to pharmacovigilance, the opinion of the Agency, in accordance with paragraph 2 of this Article, shall be adopted by the Committee for Medicinal Products for Human Use on the basis of a recommendation from the Pharmacovigilance Risk Assessment Committee and Article 107j(2) of Directive 2001/83/EC shall apply.
9. By way of derogation from paragraphs 1 to 7 of this Article, where a procedure under Article 31 or Articles 107i to 107k of Directive 2001/83/EC concerns a range of medicinal products or a therapeutic class, medicinal products that are authorised in accordance with this Regulation and that belong to that range or class shall only be included in the procedure under Article 31, or Articles 107i to 107k of that Directive.

Chapter 3 - Pharmacovigilance

Article 21

1. The obligations of marketing authorisation holders laid down in Article 104 of Directive 2001/83/EC shall apply to marketing authorisation holders for medicinal products for human use authorised in accordance with this Regulation.

   Without prejudice to paragraphs 2, 3 and 4 of this Article, holders of marketing authorisations granted before 2 July 2012 shall, by way of derogation from Article 104(3)(c) of Directive 2001/83/EC not be required to operate a risk management system for each medicinal product.
2. The Agency may impose an obligation on a marketing authorisation holder to operate a risk management system, as referred to in point (c) of Article 104(3) of Directive 2001/83/EC, if there are concerns about the risks affecting the risk-benefit balance of an authorised medicinal product. In that context, the Agency shall also oblige the marketing authorisation holder to submit a detailed description of the risk-management system which he intends to introduce for the medicinal product concerned.

   The imposition of such obligations shall be duly justified, notified in writing, and shall include the timeframe for submission of the detailed description of the risk-management system.
3. The Agency shall provide the marketing authorisation holder with an opportunity to present written observations in response to the imposition of the obligation within a time limit which it shall specify, if the marketing authorisation holder so requests within 30 days of receipt of the written notification of the obligation.
4. On the basis of the written observations submitted by the marketing authorisation holder, and of the opinion of the Agency, the Commission shall withdraw or confirm the obligation. Where the Commission confirms the obligation, the marketing authorisation shall be varied accordingly, to include the measures to

be taken as part of the risk management system as conditions of the marketing authorisation referred to in point (ca) of Article 9(4).

Article 22

The obligations of marketing authorisation holders laid down in Article 106a(1) of Directive 2001/83/EC, and the obligations of the Member States, the Agency and the Commission laid down in paragraphs 2, 3 and 4 of that Article shall apply to the safety announcements referred to in point (e) of Article 57(1) of this Regulation concerning medicinal products for human use authorised in accordance with this Regulation.

Article 23

1. The Agency shall, in collaboration with the Member States, set up, maintain and make public a list of medicinal products that are subject to additional monitoring.

   That list shall include the names and active substances of:

   (a) medicinal products authorised in the Union that contain a new active substance which, on 1 January 2011, was not contained in any medicinal product authorised in the Union;

   (b) any biological medicinal product not covered by point (a) that was authorised after 1 January 2011;

   (c) medicinal products that are authorised pursuant to this Regulation, subject to the conditions referred to in point (cb) of Article 9(4), point (a) of the first subparagraph of Article 10a(1) or Article 14(7) or (8);

   (d) medicinal products that are authorised pursuant to Directive 2001/83/EC, subject to the conditions referred to in points (b) and (c) of the first paragraph of Article 21a, Article 22, or point (a) of the first subparagraph of Article 22a(1) thereof.

   (1) (a) At the request of the Commission, following consultation with the Pharmacovigilance Risk Assessment Committee, medicinal products that are authorised pursuant to this Regulation, subject to the conditions referred to in points (c), (ca) or (cc) of Article 9(4), point (b) of the first subparagraph of Article 10a(1) or Article 21(2), may also be included in the list referred to in paragraph 1 of this Article.

   At the request of a national competent authority, following consultation with the Pharmacovigilance Risk Assessment Committee, medicinal products that are authorised pursuant to Directive 2001/83/EC, subject to the conditions referred to in points (a), (d), (e) or (f) of the first paragraph of Article 21a, point (b) of the first subparagraph of Article 22a(1) or Article 104a(2) thereof, may also be included in the list referred to in paragraph 1 of this Article.

2. The list referred to in paragraph 1 shall include an electronic link to the product information and to the summary of the risk management plan.

3. In the cases referred to in points (a) and (b) of paragraph 1 of this Article, the Agency shall remove a medicinal product from the list five years after the Union reference date referred to in Article 107c(5) of Directive 2001/83/EC.

   In the cases referred to in points (c) and (d) of paragraph 1 and in paragraph 1a of this Article, the Agency shall remove a medicinal product from the list once the conditions have been fulfilled.

4. For medicinal products included in the list referred to in paragraph 1, the summary of product characteristics and the package leaflet shall include the statement 'This medicinal product is subject to additional monitoring'. That statement shall be preceded by a black symbol which shall be selected by the Commission by 2 July 2013, following a recommendation of the Pharmacovigilance Risk Assessment Committee, and shall be followed by an appropriate standardised explanatory sentence.

4.(a) By 5 June 2018, the Commission shall present to the European Parliament and the Council a report on the use of the list referred to in paragraph 1 based on the experience and data provided by the Member States and the Agency.

The Commission shall, if appropriate, on the basis of that report, and after consultation with the Member States and other appropriate stakeholders, present a proposal in order to adjust the provisions relating to the list referred to in paragraph 1.

Article 24

1. The Agency shall, in collaboration with the Member States and the Commission, set up and maintain a database and data processing network (hereinafter the 'Eudravigilance database') to collate pharmacovigilance information regarding medicinal products authorised in the Union and to allow competent authorities to access that information simultaneously and to share it.

   The Eudravigilance database shall contain information on suspected adverse reactions in human beings arising from use of the medicinal product within the terms of the marketing authorisation as well as from uses outside the terms of the marketing authorisation, and on those occurring in the course of post-authorisation studies with the medicinal product or associated with occupational exposure.

2. The Agency shall, in collaboration with the Member States and the Commission, draw up the functional specifications for the Eudravigilance database, together with a timeframe for their implementation.

   The Agency shall prepare an annual report on the Eudravigilance database and send it to the European Parliament, the Council and the Commission. The first annual report shall be prepared by 2 January 2013.

   The Management Board of the Agency shall on the basis of an independent audit report that takes into account the recommendation of the Pharmacovigilance Risk Assessment Committee confirm and announce when the Eudravigilance database has achieved full functionality and the system meets the functional specifications drawn up pursuant to the first subparagraph.

   Any substantial change to the Eudravigilance database and the functional specifications shall take into account the recommendations of the Pharmacovigilance Risk Assessment Committee.

   The Eudravigilance database shall be fully accessible to the competent authorities of the Member States and to the Agency and the Commission. It shall also be accessible to marketing authorisation holders to the extent necessary for them to comply with their pharmacovigilance obligations.

   The Agency shall ensure that healthcare professionals and the public have appropriate levels of access to the Eudravigilance database, while guaranteeing personal data protection. The Agency shall work together with all stakeholders, including research institutions, healthcare professionals, and patient and consumer organisations, in order to define the 'appropriate level of access' for healthcare professionals and the public to the Eudravigilance database.

The data held on the Eudravigilance database shall be made publicly accessible in an aggregated format together with an explanation of how to interpret the data.

3. The Agency shall, in collaboration either with the marketing authorisation holder or with the Member State that submitted an individual suspected adverse reaction report to the Eudravigilance database, be responsible for operating procedures that ensure the quality and integrity of the information collected in the Eudravigilance database.
4. Individual suspected adverse reaction reports and follow-ups submitted to the Eudravigilance database by marketing authorisation holders shall be transmitted electronically upon receipt to the competent authority of the Member State where the reaction occurred.

Article 25

The Agency shall, in collaboration with the Member States, develop standard web-based structured forms for the reporting of suspected adverse reactions by healthcare professionals and patients in accordance with the provisions referred to in Article 107a of Directive 2001/83/EC.

Article 25a

The Agency shall, in collaboration with the national competent authorities and the Commission, set up and maintain a repository for periodic safety update reports (hereinafter the 'repository') and the corresponding assessment reports so that they are fully and permanently accessible to the Commission, the national competent authorities, the Pharmacovigilance Risk Assessment Committee, the Committee for Medicinal Products for Human Use and the coordination group referred to in Article 27 of Directive 2001/83/EC (hereinafter the 'coordination group').

The Agency shall, in collaboration with the national competent authorities and the Commission, and after consultation with the Pharmacovigilance Risk Assessment Committee, draw up the functional specifications for the repository.

The Management Board of the Agency shall, on the basis of an independent audit report that takes into account the recommendations of the Pharmacovigilance Risk Assessment Committee, confirm and announce when the repository has achieved full functionality and meets the functional specifications drawn up pursuant to the second paragraph.

Any substantial change to the repository and the functional specifications shall always take into account the recommendations of the Pharmacovigilance Risk Assessment Committee.

Article 26

1. The Agency shall, in collaboration with the Member States and the Commission, set up and maintain a European medicines web-portal for the dissemination of information on medicinal products authorised in the Union. By means of that portal, the Agency shall make public at least the following:
    (a) the names of members of the Committees referred to in points (a) and (aa) of Article 56(1) of this Regulation and the members of the coordination group, together with their professional qualifications and with the declarations referred to in Article 63(2) of this Regulation;

(b) agendas and minutes from each meeting of the Committees referred to in points (a) and (aa) of Article 56(1) of this Regulation and of the coordination group as regards pharmacovigilance activities;
(c) a summary of the risk management plans for medicinal products authorised in accordance with this Regulation;
(d) the list of medicinal products referred to in Article 23 of this Regulation;
(e) a list of the locations in the Union where pharmacovigilance system master files are kept and contact information for pharmacovigilance enquiries, for all medicinal products authorised in the Union;
(f) information about how to report to national competent authorities suspected adverse reactions to medicinal products and the standard structured forms referred to in Article 25 for their web-based reporting by patients and healthcare professionals, including links to national websites;
(g) Union reference dates and frequency of submission of periodic safety update reports established in accordance with Article 107c of Directive 2001/83/EC;
(h) protocols and public abstracts of results of the post-authorisation safety studies referred to in Articles 107n and 107p of Directive 2001/83/EC;
(i) the initiation of the procedure provided for in Articles 107i to 107k of Directive 2001/83/EC, the active substances or medicinal products concerned and the issue being addressed, any public hearings pursuant to that procedure and information on how to submit information and to participate in public hearings;
(j) conclusions of assessments, recommendations, opinions, approvals and decisions taken by the Committees referred to in points (a) and (aa) of Article 56(1) of this Regulation and by the coordination group, the national competent authorities and the Commission in the framework of the procedures of Articles 28, 28a and 28b of this Regulation and of sections 2 and 3 of Chapter 3 and Chapter 4 of Title IX of Directive 2001/83/EC.

2. Before the launch of this portal, and during subsequent reviews, the Agency shall consult relevant stakeholders, including patient and consumer groups, healthcare professionals and industry representatives.

Article 27

1. The Agency shall monitor selected medical literature for reports of suspected adverse reactions to medicinal products containing certain active substances. It shall publish the list of active substances being monitored and the medical literature subject to this monitoring.
2. The Agency shall enter into the Eudravigilance database relevant information from the selected medical literature.
3. The Agency shall, in consultation with the Commission, Member States and interested parties, draw up a detailed guide regarding the monitoring of medical literature and the entry of relevant information into the Eudravigilance database.

Article 28

1. The obligations of marketing authorisation holders and of Member States laid down in Articles 107 and 107a of Directive 2001/83/EC shall apply to the recording and reporting of suspected adverse reactions for medicinal products for human use authorised in accordance with this Regulation.
2. The obligations of marketing authorisation holders laid down in Article 107b of Directive 2001/83/EC and the procedures under Article 107b and Article 107c of that Directive shall apply to the submission of periodic safety update reports, the establishment of Union reference dates and changes to the frequency of submission of periodic safety update reports for medicinal products for human use authorised in accordance with this Regulation.

   The provisions applicable to the submission of periodic safety update reports laid down in the second subparagraph of Article 107c(2) of that Directive shall apply to holders of marketing authorisations which were granted before 2 July 2012 and for which the frequency and dates of submission of the periodic safety update reports are not laid down as a condition to the marketing authorisation until such time as another frequency or other dates of submission of the reports are laid down in the marketing authorisation or are determined in accordance with Article 107c of that Directive.
3. The assessment of the periodic safety update reports shall be conducted by a rapporteur appointed by the Pharmacovigilance Risk Assessment Committee. The rapporteur shall closely collaborate with the rapporteur appointed by the Committee for Medicinal Products for Human Use or the Reference Member State for the medicinal products concerned.

   The rapporteur shall prepare an assessment report within 60 days of receipt of the periodic safety update report and send it to the Agency and to the members of the Pharmacovigilance Risk Assessment Committee. The Agency shall send the report to the marketing authorisation holder.

   Within 30 days of receipt of the assessment report, the marketing authorisation holder and the members of the Pharmacovigilance Risk Assessment Committee may submit comments to the Agency and to the rapporteur.

   Following the receipt of the comments referred to in the third subparagraph, the rapporteur shall within 15 days update the assessment report taking into account any comments submitted, and forward it to the Pharmacovigilance Risk Assessment Committee. The Pharmacovigilance Risk Assessment Committee shall adopt the assessment report with or without further changes at its next meeting and issue a recommendation. The recommendation shall mention the divergent positions with the grounds on which they are based. The Agency shall include the adopted assessment report and the recommendation in the repository set up under Article 25a, and forward both to the marketing authorisation holder.
4. In the case of an assessment report that recommends any action concerning the marketing authorisation, the Committee for Medicinal Products for Human Use shall, within 30 days of receipt of the report by the Pharmacovigilance Risk Assessment Committee, consider the report and adopt an opinion on the maintenance, variation, suspension or revocation of the marketing authorisation concerned, including a timetable for the implementation of the opinion. Where this opinion of the Committee for Medicinal Products for Human Use differs from the recommendation of the Pharmacovigilance Risk Assessment Committee, the Committee for Medicinal Products for Human Use shall attach to its opinion a detailed explanation of the scientific grounds for the differences together with the recommendation.

   Where the opinion states that regulatory action concerning the marketing authorisation is necessary, the

Commission shall adopt a decision to vary, suspend or revoke the marketing authorisation. Article 10 of this Regulation shall apply to the adoption of that decision. Where the Commission adopts such a decision, it may also adopt a decision addressed to the Member States pursuant to Article 127a of Directive 2001/83/EC.

5. In the case of a single assessment of periodic safety update reports concerning more than one marketing authorisation in accordance with Article 107e(1) of Directive 2001/83/EC which includes at least one marketing authorisation granted in accordance with this Regulation, the procedure laid down in Articles 107e and 107g of that Directive shall apply.
6. The final recommendations, opinions and decisions referred to in paragraphs 3 to 5 of this Article shall be made public by means of the European medicines web-portal referred to in Article 26.

Article 28a

1. Regarding medicinal products for human use authorised in accordance with this Regulation, the Agency shall, in collaboration with the Member States, take the following measures:
    (a) monitor the outcome of risk minimisation measures contained in risk management plans and of conditions referred to in points (c), (ca), (cb) and (cc) of Article 9(4) or in points (a) and (b) of Article 10a(1), and in Article 14(7) and (8);
    (b) assess updates to the risk management system;
    (c) monitor the data in the Eudravigilance database to determine whether there are new risks or whether risks have changed and whether those risks impact on the risk-benefit balance.
2. The Pharmacovigilance Risk Assessment Committee shall perform the initial analysis and prioritisation of signals of new risks or risks that have changed or changes to the risk-benefit balance. Where it considers that follow-up action may be necessary, the assessment of those signals and agreement on any subsequent action concerning the marketing authorisation shall be conducted in a timescale commensurate with the extent and seriousness of the issue.
3. The Agency and national competent authorities and the marketing authorisation holder shall inform each other in the event of new risks or risks that have changed or changes to the risk-benefit balance being detected.

Article 28b

1. For non-interventional post-authorisation safety studies concerning medicinal products for human use authorised in accordance with this Regulation which fulfill one of the requirements referred to in Articles 10 and 10a of this Regulation, the procedure provided for in paragraphs 3 to 7 of Article 107m, Articles 107n to 107p and Article 107q(1) of Directive 2001/83/EC shall apply.
2. Where, in accordance with the procedure referred to in paragraph 1 of this Article, the Pharmacovigilance Risk Assessment Committee issues recommendations for the variation, suspension or revocation of the marketing authorisation, the Committee on Medicinal Products for Human Use shall adopt an opinion taking into account the recommendation, and the Commission shall adopt a decision in accordance with Article 10.

    Where the opinion of the Committee on Medicinal Products for Human Use differs from the

recommendation of the Pharmacovigilance Risk Assessment Committee, the Committee on Medicinal Products for Human Use shall attach to its opinion a detailed explanation of the scientific grounds for the differences, together with the recommendation.

Article 28c

1. The Agency shall collaborate with the World Health Organisation in matters of pharmacovigilance and shall take the necessary steps to submit to it, promptly, appropriate and adequate information regarding the measures taken in the Union which may have a bearing on public health protection in third countries.
   The Agency shall make available promptly all suspected adverse reaction reports occurring in the Union to the World Health Organisation.
2. The Agency and the European Monitoring Centre for Drugs and Drug Addiction shall exchange information that they receive on the abuse of medicinal products including information related to illicit drugs.

Article 28d

At the request of the Commission, the Agency shall participate in collaboration with the Member States in international harmonisation and standardisation of technical measures in relation to pharmacovigilance.

Article 28e

The Agency and the Member States shall cooperate to continuously develop pharmacovigilance systems capable of achieving high standards of public health protection for all medicinal products, regardless of the routes of marketing authorisation, including the use of collaborative approaches, to maximise use of resources available within the Union.

Article 28f

The Agency shall perform regular independent audits of its pharmacovigilance tasks and report the results to its Management Board on a 2-yearly basis.

Article 29

The Commission shall make public a report on the performance of pharmacovigilance tasks by the Agency on 2 January 2014 at the latest and subsequently every 3 years thereafter.

TITLE III - AUTHORISATION AND SUPERVISION OF VETERINARY MEDICINAL PRODUCTS

Chapter 1 - Submission and examination of applications — Authorisations

Article 30

1. A Committee for Medicinal Products for Veterinary Use is hereby established. The Committee shall be part of the Agency.
2. Without prejudice to Article 56 and other tasks which Community law may confer on it, in particular under Regulation (EEC) No 2377/90, the Committee for Medicinal Products for Veterinary Use shall be responsible for drawing up the opinion of the Agency on any question concerning the admissibility of files submitted in accordance with the centralised procedure, the granting, variation, suspension or revocation of an authorisation to place a veterinary medicinal product on the market arising in accordance with the provisions of this Title, and pharmacovigilance.
3. At the request of the Executive Director of the Agency or the Commission representative, the Committee for Medicinal Products for Veterinary Use shall also draw up opinions on any scientific matters concerning the evaluation of veterinary medicinal products. The Committee shall take due account of any requests from Member States for an opinion. The Committee shall also formulate an opinion whenever there is disagreement in the assessment of a veterinary medicinal product through the mutual recognition procedure. The opinion of the Committee shall be made publicly accessible.

Article 31

1. Each application for the authorisation of a medicinal product for veterinary use shall specifically and exhaustively include the particulars and documents as referred to in Articles 12(3), 13, 13a, 13b and 14 of, and Annex I to, Directive 2001/82/EC. These particulars and documents shall take account of the unique, Community nature of the authorisation requested and, otherwise than in exceptional cases relating to the application of the law on trade marks, shall include the use of a single name for the medicinal product.

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

   Articles 13 to 24 of Directive 2001/18/EC shall not apply to veterinary medicinal products containing or consisting of genetically modified organisms.
3. The Agency shall ensure that the opinion of the Committee for Medicinal Products for Veterinary Use is given within 210 days after the receipt of a valid application.

   In the case of a veterinary medicinal product containing or consisting of genetically modified organisms, the opinion of the said Committee must respect the environmental safety requirements laid down by

Directive 2001/18/EC. During the process of evaluating applications for marketing authorisations for veterinary medicinal products containing or consisting of genetically modified organisms, necessary consultations shall be held by the rapporteur with the bodies set up by the Community or the Member States in accordance with Directive 2001/18/EC.

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

Article 32

1. In order to prepare its opinion, the Committee for Medicinal Products for Veterinary Use:
    (a) shall verify that the particulars and documents submitted in accordance with Article 31 comply with the requirements of Directive 2001/82/EC and examine whether the conditions specified in this Regulation for granting a marketing authorisation are satisfied;
    (b) may request that an Official Medicines Control Laboratory or a laboratory that a Member State has designated for that purpose test the veterinary medicinal product, its starting materials and, where appropriate, its intermediate products or other constituent materials in order to ensure that the control methods employed by the manufacturer and described in the application are satisfactory;
    (c) may request a Community reference laboratory, Official Medicines Control Laboratory or laboratory that a Member State has designated for that purpose to verify, using samples provided by the applicant, that the analytical detection method proposed by the applicant for the purposes of Article 12(3)(j), second indent, of Directive 2001/82/EC is satisfactory and is suitable for use to reveal the presence of residue levels, particularly those above the maximum residue level accepted by the Community in accordance with the provisions of Regulation (EEC) No 2377/90;
    (d) may request the applicant to supplement the particulars accompanying the application within a specific time-limit. Where the said Committee avails itself of this option, the time-limit laid down in Article 31(3), first subparagraph shall be suspended until such time as the supplementary information requested has been provided. Likewise, the time-limit shall be suspended for the time allowed to the applicant to prepare oral or written explanations.
2. In those cases where the analytical method has not been subject to verification by one of the above mentioned laboratories under the procedures established by Regulation (EEC) No 2377/90, the verification shall be carried out within the framework of this Article.

Article 33

1. Upon receipt of a written request from the Committee for Medicinal Products for Veterinary Use, a Member State shall forward the information establishing that the manufacturer of a veterinary medicinal product or the importer from a third country is able to manufacture the veterinary medicinal product concerned and/or carry out the necessary control tests in accordance with the particulars and documents supplied pursuant to Article 31.
2. Where it considers it necessary in order to complete its examination of the application, the said Committee may require the applicant to undergo a specific inspection of the manufacturing site of the veterinary

medicinal product concerned. Such inspections may be made unannounced.

The inspection, which shall be completed within the time-limit referred to in Article 31(3), first subparagraph, shall be undertaken by inspectors from the Member State who possess the appropriate qualifications; they may be accompanied by a rapporteur or expert appointed by the said Committee.

Article 34

1. The Agency shall forthwith inform the applicant if the opinion of the Committee for Medicinal Products for Veterinary Use is that:
    (a) the application does not satisfy the criteria for authorisation set out in this Regulation;
    (b) the summary of the product characteristics should be amended;
    (c) the labelling or package leaflet of the product is not in compliance with Title V of Directive 2001/82/EC;
    (d) the authorisation should be granted subject to the conditions provided for in Article 39(7).
2. Within 15 days after receipt of the opinion referred to in paragraph 1, the applicant may provide written notice to the Agency that he wishes to request a re-examination of the opinion. In that case the applicant shall forward to the Agency the detailed grounds for the request within 60 days after receipt of the opinion.

    Within 60 days after receipt of the grounds for the request, the said Committee shall re-examine its opinion in accordance with the conditions laid down in Article 62(1), fourth subparagraph. The reasons for the conclusion reached shall be annexed to the final opinion.
3. Within 15 days after its adoption, the Agency shall forward the final opinion of the said Committee to the Commission, to Member States and to the applicant, together with a report describing the assessment of the veterinary medicinal product by the Committee and stating the reasons for its conclusions.
4. If an opinion is favourable to the granting of the relevant authorisation to place the relevant veterinary medicinal product on the market, the following documents shall be annexed to the opinion:
    (a) a draft summary of the product characteristics, as referred to in Article 14 of Directive 2001/82/EC; where appropriate, this draft shall reflect differences in the veterinary conditions in the Member States;
    (b) in the case of a veterinary medicinal product intended for administration to food-producing animals, a statement of the maximum residue level which may be accepted by the Community in accordance with Regulation (EEC) No 2377/90;
    (c) details of any conditions or restrictions which should be imposed on the supply or use of the veterinary medicinal product concerned, including the conditions under which the veterinary medicinal product may be made available to users, in conformity with the criteria laid down in Directive 2001/82/EC;
    (d) details of any recommended conditions or restrictions with regard to the safe and effective use of the medicinal product;
    (e) the draft text of the labelling and package leaflet proposed by the applicant, presented in accordance with Title V of Directive 2001/82/EC;
    (f) the assessment report.

Article 35

1. Within 15 days after receipt of the opinion referred to in Article 30(2), the Commission shall prepare a draft of the decision to be taken in respect of the application.

   Where a draft decision envisages the granting of marketing authorisation, it shall include or make reference to the documents mentioned in Article 34(4)(a) to (e).

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

   The draft decision shall be forwarded to Member States and the applicant.
2. The Commission shall take a final decision in accordance with, and within 15 days after the end of, the procedure referred to in Article 87(3).
3. The Standing Committee for Veterinary Medicinal Products referred to in Article 87(1) shall adjust its rules of procedure so as to take account of the tasks assigned to it by this Regulation.

   The adjustments shall provide that:

   (a) the opinion of the said Standing Committee is to 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 may request in writing that the draft decision referred to in paragraph 1 be discussed at a plenary meeting of the said Standing Committee, stating their reasons in detail.
4. Where, in the opinion of the Commission, the written observations of a Member State raise important new questions of a scientific or technical nature which have not been addressed in the opinion delivered by the Agency, the Chairman shall suspend the procedure and refer the application back to the Agency for further consideration.
5. The provisions necessary for the implementation of paragraph 4 shall be adopted by the Commission in accordance with the procedure referred to in Article 87(2).
6. The Agency shall disseminate the documents referred to in Article 34(4) (a) to (e).

Article 36

If an applicant withdraws an application for a marketing authorisation submitted to the Agency before an opinion has been given on the application, the applicant shall communicate its reasons for doing so to the Agency. The Agency shall make this information publicly accessible and shall publish the assessment report, if available, after deletion of all information of a commercially confidential nature.

Article 37

1. The marketing authorisation shall be refused if, after verification of the particulars and documents submitted in accordance with Article 31, it appears that:

   (a) the applicant has not properly or sufficiently demonstrated the quality, safety or efficacy of the veterinary medicinal product;

(b) in the case of zootechnical veterinary medicinal products and performance enhancers, when the safety and welfare of the animals and/or consumer safety have not been sufficiently taken into account;

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

(d) The veterinary medicinal product is presented for a use prohibited under other Community provisions.

Authorisation shall likewise be refused if particulars or documents provided by the applicant in accordance with Article 31 are incorrect or if the labelling and package leaflets proposed by the applicant are not in accordance with Title V of Directive 2001/82/EC.

2. The refusal of a Community marketing authorisation shall constitute a prohibition on the placing on the market of the veterinary medicinal product concerned throughout the Community.
3. Information about all refusals and the reasons for them shall be made publicly accessible.

Article 38

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

   Authorised veterinary medicinal products shall be entered in the Community Register of Medicinal Products and shall be given a number which shall appear on the packaging.
2. Notification of marketing authorisation shall be published in the Official Journal of the European Union, quoting in particular the date of authorisation and the number in the Community Register, any International Non-proprietary Name (INN) of the active substance of the medicinal product, its pharmaceutical form, and any Anatomical Therapeutic Chemical Veterinary Code (ATC Vet Code).
3. The Agency shall immediately publish the assessment report on the veterinary medicinal product drawn up by the Committee for Medicinal Products for Veterinary Use and the reasons for its opinion in favour of granting authorisation, after deletion of any information of a commercially confidential nature.

   The European Public Assessment Report (EPAR) shall include a summary written in a manner that is understandable to the public. The summary shall contain in particular a section relating to the conditions of use of the medicinal product.
4. After a marketing authorisation has been granted, the holder of the authorisation shall inform the Agency of the dates of actual placing on the market of the veterinary medicinal product in Member States, taking into account the various presentations authorised.

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

   Upon request by the Agency, particularly in the context of pharmacovigilance, the marketing authorisation holder shall provide the Agency with all data relating to the volume of sales of the medicinal product at

Community level, broken down by Member State, and any data in the holder's possession relating to the volume of prescriptions.

Article 39

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 by the Agency of the risk-benefit balance.

   To this end, the marketing authorisation holder shall submit a consolidated list of all documents submitted 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. The Agency may require the applicant to submit the listed documents at any time.
3. Once renewed, the marketing authorisation shall be valid for an unlimited period, unless the Commission decides, on justified grounds relating to pharmacovigilance, to proceed with one additional five-year renewal in accordance with paragraph 2.
4. Any authorisation which is not followed by the actual placing of the medicinal product for veterinary use on the Community market within three years after authorisation shall cease to be valid.
5. When an authorised medicinal product previously placed on the market is no longer actually present on the market for three consecutive years, the authorisation shall cease to be valid.
6. In exceptional circumstances and on public and/or animal health grounds the Commission may grant exemptions from the provisions of paragraphs 4 and 5. Such exemptions must be duly justified.
7. In exceptional circumstances and following consultation with the applicant, authorisation may be granted subject to a requirement for the applicant to introduce specific procedures, in particular concerning product safety, notification to the relevant authorities of any incident relating to its use, and action to be taken. This authorisation may be granted only for objective, verifiable reasons. Continuation of the authorisation shall be linked to the annual reassessment of these conditions.
8. When an application is submitted for a marketing authorisation in respect of veterinary medicinal products of major interest, particularly from the point of view of animal health and from the viewpoint of therapeutic innovation, the applicant may request an accelerated assessment procedure. The request shall be duly substantiated.

   If the Committee for Medicinal Products for Veterinary Use accepts the request, the time-limit laid down in Article 31(3), first subparagraph, shall be reduced to 150 days.
9. When adopting its opinion, the said Committee shall include a proposal concerning the conditions for the prescription or use of the veterinary medicinal products.
10. Veterinary medicinal products which have been authorised in accordance with the provisions of this Regulation shall benefit from the provisions on protection in Articles 13 and 13a of Directive 2001/82/EC.

Article 40

The granting of authorisation shall not affect the civil or criminal liability of the manufacturer or the holder of the marketing authorisation pursuant to the applicable national law in Member States.

Chapter 2 - Supervision and sanctions

Article 41

1. After an authorisation has been granted in accordance with this Regulation, the holder of the marketing authorisation shall, in respect of the methods of manufacture and control provided for in Article 12(3)(d) and (i) of Directive 2001/82/EC, take account of technical and scientific progress and make any variations that may be required to enable the medicinal products to be manufactured and checked by means of generally accepted scientific methods. He shall apply for approval of these variations in accordance with this Regulation.
2. The competent authority of a Member State or the Agency may require the holder of the marketing authorisation to provide substances in sufficient quantities for the performance of tests to detect the presence of residues of the veterinary medicinal products concerned in foodstuffs of animal origin.
3. At the request of the competent authority of a Member State or the Agency, the holder of the marketing authorisation shall provide technical expertise to facilitate the implementation of the analytical method for detecting residues of veterinary medicinal products by the Community reference laboratory or, where appropriate, national reference laboratories designated in accordance with Council Directive 96/23/EC of 29 April 1996 on measures to monitor certain substances and residues thereof in live animals and animal products.
4. The holder of the marketing authorisation shall forthwith supply to the Agency, the Commission and the Member States any new information which might entail the variation of the particulars or documents referred to in Articles 12(3), 13, 13a, 13b and 14 of Directive 2001/82/EC, in Annex I thereto, or in Article 34(4) of this Regulation.

   He shall forthwith inform the Agency, the Commission and the Member States of any prohibition or restriction imposed by the competent authorities of any country in which the veterinary medicinal product is marketed and of any other new information which might influence the evaluation of the benefits and risks of the veterinary medicinal product concerned.

   In order that the risk-benefit balance may be continuously assessed, the Agency may at any time ask the holder of the marketing authorisation to forward data justifying that the risk-benefit balance remains favourable.
5. If the holder of the marketing authorisation for the veterinary medicinal product proposes to make any variation of the particulars and documents referred to in paragraph 4, he shall submit the relevant application to the Agency.
6. The Commission shall, after consulting the Agency, adopt appropriate provisions for the examination of variations to marketing authorisations in the form of a regulation. Those measures, designed to amend non-essential elements of this regulation by supplementing it, shall be adopted in accordance with the regulatory procedure with scrutiny referred to in Article 87(2a).

Article 42

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

Article 43

1. In the case of veterinary medicinal products manufactured within the Community, the supervisory authorities shall be the competent authorities of the Member State or Member States which granted the manufacturing authorisation provided for in Article 44(1) of Directive 2001/82/EC in respect of the manufacture of the medicinal product concerned.
2. In the case of veterinary medicinal products imported from third countries, the supervisory authorities shall be the competent authorities of the Member State or Member States that granted the authorisation provided for in Article 44(3) of Directive 2001/82/EC to the importer, unless appropriate agreements have been made between the Community and the exporting country to ensure that those controls are carried out in the exporting country and that the manufacturer applies standards of good manufacturing practice at least equivalent to those laid down by the Community.

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

Article 44

1. The supervisory authorities shall be responsible for verifying on behalf of the Community that the holder of the marketing authorisation for the veterinary medicinal product or the manufacturer or importer established within the Community satisfies the requirements laid down in Titles IV, VII and VIII of Directive 2001/82/EC.
2. Where, in accordance with Article 90 of Directive 2001/82/EC, the Commission is informed of serious differences of opinion between Member States as to whether the holder of the marketing authorisation for the veterinary medicinal product or a manufacturer or importer established within the Community satisfies the requirements referred to in paragraph 1, the Commission may, after consultation with the Member States concerned, request an inspector from the supervisory authority to undertake a new inspection of the holder of the marketing authorisation, the manufacturer or the importer; the inspector in question shall be accompanied by two inspectors from Member States which are not party to the dispute and/or by two experts nominated by the Committee for Medicinal Products for Veterinary Use.
3. Subject to any agreements which may have been concluded between the Community and third countries in accordance with Article 43(2), the Commission may, upon receipt of a reasoned request from a Member State or from the said Committee, or on its own initiative, require a manufacturer established in a third country to submit to an inspection.

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

Article 45

1. Where the supervisory authorities or the competent authorities of any other Member State are of the opinion that the manufacturer or importer established within the Community is no longer fulfillling the obligations laid down in Title VII of Directive 2001/82/EC, they shall forthwith inform the Committee for Medicinal Products for Veterinary Use and the Commission, stating their reasons in detail and indicating the course of action proposed.

   The same shall apply where a Member State or the Commission considers that one of the measures envisaged in Title VIII of Directive 2001/82/EC should be applied in respect of the veterinary medicinal product concerned or where the said Committee has delivered an opinion to that effect in accordance with Article 30 of this Regulation.
2. The Commission shall request the opinion of the Agency within a time-limit which it shall determine in the light of the urgency of the matter, in order to examine the reasons advanced. Whenever practicable, the holder of the marketing authorisation for the medicinal product shall be invited to provide oral or written explanations.
3. Following an opinion by the Agency, the Commission shall adopt the necessary provisional measures, which shall be applied immediately.

   A final decision shall be adopted within six months, in accordance with the procedure referred to in Article 87(3).
4. Where urgent action is essential to protect human or animal health or the environment, a Member State may, on its own initiative or at the Commission's request, suspend the use on its territory of a veterinary medicinal product which has been authorised in accordance with this Regulation.

   When it does so on its own initiative, the Member State shall inform the Commission and the Agency of the reasons for its action at the latest on the next working day following the suspension. The Agency shall inform the other Member States without delay. The Commission shall immediately initiate the procedure provided for in paragraphs 2 and 3.
5. In this case, the Member State shall ensure that health-care professionals are rapidly informed of its action and the reasons for the action. Networks set up by professional associations may be used to this effect. Member States shall inform the Commission and the Agency of actions taken for this purpose.
6. The suspensive measures referred to in paragraph 4 may be maintained until such time as a definitive decision has been reached in accordance with the procedure referred to in Article 87(3).
7. The Agency shall, upon request, inform any person concerned of the final decision and make the decision publicly accessible, immediately after it has been taken.

Chapter 3 - Pharmacovigilance

Article 46

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

Article 47

The Agency, acting in close cooperation with the national pharmacovigilance systems established in accordance with Article 73 of Directive 2001/82/EC, shall receive all relevant information about suspected

adverse reactions to veterinary medicinal products which have been authorised by the Community in accordance with this Regulation. Where appropriate the Committee for Medicinal Products for Veterinary Use shall, in accordance with Article 30 of this Regulation, draw up opinions on the measures necessary. These opinions shall be made publicly accessible.

These measures may include amendments to the marketing authorisation granted in accordance with Article 35. They shall be adopted in accordance with the procedure referred to in Article 87(3).

The holder of the marketing authorisation and the competent authorities of the Member States shall ensure all relevant information about suspected adverse reactions to the veterinary medicinal products authorised under this Regulation is brought to the attention of the Agency in accordance with the provisions of this Regulation. Animal owners and breeders shall be encouraged to communicate any adverse reaction to health-care professionals or to the competent national authorities responsible for pharmacovigilance.

Article 48

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

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

(a) establishing and managing a system which ensures that information about all suspected adverse reactions which are reported to the personnel of the company and to medical representatives is collected, evaluated and collated so that it may be accessed at a single point within the Community;

(b) preparing the reports referred to in Article 49(3) for the competent authorities of the Member States and the Agency in accordance with the requirements of this Regulation;

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

(d) providing the competent authorities with any other information relevant to the evaluation of the risks and benefits of a veterinary medicinal product, particularly information concerning post-authorisation safety studies, including information regarding the validity of the withdrawal period or lack of expected efficacy or potential environmental problems.

Article 49

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

   The holder of the marketing authorisation shall record any other suspected serious adverse reactions and human adverse reactions occurring within the Community, in accordance with the guidelines referred to in

Article 51, of which he may reasonably be expected to be aware, and promptly notify Member States in the territory of which the incident occurred and the Agency, and no later than 15 days following receipt of the information.

2. The holder of the marketing authorisation for a veterinary medicinal product shall ensure that all suspected serious unexpected adverse reactions, and adverse human reactions, and any suspected transmission via a medicinal product of any infectious agent occurring in the territory of a third country are reported promptly to the Member States and the Agency, and no later than 15 days following receipt of the information. The Commission shall adopt provisions for the reporting of suspected unexpected adverse reactions which are not serious, whether occurring in the Community or in a third country. Those measures, designed to amend non-essential elements of this Regulation by supplementing it, shall be adopted in accordance with the regulatory procedure with scrutiny referred to in Article 87(2a).

   Save in exceptional circumstances, these reactions shall be transmitted electronically in the form of a report and in accordance with the guide referred to in Article 51.

3. The holder of the marketing authorisation for a veterinary medicinal product shall maintain detailed records of all suspected adverse reactions occurring within or outside the Community which are reported to him.

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

   These reports shall be accompanied by a scientific evaluation, particularly of the risk-benefit balance of the medicinal product.

4. The Commission may lay down provisions to amend paragraph 3 in view of experience gained with its operation. Those measures, designed to amend non-essential elements of this regulation, shall be adopted in accordance with the procedure referred to in Article 87(2a).

5. 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 Agency.

   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 50

Each Member State shall ensure that all suspected serious adverse reactions, and adverse human reactions, occurring within its territory to a veterinary medicinal product authorised in accordance with the provisions of this Regulation which are brought to its attention are recorded and reported promptly to the Agency and the

holder of the marketing authorisation for the veterinary medicinal product, and no later than 15 days following receipt of the information.

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

Article 51

The Commission, in consultation with the Agency, Member States and interested parties, shall draw up a guide on the collection, verification and presentation of adverse-reaction reports. This guide shall contain, in particular, for the benefit of health-care professionals, recommendations concerning the communication of information on adverse reactions.

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

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

For a period of five years following the initial placing on the market in the Community, the Agency may request that the marketing authorisation holder arrange for specific pharmacovigilance data to be collected from targeted groups of animals. The Agency shall state the reasons for the request. The marketing authorisation holder shall collate and assess the data collected and submit it to the Agency for evaluation.

Article 52

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

Article 53

The Agency and the Member States' competent authorities shall cooperate to continuously develop pharmacovigilance systems capable of achieving high standards of public health protection for all medicinal products, regardless of routes of authorisation, including the use of collaborative approaches, to maximise use of resources available within the Community.

Article 54

The Commission may adopt any amendment which may be necessary to update the provisions of this Chapter in order to take account of scientific and technical progress. Those measures, designed to amend non-essential elements of this regulation, shall be adopted in accordance with the regulatory procedure with scrutiny referred to in Article 87(2a).

TITLE IV - THE EUROPEAN MEDICINES AGENCY — RESPONSIBILITIES AND ADMINISTRATIVE STRUCTURE

Chapter 1 - Tasks of the Agency

Article 55

A European Medicines Agency is hereby established.

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

Article 56

1. The Agency shall comprise:
   - (a) the Committee for Medicinal Products for Human Use, which shall be responsible for preparing the opinion of the Agency on any question relating to the evaluation of medicinal products for human use;
   - (a)(a)the Pharmacovigilance Risk Assessment Committee, which shall be responsible for providing recommendations to the Committee for Medicinal Products for Human Use and the coordination group on any question relating to pharmacovigilance activities in respect of medicinal products for human use and on risk management systems and it shall be responsible for monitoring the effectiveness of those risk management systems;
   - (b) the Committee for Medicinal Products for Veterinary Use, which shall be responsible for preparing the opinion of the Agency on any question relating to the evaluation of medicinal products for veterinary use;
   - (c) the Committee on Orphan Medicinal Products;
   - (d) the Committee on Herbal Medicinal Products;
   - (d)(a)the Committee for Advanced Therapies;
   - (e) the Paediatric Committee;
   - (f) a Secretariat, which shall provide technical, scientific and administrative support for the Committees and ensure appropriate coordination between them, and which shall provide technical and administrative support for the coordination group and ensure appropriate coordination between it and the Committees;
   - (g) an Executive Director, who shall exercise the responsibilities set out in Article 64;
   - (h) a Management Board, which shall exercise the responsibilities set out in Articles 65, 66 and 67.
2. The committees referred to in paragraph (paragraph 1(a) to (da)) may each establish standing and temporary working parties. The committees referred to in paragraph paragraph 1(a) and (b) may establish scientific advisory groups in connection with the evaluation of specific types of medicinal products or treatments, to which the committee concerned may delegate certain tasks associated with drawing up the scientific opinions referred to in Articles 5 and 30.

   When establishing working parties and scientific advisory groups, the committees shall in their rules of procedures referred to in Article 61(8) provide for:
   - (a) the appointment of members of these working parties and scientific advisory groups on the basis of the lists of experts referred to in the second subparagraph of Article 62(2); and
   - (b) consultation of these working parties and scientific advisory groups.

3. The Executive Director, in close consultation with the Committee for Medicinal Products for Human Use and the Committee for Medicinal Products for Veterinary Use, shall set up the administrative structures and procedures allowing the development of advice for undertakings, as referred to in Article 57(1)(n), particularly regarding the development of new therapies.
   Each committee shall establish a standing working party with the sole remit of providing scientific advice to undertakings.
4. The Committee for Medicinal Products for Human Use and the Committee for Medicinal Products for Veterinary Use may, if they consider it appropriate, seek guidance on important questions of a general scientific or ethical nature.

Article 57

1. The Agency shall provide the Member States and the institutions of the Community with the best possible scientific advice on any question relating to the evaluation of the quality, safety and efficacy of medicinal products for human or veterinary use which is referred to it in accordance with the provisions of Community legislation relating to medicinal products.
   To this end, the Agency, acting particularly through its committees, shall undertake the following tasks:
   (a) coordination of the scientific evaluation of the quality, safety and efficacy of medicinal products which are subject to Community marketing authorisation procedures;
   (b) transmitting on request and making publicly available assessment reports, summaries of product characteristics, labels and package leaflets or inserts for these medicinal products;
   (c) coordinating the monitoring of medicinal products which have been authorised within the Union and providing advice on the measures necessary to ensure the safe and effective use of those medicinal products, in particular by coordinating the evaluation and implementation of pharmacovigilance obligations and systems and the monitoring of such implementation;
   (d) ensuring the collation and dissemination of information on suspected adverse reactions to medicinal products authorised in the Union by means of a database which is permanently accessible to all Member States;
   (e) assisting Member States with the rapid communication of information on pharmacovigilance concerns to healthcare professionals and coordinating the safety announcements of the national competent authorities;
   (f) distributing appropriate information on pharmacovigilance concerns to the general public, in particular by setting up and maintaining a European medicines web-portal;
   (g) advising on the maximum limits for residues of veterinary medicinal products and biocidal products used in animal husbandry which may be accepted in foodstuffs of animal origin in accordance with Regulation (EC) No 470/2009 of the European Parliament and of the Council of 6 May 2009 laying down Community procedures for the establishment of residue limits of pharmacologically active substances in foodstuffs of animal origin;
   (h) providing scientific advice on the use of antibiotics in food-producing animals in order to minimise the occurrence of bacterial resistance in the Community; this advice shall be updated when needed;

(i) coordinating the verification of compliance with the principles of good manufacturing practice, good laboratory practice, good clinical practice and the verification of compliance with pharmacovigilance obligations;

(j) upon request, providing technical and scientific support in order to improve cooperation between the Community, its Member States, international organisations and third countries on scientific and technical issues relating to the evaluation of medicinal products, in particular in the context of discussions organised in the framework of international conferences on harmonisation;

(k) recording the status of marketing authorisations for medicinal products granted in accordance with Community procedures;

(l) creating a database on medicinal products, to be accessible to the general public, and ensuring that it is updated, and managed independently of pharmaceutical companies; the database shall facilitate the search for information already authorised for package leaflets; it shall include a section on medicinal products authorised for the treatment of children; the information provided to the public shall be worded in an appropriate and comprehensible manner;

(m) assisting the Community and Member States in the provision of information to health-care professionals and the general public about medicinal products evaluated by the Agency;

(n) advising undertakings on the conduct of the various tests and trials necessary to demonstrate the quality, safety and efficacy of medicinal products;

(o) checking that the conditions laid down in Community legislation on medicinal products and in the marketing authorisations are observed in the case of parallel distribution of medicinal products authorised in accordance with this Regulation;

(p) drawing up, at the Commission's request, any other scientific opinion concerning the evaluation of medicinal products or the starting materials used in the manufacture of medicinal products;

(q) with a view to the protection of public health, compilation of scientific information concerning pathogenic agents which might be used in biological warfare, including the existence of vaccines and other medicinal products available to prevent, or to treat, the effects of such agents;

(r) coordination of the supervision of the quality of medicinal products placed on the market by requesting testing of compliance with their authorised specifications by an Official Medicines Control Laboratory or by a laboratory that a Member State has designated for that purpose;

(s) forwarding annually to the budgetary authority any information relevant to the outcome of the evaluation procedures;

(t) taking decisions as referred to in Article 7(1) of Regulation (EC) No 1901/2006 of the European Parliament and of the Council of 12 December 2006 on medicinal products for paediatric use.

2. The database provided for in paragraph 1(l) shall include the summaries of product characteristics, the patient or user package leaflet and the information shown on the labelling. The database shall be developed in stages, priority being given to medicinal products authorised under this Regulation and those authorised under Chapter 4 of Title III of Directive 2001/83/EC and of Directive 2001/82/EC respectively. The database shall subsequently be extended to include any medicinal product placed on the market within the Community.

For the purposes of the database, the Agency shall set up and maintain a list of all medicinal products for human use authorised in the Union. To this effect the following measures shall be taken:

(a) the Agency shall, by 2 July 2011 at the latest, make public a format for the electronic submission of information on medicinal products for human use;

(b) marketing authorisation holders shall, by 2 July 2012 at the latest, electronically submit to the Agency information on all medicinal products for human use authorised in the Union, using the format referred to in point (a);

(c) from the date set out in point (b), marketing authorisation holders shall inform the Agency of any new or varied marketing authorisations granted in the Union, using the format referred to in point (a).

Where appropriate, the database shall also include references to data on clinical trials currently being carried out or already completed, contained in the clinical trials database provided for in Article 11 of Directive 2001/20/EC. The Commission shall, in consultation with the Member States, issue guidelines on data fields which could be included and which may be accessible to the public.

Article 58

1. The Agency may give a scientific opinion, in the context of cooperation with the World Health Organisation, for the evaluation of certain medicinal products for human use intended exclusively for markets outside the Community. For this purpose, an application shall be submitted to the Agency in accordance with the provisions of Article 6. The Committee for Medicinal Products for Human Use may, after consulting the World Health Organisation, draw up a scientific opinion in accordance with Articles 6 to 9. The provisions of Article 10 shall not apply.
2. The said Committee shall establish specific procedural rules for the implementation of paragraph 1, as well as for the provision of scientific advice.

Article 59

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

a joint document clarifying the scientific points of conflict. This document shall be published immediately after its adoption.

Article 60

At the request of the Commission, the Agency shall, in respect of authorised medicinal products, collect any available information on methods that Member States' competent authorities use to determine the added therapeutic value that any new medicinal product provides.

Article 61

1. Each Member State shall, after consultation of the Management Board, appoint, for a three-year term which may be renewed, one member and one alternate to the Committee for Medicinal Products for Human Use and one member and one alternate to the Committee for Medicinal Products for Veterinary Use.

   The alternates shall represent and vote for the members in their absence and may act as rapporteurs in accordance with Article 62.
2. Members and alternates shall be chosen for their role and experience in the evaluation of medicinal products for human and veterinary use as appropriate and shall represent the competent national authorities.

   The committees 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 committees 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.
3. The members of each Committee may be accompanied by experts in specific scientific or technical fields.
4. The Executive Director of the Agency or his representative and representatives of the Commission shall be entitled to attend all meetings of the committees, working parties and scientific advisory groups and all other meetings convened by the Agency or its committees.
5. In addition to their task of providing objective scientific opinions to the Community and Member States on the questions which are referred to them, the members of each committee shall ensure that there is appropriate coordination between the tasks of the Agency and the work of competent national authorities, including the consultative bodies concerned with the marketing authorisation.
6. Members of the committees and experts responsible for evaluating medicinal products shall rely on the scientific evaluation and resources available to national marketing authorisation bodies. Each competent national authority shall monitor the scientific level and independence of the evaluation carried out and facilitate the activities of nominated committee members and experts. Member States shall refrain from giving committee members and experts any instruction which is incompatible with their own individual tasks or with the tasks and responsibilities of the Agency.

7. When preparing the opinion, each committee shall use its best endeavours to reach a scientific consensus. If such a consensus cannot be reached, the opinion shall consist of the position of the majority of members and divergent positions, with the grounds on which they are based.
8. Each committee shall establish its own rules of procedure.
   These rules shall, in particular, lay down:
   (a) procedures for appointing and replacing the Chairman;
   (b) procedures relating to working parties and scientific advisory groups; and
   (c) a procedure for the urgent adoption of opinions, particularly in relation to the provisions of this Regulation on market surveillance and pharmacovigilance.
   They shall enter into force after receiving a favourable opinion from the Commission and the Management Board.

Article 61a

1. The Pharmacovigilance Risk Assessment Committee shall be composed of the following:
   (a) one member and one alternate member appointed by each Member State, in accordance with paragraph 3 of this Article;
   (b) six members appointed by the Commission, with a view to ensuring that the relevant expertise is available within the Committee, including clinical pharmacology and pharmacoepidemiology, on the basis of a public call for expressions of interest;
   (c) one member and one alternate member appointed by the Commission, on the basis of a public call for expressions of interest, after consulting the European Parliament, in order to represent healthcare professionals;
   (d) one member and one alternate member appointed by the Commission, on the basis of a public call for expressions of interest, after consulting the European Parliament, in order to represent patient organisations.
   The alternate members shall represent and vote for the members in their absence. The alternate members referred to in point (a) may be appointed to act as rapporteurs in accordance with Article 62.
2. A Member State may delegate its tasks in the Pharmacovigilance Risk Assessment Committee to another Member State. Each Member State may represent no more than one other Member State.
3. The members and alternate members of the Pharmacovigilance Risk Assessment Committee shall be appointed on the basis of their relevant expertise in pharmacovigilance matters and risk assessment of medicinal products for human use, in order to guarantee the highest levels of specialist qualifications and a broad spectrum of relevant expertise. For this purpose, Member States shall liaise with the Management Board and the Commission in order to ensure that the final composition of the Committee covers the scientific areas relevant to its tasks.
4. The members and alternate members of the Pharmacovigilance Risk Assessment Committee shall be appointed for a term of 3 years, which may be prolonged once and thereafter renewed following the procedures referred to in paragraph 1. The Committee shall elect its Chairman from among its members for a term of 3 years, which may be prolonged once.

5. Paragraphs 3, 4, 6, 7 and 8 of Article 61 shall apply to the Pharmacovigilance Risk Assessment Committee.
6. The mandate of the Pharmacovigilance Risk Assessment Committee shall cover all aspects of the risk management of the use of medicinal products for human use including the detection, assessment, minimisation and communication relating to the risk of adverse reactions, having due regard to the therapeutic effect of the medicinal product for human use, the design and evaluation of post-authorisation safety studies and pharmacovigilance audit.

Article 62

1. Where, in accordance with this Regulation, any of the Committees referred to in Article 56(1) is required to evaluate a medicinal product for human use, it shall appoint one of its members to act as rapporteur, taking into account existing expertise in the Member State. The Committee concerned may appoint a second member to act as co-rapporteur.

   A rapporteur appointed for this purpose by the Pharmacovigilance Risk Assessment Committee shall closely collaborate with the rapporteur appointed by the Committee for Medicinal Products for Human Use or the Reference Member State for the medicinal product for human use concerned.

   When consulting the scientific advisory groups referred to in Article 56(2), the Committee shall forward to them the draft assessment report(s) drawn up by the rapporteur or the co-rapporteur. The opinion issued by the scientific advisory group shall be forwarded to the chairman of the relevant Committee in such a way as to ensure that the deadlines laid down in Article 6(3) and Article 31(3) are met.

   The substance of the opinion shall be included in the assessment report published pursuant to Article 13(3) and Article 38(3).

   If there is a request for re-examination of one of its opinions where this possibility is provided for in Union law, the Committee concerned shall appoint a different rapporteur and, where necessary, a different co-rapporteur from those appointed for the initial opinion. The re-examination procedure may deal only with the points of the opinion initially identified by the applicant and may be based only on the scientific data available when the Committee adopted the initial opinion. The applicant may request that the Committee consult a scientific advisory group in connection with the re-examination.
2. Member States shall transmit to the Agency the names of national experts with proven experience in the evaluation of medicinal products for human use who, taking into account Article 63(2), would be available to serve on working parties or scientific advisory groups of any of the Committees referred to in Article 56(1), together with an indication of their qualifications and specific areas of expertise.

   The Agency shall keep an up-to-date list of accredited experts. The list shall include the experts referred to in the first subparagraph and other experts appointed directly by the Agency. The list shall be updated.
3. The provision of services by rapporteurs or experts shall be governed by a written contract between the Agency and the person concerned, or where appropriate between the Agency and his employer.

   The person concerned, or his employer, shall be remunerated in accordance with a scale of fees to be included in the financial arrangements established by the Management Board.

   The first and second subparagraphs shall also apply to the work of rapporteurs in the coordination group

as regards the fulfillment of its tasks in accordance with Articles 107c, 107e, 107g, 107k and 107q of Directive 2001/83/EC.

4. The performance of scientific services for which there are several potential providers may result in a call for an expression of interest, if the scientific and technical context allows, and if it is compatible with the tasks of the Agency, in particular to ensure a high level of public health protection.
   The Management Board shall adopt the appropriate procedures on a proposal from the Executive Director.
5. The Agency or any of the committees referred to in Article 56(1) may use the services of experts for the discharge of other specific tasks for which they are responsible.

Article 63

1. The membership of the committees refe
2. rred to in Article 56(1) shall be made public. When each appointment is published, the professional qualifications of each member shall be specified.
3. Members of the Management Board, members of the committees, rapporteurs and experts shall not have financial or other interests in the pharmaceutical industry which could affect their impartiality. They shall undertake to act in the public interest and in an independent manner, and shall make an annual declaration of their financial interests. All indirect interests which could relate to this industry shall be entered in a register held by the Agency which is accessible to the public, on request, at the Agency's offices.
   The Agency's code of conduct shall provide for the implementation of this Article with particular reference to the acceptance of gifts.
   Members of the Management Board, members of the committees, rapporteurs and experts who participate in meetings or working groups of the Agency shall declare, at each meeting, any specific interests which could be considered to be prejudicial to their independence with respect to the items on the agenda. These declarations shall be made available to the public.

Article 64

1. The Executive Director shall be appointed by the Management Board, on a proposal from the Commission, for a period of five years on the basis of a list of candidates proposed by the Commission following a call for expressions of interest published in the Official Journal of the European Union and elsewhere. Before appointment, the candidate nominated by the Management Board shall be invited forthwith to make a statement to the European Parliament and to answer any questions put by its Members. His mandate may be renewed once. The Management Board may, upon a proposal from the Commission, remove the Executive Director from his post.
2. The Executive Director shall be the legal representative of the Agency. He shall be responsible:
   (a) for the day-to-day administration of the Agency;
   (b) for managing all the Agency resources necessary for conducting the activities of the Committees referred to in Article 56(1), including making available appropriate scientific and technical support to those Committees, and for making available appropriate technical support to the coordination group;
   (c) for ensuring that the time-limits laid down in Community legislation for the adoption of opinions by the Agency are complied with;

(d) for ensuring appropriate coordination between the Committees referred to in Article 56(1) and, where necessary, between the Committees and the coordination group;
(e) for the preparation of the draft statement of estimates of the Agency's revenue and expenditure, and execution of its budget;
(f) for all staff matters;
(g) for providing the secretariat for the Management Board.

3. Each year the Executive Director shall submit a draft report covering the activities of the Agency in the previous year and a draft work programme for the coming year to the Management Board for approval, making a distinction between the Agency's activities concerning medicinal products for human use, those concerning herbal medicinal products and those concerning veterinary medicinal products.
   The draft report covering the activities of the Agency in the previous year shall include information about the number of applications evaluated within the Agency, the time taken for completion of the evaluation and the medicinal products authorised, rejected or withdrawn.

Article 65

1. The Management Board shall consist of one representative of each Member State, two representatives of the Commission and two representatives of the European Parliament.
   In addition, two representatives of patients' organisations, one representative of doctors' organisations and one representative of veterinarians' organisations shall be appointed by the Council in consultation with the European Parliament on the basis of a list drawn up by the Commission which includes appreciably more names than there are posts to be filled. The list drawn up by the Commission shall be forwarded to the European Parliament, together with the relevant background documents. As quickly as possible, and within three months of notification, the European Parliament may submit its views for consideration to the Council, which shall then appoint the Management Board.
   The members of the Management Board shall be appointed in such a way as to guarantee the highest levels of specialist qualifications, a broad spectrum of relevant expertise and the broadest possible geographic spread within the European Union.
2. The members of the Management Board shall be appointed on the basis of their relevant expertise in management and, if appropriate, experience in the field of medicinal products for human or veterinary use.
3. Each Member State and the Commission shall appoint their members of the Management Board as well as an alternate who will replace the member in his absence and vote on his behalf.
4. The term of office of the representatives shall be three years. The term of office may be renewed.
5. The Management Board shall elect its Chairman from among its members.
   The term of office of the Chairman shall be three years and shall expire when he ceases to be a member of the Management Board. The term of office may be renewed once.
6. Decisions of the Management Board shall be adopted by a majority of two-thirds of its members.
7. The Management Board shall adopt its rules of procedure.
8. The Management Board may invite the chairmen of the scientific committees to attend its meetings, but they shall not have the right to vote.

9. The Management Board shall approve the annual work programme of the Agency programme and forward it to the European Parliament, the Council, the Commission and the Member States.
10. The Management Board shall adopt the annual report on the Agency's activities and forward it by 15 June at the latest to the European Parliament, the Council, the Commission, the European Economic and Social Committee, the Court of Auditors and the Member States.

Article 66

The Management Board shall:

(a) adopt an opinion on the rules of procedures of the Committee for Medicinal Products for Human Use and the Committee for Medicinal Products for Veterinary Use (Article 61);
(b) adopt procedures for the performance of scientific services (Article 62);
(c) appoint the Executive Director (Article 64);
(d) adopt the annual work programme and forward it to the European Parliament, the Council, the Commission and the Member States (Article 65);
(e) approve the annual report on the Agency's activities and forward it by 15 June at the latest to the European Parliament, the Council, the Commission, the European Economic and Social Committee, the Court of Auditors and the Member States (Article 65);
(f) adopt the budget of the Agency (Article 67);
(g) adopt the internal financial provisions >>>Article 68
(h) adopt provisions implementing the Staff Regulations (Article 75);
(i) develop contacts with stakeholders and stipulate the conditions applicable (Article 78);
(j) adopt provisions for providing assistance to pharmaceutical companies (Article 79);
(k) adopt rules to ensure the availability to the public of information concerning the authorisation or supervision of medicinal products (Article 80).

Chapter 2 - Financial Provisions

Article 67

1. Estimates of all the revenue and expenditure of the Agency shall be prepared for each financial year, corresponding to the calendar year, and shall be shown in the budget of the Agency.
2. The revenue and expenditure shown in the budget shall be in balance.
3. The Agency's revenue shall consist of a contribution from the Union and fees paid by undertakings for obtaining and maintaining Union marketing authorisations and for other services provided by the Agency, or by the coordination group as regards the fulfillment of its tasks in accordance with Articles 107c, 107e, 107g, 107k and 107q of Directive 2001/83/EC.
   The European Parliament and the Council (hereinafter referred to as 'the budgetary authority') shall re-examine, when necessary, the level of the Community contribution on the basis of an evaluation of needs and taking account of the level of fees.
4. Activities relating to pharmacovigilance, to the operation of communications networks and to market surveillance shall be under the permanent control of the Management Board in order to guarantee the

independence of the Agency. This shall not preclude the Agency from charging fees to marketing authorisation holders for performing these activities by the Agency on the condition that its independence is strictly guaranteed.

5. The expenditure of the Agency shall include staff remuneration, administrative and infrastructure costs, and operating expenses as well as expenses resulting from contracts entered into with third parties.
6. Each year the Management Board, on the basis of a draft drawn up by the Executive Director, shall produce an estimate of revenue and expenditure for the Agency for the following financial year. This estimate, which shall include a draft establishment plan, shall be forwarded by the Management Board to the Commission by 31 March at the latest.
7. The estimate shall be forwarded by the Commission to the budgetary authority together with the preliminary draft general budget of the European Union.
8. On the basis of the estimate, the Commission shall enter in the preliminary draft general budget of the European Union the estimates it deems necessary for the establishment plan and the amount of the subsidy to be charged to the general budget, which it shall place before the budgetary authority in accordance with Article 272 of the Treaty.
9. The budgetary authority shall authorise the appropriations for the subsidy to the Agency.
   The budgetary authority shall adopt the establishment plan for the Agency.
10. The budget shall be adopted by the Management Board. It shall become final following final adoption of the general budget of the European Union. Where appropriate, it shall be adjusted accordingly.
11. Any modification of the establishment plan and of the budget shall be the subject of an amending budget, which is forwarded for the purposes of information to the budgetary authority.
12. The Management Board shall, as soon as possible, notify the budgetary authority of its intention to implement any project which may have significant financial implications for the funding of its budget, in particular any projects relating to property such as the rental or purchase of buildings. It shall inform the Commission thereof.
    Where a branch of the budgetary authority has notified its intention to deliver an opinion, it shall forward its opinion to the Management Board within a period of six weeks from the date of notification of the project.

Article 68

1. The Executive Director shall implement the budget of the Agency.
2. By 1 March at the latest following each financial year, the Agency's accounting officer shall communicate the provisional accounts to the Commission's accounting officer together with a report on the budgetary and financial management for that financial year. The Commission's accounting officer shall consolidate the provisional accounts of the institutions and decentralised bodies in accordance with Article 128 of the Financial Regulation applicable to the general budget of the European Communities (hereinafter referred to as the 'general Financial Regulation').
3. By 31 March at the latest following each financial year, the Commission's accounting officer shall submit the Agency's provisional accounts to the Court of Auditors, together with a report on the budgetary and

financial management for that financial year. The report on the budgetary and financial management for the financial year shall also be forwarded to the European Parliament and the Council.

4. On receipt of the Court of Auditors' observations on the Agency's provisional accounts, pursuant to Article 129 of the general Financial Regulation, the Executive Director shall draw up the Agency's final accounts under his own responsibility and submit them to the Management Board for an opinion.
5. The Management Board of the Agency shall deliver an opinion on the Agency's final accounts.
6. The Executive Director shall, by 1 July at the latest following each financial year, forward the final accounts to the European Parliament, the Council, the Commission and the Court of Auditors, together with the Management Board's opinion.
7. The final accounts shall be published.
8. The Agency's Executive Director shall send the Court of Auditors a reply to its observations by 30 September at the latest. He shall also send this reply to the Management Board.
9. The Executive Director shall submit to the European Parliament, at the latter's request, any information required for the smooth application of the discharge procedure for the financial year in question, as laid down in Article 146(3) of the general Financial Regulation.
10. The European Parliament, on a recommendation from the Council acting by a qualified majority, shall, before 30 April of year N + 2, give a discharge to the Executive Director in respect of the implementation of the budget for year N.
11. The financial rules applicable to the Agency shall be adopted by the Management Board after the Commission has been consulted. They may not depart from Commission Regulation (EC, Euratom) No 2343/2002 of 19 November 2002 on the framework Financial Regulation for the bodies referred to in Article 185 of Council Regulation (EC, Euratom) No 1605/2002 on the Financial Regulation applicable to the general budget of the European Communities, unless specifically required for the Agency's operation and with the Commission's prior consent.

Article 69

1. In order to combat fraud, corruption and other unlawful activities the provisions of Regulation (EC) No 1073/1999 of the European Parliament and of the Council of 25 May 1999 concerning investigations conducted by the European Anti-Fraud Office (OLAF) shall apply without restriction.
2. The Agency shall accede to the Interinstitutional Agreement of 25 May 1999 concerning internal investigations by the European Anti-Fraud Office (OLAF) and shall issue, without delay, the appropriate provisions applicable to all the employees of the Agency.

Article 70

1. The structure and the level of the fees referred to in Article 67(3) shall be established by the Council acting under the conditions provided for by the Treaty on a proposal from the Commission, once the Commission has consulted organisations representing the interests of the pharmaceutical industry at Community level.
2. However, the Commission shall adopt provisions establishing the circumstances in which small and medium-sized enterprises may pay reduced fees, defer payment of the fee, or receive administrative

assistance. Those measures, designed to amend non-essential elements of this Regulation by supplementing it, shall be adopted in accordance with the regulatory procedure with scrutiny referred to in Article 87(2a).

Chapter 3 - General Provisions governing the Agency

Article 71

The Agency shall have legal personality. In all Member States it shall enjoy the most extensive legal capacity accorded to legal persons under their laws. It may in particular acquire or dispose of movable and immovable property and may be a party to legal proceedings.

Article 72

1. The contractual liability of the Agency s
2. hall be governed by the law applicable to the contract in question.
   The Court of Justice of the European Communities shall have jurisdiction pursuant to any arbitration clause contained in a contract concluded by the Agency.
3. In the case of non-contractual liability, the Agency shall, in accordance with the general principles common to the laws of the Member States, make good any damage caused by it or by its servants in the performance of their duties.
   The Court of Justice shall have jurisdiction in any dispute relating to compensation for any such damage.
4. The personal liability of its servants towards the Agency shall be governed by the relevant rules applying to the staff of the Agency.

Article 73

Regulation (EC) No 1049/2001 of the European Parliament and of the Council of 30 May 2001 regarding public access to European Parliament, Council and Commission documents shall apply to documents held by the Agency.

The Agency shall set up a register pursuant to Article 2(4) of Regulation (EC) No 1049/2001 to make available all documents that are publicly accessible pursuant to this Regulation.

The Management Board shall adopt the arrangements for implementing Regulation (EC) No 1049/2001 within six months of entry into force of this Regulation.

Decisions taken by the Agency pursuant to Article 8 of Regulation (EC) No 1049/2001 may give rise to the lodging of a complaint with the Ombudsman or form the subject of an action before the Court of Justice, under the conditions laid down in Articles 195 and 230 of the Treaty respectively.

Article 73a

Decisions taken by the Agency under Regulation (EC) No 1901/2006 may form the subject of an action before the Court of Justice of the European Communities under the conditions laid down in Article 230 of the Treaty.

Article 74

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

Article 75

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

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

Article 76

Members of the Management Board, members of the committees referred to in Article 56(1), and experts and officials and other servants of the Agency, shall be required, even after their duties have ceased, not to disclose information of the kind covered by the obligation of professional secrecy.

Article 77

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

Article 78

1. The Management Board shall, in agreement with the Commission, develop appropriate contacts between the Agency and the representatives of the industry, consumers and patients and the health professions. These contacts may include the participation of observers in certain aspects of the Agency's work, under conditions determined beforehand by the Management Board, in agreement with the Commission.
2. The committees referred to in Article 56(1) and any working parties and scientific advisory groups established in accordance with that Article shall in general matters establish contacts, on an advisory basis, with parties concerned with the use of medicinal products, in particular patient organisations and health-care professionals' associations. Rapporteurs appointed by these committees may, on an advisory basis, establish contacts with representatives of patient organisations and health-care professionals' associations relevant to the indication of the medicinal product concerned.

Article 79

The Management Board shall, in the case of veterinary medicinal products which have limited markets, or in the case of veterinary medicinal products intended for diseases with a regional distribution, adopt the necessary measures to provide assistance to companies at the time of submission of their applications.

Article 80

To ensure an appropriate level of transparency, the Management Board, on the basis of a proposal by the Executive Director and in agreement with the Commission, shall adopt rules to ensure the availability to the

public of regulatory, scientific or technical information concerning the authorisation or supervision of medicinal products which is not of a confidential nature.

The internal rules and procedures of the Agency, its committees and its working groups shall be made available to the public at the Agency and on the Internet.

TITLE V - GENERAL AND FINAL PROVISIONS

Article 81

1. All decisions to grant, refuse, vary, suspend, withdraw or revoke a marketing authorisation which are taken in accordance with this Regulation shall state in detail the reasons on which they are based. Such decisions shall be notified to the party concerned.
2. An authorisation to place a medicinal product governed by this Regulation on the market shall not be granted, refused, varied, suspended, withdrawn or revoked except through the procedures and on the grounds set out in this Regulation.

Article 82

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

   However, the Commission shall authorise the same applicant to submit more than one application to the Agency for that medicinal product when there are objective verifiable reasons relating to public health regarding the availability of medicinal products to health-care professionals and/or patients, or for co-marketing reasons.
2. As regards medicinal products for human use, Article 98(3) of Directive 2001/83/EC shall apply to medicinal products authorised under this Regulation.
3. Without prejudice to the unique, Union nature of the content of the documents referred to in points (a) to (d) of Article 9(4) and in points (a) to (e) of Article 34(4), this Regulation shall not prohibit the use of two or more commercial designs for a given medicinal product for human use covered by a single marketing authorisation.

Article 83

1. By way of exemption from Article 6 of Directive 2001/83/EC Member States may make a medicinal product for human use belonging to the categories referred to in Article 3(1) and (2) of this Regulation available for compassionate use.
2. For the purposes of this Article, 'compassionate use' shall mean making a medicinal product belonging to the categories referred to in Article 3(1) and (2) available for compassionate reasons to a group of patients with a chronically or seriously debilitating disease or whose disease is considered to be life-threatening, and who can not be treated satisfactorily by an authorised medicinal product. The medicinal product concerned must either be the subject of an application for a marketing authorisation in accordance with Article 6 of this Regulation or must be undergoing clinical trials.
3. When a Member State makes use of the possibility provided for in paragraph 1 it shall notify the Agency.

4. When compassionate use is envisaged, the Committee for Medicinal Products for Human Use, after consulting the manufacturer or the applicant, may adopt opinions on the conditions for use, the conditions for distribution and the patients targeted. The opinions shall be updated on a regular basis.
5. Member States shall take account of any available opinions.
6. The Agency shall keep an up-to-date list of the opinions adopted in accordance with paragraph 4, which shall be published on its website. Article 28(1) and (2) shall apply mutatis mutandis.
7. The opinions referred to in paragraph 4 shall not affect the civil or criminal liability of the manufacturer or of the applicant for marketing authorisation.
8. Where a compassionate use programme has been set up, the applicant shall ensure that patients taking part also have access to the new medicinal product during the period between authorisation and placing on the market.
9. This Article shall be without prejudice to Directive 2001/20/EC and to Article 5 of Directive 2001/83/EC.

Article 84

1. Without prejudice to the Protocol on the Privileges and Immunities of the European Communities, each Member State shall determine the penalties to be applied for infringement of the provisions of this Regulation or the regulations adopted pursuant to it and shall take all measures necessary for their implementation. The penalties shall be effective, proportionate and dissuasive.

   Member States shall inform the Commission of these provisions no later than 31 December 2004. They shall notify any subsequent alterations as soon as possible.
2. Member States shall inform the Commission immediately of any litigation instituted for infringement of this Regulation.
3. At the Agency's request, the Commission may impose financial penalties on the holders of marketing authorisations granted under this Regulation if they fail to observe certain obligations laid down in connection with the authorisations. The maximum amounts as well as the conditions and methods for collection of these penalties shall be laid down by the Commission. Those measures, designed to amend non-essential elements of this Regulation by supplementing it, shall be adopted in accordance with the regulatory procedure with scrutiny referred to in Article 87(2a).

   The Commission shall publish the names of the marketing authorisation holders involved and the amounts of and reasons for the financial penalties imposed.

Article 85

This Regulation shall not affect the competences vested in the European Food Safety Authority created by Regulation (EC) No 178/2002.

Article 86

At least every ten years, the Commission shall publish a general report on the experience acquired as a result of the operation of the procedures laid down in this Regulation, in Chapter 4 of Title III of Directive 2001/83/EC and in Chapter 4 of Title III of Directive 2001/82/EC.

Article 87

1. The Commission shall be assisted by the Standing Committee on Medicinal Products for Human Use set up by Article 121 of Directive 2001/83/EC and by the Standing Committee on Veterinary Medicinal Products set up by Article 89 of Directive 2001/82/EC.
2. Where reference is made to this paragraph, 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.

   2.(a) Where reference is made to this paragraph, Article 5a(1) to (4) and Article 7 of Decision 1999/468/EC shall apply, having regard to the provisions of Article 8 thereof.
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.

Article 87a

In order to harmonise the performance of the pharmacovigilance activities provided for in this Regulation, the Commission shall adopt implementing measures as provided for in Article 108 of Directive 2001/83/EC covering the following areas:

(a) the content and maintenance of the pharmacovigilance system master file kept by the marketing authorisation holder;
(b) the minimum requirements for the quality system for the performance of pharmacovigilance activities by the Agency;
(c) the use of internationally agreed terminology, formats and standards for the performance of pharmacovigilance activities;
(d) the minimum requirements for the monitoring of data included in the Eudravigilance database to determine whether there are new risks or whether risks have changed;
(e) the format and content of electronic transmission of suspected adverse reactions by Member States and marketing authorisation holders;
(f) the format and content of electronic periodic safety update reports and risk management plans;
(g) the format of protocols, abstracts and final study reports of the post-authorisation safety studies.

Those measures shall take account of the work on international harmonisation carried out in the area of pharmacovigilance and shall, where necessary, be revised to take account of technical and scientific progress. Those measures shall be adopted in accordance with the regulatory procedure referred to in Article 87(2).

Article 87b

1. The power to adopt the delegated acts referred to in Article 10b shall be conferred on the Commission for a period of 5 years from 1 January 2011. The Commission shall draw up a report in respect of the delegated powers not later than 6 months before the end of the 5 year period. The delegation of powers shall be automatically extended for periods of an identical duration, unless the European Parliament or the Council revokes it in accordance with Article 87c.

2. As soon as it adopts a delegated act, the Commission shall notify it simultaneously to the European Parliament and to the Council.
3. The power to adopt delegated acts is conferred on the Commission subject to the conditions laid down in Articles 87c and 87d.

Article 87c

1. The delegation of powers referred to in Article 10b may be revoked at any time by the European Parliament or by the Council.
2. The institution which has commenced an internal procedure for deciding whether to revoke the delegation of powers shall endeavour to inform the other institution and the Commission within a reasonable time before the final decision is taken, indicating the delegated powers which could be subject to revocation and possible reasons for a revocation.
3. The decision of revocation shall put an end to the delegation of the powers specified in that decision. It shall take effect immediately or at a later date specified therein. It shall not affect the validity of the delegated acts already in force. It shall be published in the Official Journal of the European Union.

Article 87d

1. The European Parliament or the Council may object to a delegated act within a period of 2 months from the date of notification.
   At the initiative of the European Parliament or the Council that period shall be extended by 2 months.
2. If, on expiry of the period referred to in paragraph 1, neither the European Parliament nor the Council has objected to the delegated act, it shall be published in the Official Journal of the European Union and shall enter into force on the date stated therein.
   The delegated act may be published in the Official Journal of the European Union and enter into force before the expiry of that period if the European Parliament and the Council have both informed the Commission of their intention not to raise objections.
3. If either the European Parliament or the Council objects to the delegated act within the period referred to in paragraph 1, it shall not enter into force. The institution which objects shall state the reasons for objecting to the delegated act.

Article 88

Regulation (EEC) No 2309/93/EC is hereby repealed.
References to the repealed Regulation shall be construed as references to this Regulation.

Article 89

The periods of protection provided for in Articles 14(11) and 39(10) shall not apply to reference medicinal products for which an application for authorisation has been submitted before the date referred to in Article 90, second paragraph.

Article 90

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

By way of derogation from the first paragraph, Titles I, II, III and V shall apply from 20 November 2005 and point 3, fifth and sixth indent of the Annex shall apply from 20 May 2008.

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

ANNEX - MEDICINAL PRODUCTS TO BE AUTHORISED BY THE COMMUNITY

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

recombinant DNA technology,

controlled expression of genes coding for biologically active proteins in prokaryotes and eukaryotes including transformed mammalian cells,

hybridoma and monoclonal antibody methods.

1a. Advanced therapy medicinal products as defined in Article 2 of Regulation (EC) No 1394/2007 of the European Parliament and of the Council of 13 November 2007 on advanced therapy medicinal products

2. Medicinal products for veterinary use intended primarily for use as performance enhancers in order to promote the growth of treated animals or to increase yields from treated animals.
3. Medicinal products for human use containing a new active substance which, on the date of entry into force of this Regulation, was not authorised in the Community, for which the therapeutic indication is the treatment of any of the following diseases:
   - acquired immune deficiency syndrome,
   - cancer,
   - neurodegenerative disorder,
   - diabetes,
   - auto-immune diseases and other immune dysfunctions,
   - viral diseases.

   After 20 May 2008, the Commission, having consulted the Agency, may present any appropriate proposal to amend this point and the European Parliament and the Council shall take a decision thereon in accordance with the Treaty.
4. Medicinal products that are designated as orphan medicinal products pursuant to Regulation (EC) No 141/2000.

Regulation (EC) No 141/2000 - Orphan Medicinal Products

REGULATION (EC) NO 141/2000 OF THE EUROPEAN PARLIAMENT AND OF THE COUNCIL OF 16 DECEMBER 1999 ON ORPHAN MEDICINAL PRODUCTS

THE EUROPEAN PARLIAMENT AND THE COUNCIL OF THE EUROPEAN UNION,
Having regard to the Treaty establishing the European Community, and in particular Article 95 thereof,
Having regard to the proposal from the Commission,
Having regard to the opinion of the Economic and Social Committee,
Acting in accordance with the procedure laid down in Article 251 of the Treaty,
Whereas:

1. some conditions occur so infrequently that the cost of developing and bringing to the market a medicinal product to diagnose, prevent or treat the condition would not be recovered by the expected sales of the medicinal product; the pharmaceutical industry would be unwilling to develop the medicinal product under normal market conditions; these medicinal products are called 'orphan';
2. patients suffering from rare conditions should be entitled to the same quality of treatment as other patients; it is therefore necessary to stimulate the research, development and bringing to the market of appropriate medications by the pharmaceutical industry; incentives for the development of orphan medicinal products have been available in the United States of America since 1983 and in Japan since 1993;
3. in the European Union, only limited action has been taken so far, whether at national or at Community level, to stimulate the development of orphan medicinal products; such action is best taken at Community level in order to take advantage of the widest possible market and to avoid the dispersion of limited resources; action at Community level is preferable to uncoordinated measures by the Member States which may result in distortions of competition and barriers to intra-Community trade;
4. orphan medicinal products eligible for incentives should be easily and unequivocally identified; it seems most appropriate to achieve this result through the establishment of an open and transparent Community procedure for the designation of potential medicinal products as orphan medicinal products;
5. objective criteria for designation should be established; those criteria should be based on the prevalence of the condition for which diagnosis, prevention or treatment is sought; a prevalence of not more than five affected persons per 10 thousand is generally regarded as the appropriate threshold; medicinal products intended for a life-threatening, seriously debilitating or serious and chronic condition should be eligible even when the prevalence is higher than five per 10 thousand;
6. a Committee composed of experts appointed by the Member States should be established to examine applications for designation; this Committee should also include three representatives of patients' associations, designated by the Commission, and three other persons, also designated by the Commission, on a recommendation from the European Agency for the Evaluation of Medicinal Products (hereinafter referred to as 'the Agency'); the Agency should be responsible for the adequate coordination between the Committee on orphan medicinal products and the Committee on proprietary medicinal products;

7. patients with such conditions deserve the same quality, safety and efficacy in medicinal products as other patients; orphan medicinal products should therefore be submitted to the normal evaluation process; sponsors of orphan medicinal products should have the possibility of obtaining a Community authorisation; in order to facilitate the granting or the maintenance of a Community authorisation, fees to be paid to the Agency should be waived at least in part; the Community budget should compensate the Agency for the loss in revenue thus occasioned;
8. experience in the United States of America and Japan shows that the strongest incentive for industry to invest in the development and marketing of orphan medicinal products is where there is a prospect of obtaining market exclusivity for a certain number of years during which part of the investment might be recovered; data protection under Article 4(8)(a)(iii) of Council Directive 65/65/EEC of 26 January 1965 on the approximation of provisions laid down by law, regulation or administrative action relating to medicinal products is not a sufficient incentive for that purpose; Member States acting independently cannot introduce such a measure without a Community dimension as such a provision would be contradictory to Directive 65/65/EEC; if such measures were adopted in an uncoordinated manner by the Member States, this would create obstacles to intra-Community trade, leading to distortions of competition and running counter to the single market; market exclusivity should however be limited to the therapeutic indication for which orphan medicinal product designation has been obtained, without prejudice to existing intellectual property rights; in the interest of patients, the market exclusivity granted to an orphan medicinal product should not prevent the marketing of a similar medicinal product which could be of significant benefit to those affected by the condition;
9. sponsors of orphan medicinal products designated under this Regulation should be entitled to the full benefit of any incentives granted by the Community or by the Member States to support the research and development of medicinal products for the diagnosis, prevention or treatment of such conditions, including rare diseases;
10. the specific programme Biomed 2, of the fourth framework programme for research and technological development (1994 to 1998), supported research on the treatment of rare diseases, including methodologies for rapid schemes for the development of orphan medicinal products and inventories of available orphan medicinal products in Europe; those grants were intended to promote the establishment of cross national cooperation in order to implement basic and clinical research on rare diseases; research on rare diseases continues to be a priority for the Community, as it has been included in the fifth framework programme for research and technological development (1998 to 2002); this Regulation establishes a legal framework which will allow the swift and effective implementation of the outcome of this research;
11. rare diseases have been identified as a priority area for Community action within the framework for action in the field of public health; the Commission, in its communication concerning a programme of Community action on rare diseases within the framework for action in the field of public health has decided to give rare diseases priority within the public health framework; the European Parliament and the Council have adopted Decision No 1295/1999/EC of 29 April 1999 adopting a programme of Community action on rare diseases within the framework for action in the field of public health (1999 to 2003), including actions to provide information, to deal with clusters of rare diseases in a population and to support relevant patient organisations; this Regulation implements one of the priorities laid down in this programme of action,

HAVE ADOPTED THIS REGULATION :

Article 1 - Purpose

The purpose of this Regulation is to lay down a Community procedure for the designation of medicinal products as orphan medicinal products and to provide incentives for the research, development and placing on the market of designated orphan medicinal products.

Article 2 - Definitions

For the purposes of this Regulation:

(a) 'medicinal product' means a medicinal product for human use, as defined in Article 2 of Directive 65/65/EEC;

(b) 'orphan medicinal product' means a medicinal product designated as such under the terms and conditions of this Regulation;

(c) 'sponsor' means any legal or natural person, established in the Community, seeking to obtain or having obtained the designation of a medicinal product as an orphan medicinal product;

(d) 'Agency' means the European Agency for the Evaluation of Medicinal Products.

Article 3 - Criteria for designation

1. A medicinal product shall be designated as an orphan medicinal product if its sponsor can establish:
   (a) that it is intended for the diagnosis, prevention or treatment of a life-threatening or chronically debilitating condition affecting not more than five in 10 thousand persons in the Community when the application is made, or
   that it is intended for the diagnosis, prevention or treatment of a life-threatening, seriously debilitating or serious and chronic condition in the Community and that without incentives it is unlikely that the marketing of the medicinal product in the Community would generate sufficient return to justify the necessary investment;
   and
   (b) that there exists no satisfactory method of diagnosis, prevention or treatment of the condition in question that has been authorised in the Community or, if such method exists, that the medicinal product will be of significant benefit to those affected by that condition.
2. The Commission shall, in accordance with the regulatory procedure referred to in Article 10a(2), adopt the necessary provisions for implementing paragraph 1 of this Article in the form of an implementing Regulation.

Article 4 - Committee for Orphan Medicinal Products

1. A Committee for Orphan Medicinal Products, hereinafter referred to as 'the Committee', is hereby set up within the Agency.
2. The task of the Committee shall be:

(a) to examine any application for the designation of a medicinal product as an orphan medicinal product which is submitted to it in accordance with this Regulation;
(b) to advise the Commission on the establishment and development of a policy on orphan medicinal products for the European Union;
(c) to assist the Commission in liaising internationally on matters relating to orphan medicinal products, and in liaising with patient support groups;
(d) to assist the Commission in drawing up detailed guidelines.

3. The Committee shall consist of one member nominated by each Member State, three members nominated by the Commission to represent patients' organisations and three members nominated by the Commission on the basis of a recommendation from the Agency. The members of the Committee shall be appointed for a term of three years, which shall be renewable. They may be accompanied by experts.
4. The Committee shall elect its Chairman for a term of three years, renewable once.
5. The representatives of the Commission and the Executive Director of the Agency or his representative may attend all meetings of the Committee.
6. The Agency shall provide the secretariat of the Committee.
7. Members of the Committee shall be required, even after their duties have ceased, not to disclose any information of the kind covered by the obligation of professional secrecy.

Article 5 - Procedure for designation and removal from the register

1. In order to obtain the designation of a medicinal product as an orphan medicinal product, the sponsor shall submit an application to the Agency at any stage of the development of the medicinal product before the application for marketing authorisation is made.
2. The application shall be accompanied by the following particulars and documents:
   (a) name or corporate name and permanent address of the sponsor;
   (b) active ingredients of the medicinal product;
   (c) proposed therapeutic indication;
   (d) justification that the criteria laid down in Article 3(1) are met and a description of the stage of development, including the indications expected.
3. The Commission shall, in consultation with the Member States, the Agency and interested parties, draw up detailed guidelines on the required format and content of applications for designation.
4. The Agency shall verify the validity of the application and prepare a summary report to the Committee. Where appropriate, it may request the sponsor to supplement the particulars and documents accompanying the application.
5. The Agency shall ensure that an opinion is given by the Committee within 90 days of the receipt of a valid application.
6. When preparing its opinion, the Committee shall use its best endeavours to reach a consensus. If such a consensus cannot be reached, the opinion shall be adopted by a majority of two-thirds of the members of the Committee. The opinion may be obtained by written procedure.
7. Where the opinion of the Committee is that the application does not satisfy the criteria set out in Article 3(1), the Agency shall forthwith inform the sponsor. Within 90 days of receipt of the opinion, the sponsor

may submit detailed grounds for appeal, which the Agency shall refer to the Committee. The Committee shall consider whether its opinion should be revised at the following meeting.

8. The Agency shall forthwith forward the final opinion of the Committee to the Commission, which shall adopt a decision within 30 days of receipt of the opinion. Where, in exceptional circumstances, the draft decision is not in accordance with the opinion of the Committee, the decision shall be adopted in accordance with the regulatory procedure referred to in Article 10a(2). The decision shall be notified to the sponsor and communicated to the Agency and to the competent authorities of the Member States.
9. The designated medicinal product shall be entered in the Community Register of Orphan Medicinal Products.
10. Each year the sponsor shall submit to the Agency a report on the state of development of the designated medicinal product.
11. To have the designation of an orphan medicinal product transferred to another sponsor, the holder of the designation shall make specific application to the Agency. In consultation with the Member States, the Agency and interested parties, the Commission shall draw up detailed guidelines on the form in which applications for transfer shall be made and the content of such applications and all the particulars of the new sponsor.
12. A designated orphan medicinal product shall be removed from the Community Register of Orphan Medicinal Products:
    (a) at the request of the sponsor;
    (b) if it is established before the market authorisation is granted that the criteria laid down in Article 3 are no longer met in respect of the medicinal product concerned;
    (c) at the end of the period of market exclusivity as laid down in Article 8.

Article 6 - Protocol assistance

1. The sponsor of an orphan medicinal product may, prior to the submission of an application for marketing authorisation. request advice from the Agency on the conduct of the various tests and trials necessary to demonstrate the quality, safety and efficacy of the medicinal product, in accordance with Article 51(j) of Regulation (EEC) No 2309/93.
2. The Agency shall draw up a procedure on the development of orphan medicinal products, covering regulatory assistance for the definition of the content of the application for authorisation within the meaning of Article 6 of Regulation (EEC) No 2309/93.

Article 7 - Community marketing authorisation

1. The person responsible for placing on the market an orphan medicinal product may request that authorisation to place the medicinal product on the market be granted by the Community in accordance with the provisions of Regulation (EEC) No 2309/93 without having to justify that the medicinal product qualifies under Part B of the Annex to that Regulation.
2. A special contribution from the Community, distinct from that provided for in Article 57 of Regulation (EEC) No 2309/93, shall be allocated every year to the Agency. The contribution shall be used exclusively by the Agency to waive, in part or in total, all the fees payable under Community rules adopted pursuant to

Regulation (EEC) No 2309/93. A detailed report of the use made of this special contribution shall be presented by the Executive Director of the Agency at the end of each year. Any surplus occurring in a given year shall be carried forward and deducted from the special contribution for the following year.

3. The marketing authorisation granted for an orphan medicinal product shall cover only those therapeutic indications which fulfill the criteria set out in Article 3. This is without prejudice to the possibility of applying for a separate marketing authorisation for other indications outside the scope of this Regulation.

Article 8 - Market exclusivity

1. Where a marketing authorisation in respect of an orphan medicinal product is granted pursuant to Regulation (EEC) No 2309/93 or where all the Member States have granted marketing authorisations in accordance with the procedures for mutual recognition laid down in Articles 7 and 7a of Directive 65/65/EEC or Article 9(4) of Council Directive 75/319/EEC of 20 May 1975 on the approximation of provisions laid down by law, regulation or administrative action relating to medicinal products, and without prejudice to intellectual property law or any other provision of Community law, the Community and the Member States shall not, for a period of 10 years, accept another application for a marketing authorisation, or grant a marketing authorisation or accept an application to extend an existing marketing authorisation, for the same therapeutic indication, in respect of a similar medicinal product.
2. This period may however be reduced to six years if, at the end of the fifth year, it is established, in respect of the medicinal product concerned, that the criteria laid down in Article 3 are no longer met, inter alia, where it is shown on the basis of available evidence that the product is sufficiently profitable not to justify maintenance of market exclusivity. To that end, a Member State shall inform the Agency that the criterion on the basis of which market exclusivity was granted may not be met and the Agency shall then initiate the procedure laid down in Article 5. The sponsor shall provide the Agency with the information necessary for that purpose.
3. By way of derogation from paragraph 1, and without prejudice to intellectual property law or any other provision of Community law, a marketing authorisation may be granted, for the same therapeutic indication, to a similar medicinal product if:
    (a) the holder of the marketing authorisation for the original orphan medicinal product has given his consent to the second applicant, or
    (b) the holder of the marketing authorisation for the original orphan medicinal product is unable to supply sufficient quantities of the medicinal product, or
    (c) the second applicant can establish in the application that the second medicinal product, although similar to the orphan medicinal product already authorised, is safer, more effective or otherwise clinically superior.
4. The Commission shall adopt definitions of 'similar medicinal product' and 'clinical superiority' in the form of an implementing Regulation.

    Those measures, designed to amend non-essential elements of this Regulation by supplementing it, shall be adopted in accordance with the regulatory procedure with scrutiny referred to in Article 10a(3).
5. The Commission shall draw up detailed guidelines for the application of this Article in consultation with the Member States, the Agency and interested parties.

Article 9 - Other incentives

1. Medicinal products designated as orphan medicinal products under the provisions of this Regulation shall be eligible for incentives made available by the Community and by the Member States to support research into, and the development and availability of, orphan medicinal products and in particular aid for research for small- and medium-sized undertakings provided for in framework programmes for research and technological development.
2. Before 22 July 2000, the Member States shall communicate to the Commission detailed information concerning any measure they have enacted to support research into, and the development and availability of, orphan medicinal products or medicinal products that may be designated as such. That information shall be updated regularly.
3. Before 22 January 2001, the Commission shall publish a detailed inventory of all incentives made available by the Community and the Member States to support research into, and the development and availability of, orphan medicinal products. That inventory shall be updated regularly.

Article 10 - General report

Before 22 January 2006, the Commission shall publish a general report on the experience acquired as a result of the application of this Regulation, together with an account of the public health benefits which have been obtained.

Article 10a

1. The Commission shall be assisted by the Standing Committee on Medicinal Products for Human Use, referred to in Article 121(1) of 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.
2. Where reference is made to this paragraph, Articles 5 and 7 of Council 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, Article 5a(1) to (4) and Article 7 of Decision 1999/468/EC shall apply, having regard to the provisions of Article 8 thereof.

Article 11 - Entry into force

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

It shall apply as from the date of adoption of the implementing Regulations provided for in Article 3(2) and Article 8(4).

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

Regulation (EC) No 1901/2006 - Paediatric use

REGULATION (EC) NO 1901/2006 OF THE EUROPEAN PARLIAMENT AND OF THE COUNCIL OF 12 DECEMBER 2006ON MEDICINAL PRODUCTS FOR PAEDIATRIC USE AND AMENDING REGULATION (EEC) NO 1768/92, DIRECTIVE 2001/20/EC, DIRECTIVE 2001/83/EC AND REGULATION (EC) NO 726/2004

(Text with EEA relevance)

THE EUROPEAN PARLIAMENT AND THE COUNCIL OF THE EUROPEAN UNION,

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

Having regard to the proposal from the Commission,

Having regard to the Opinion of the European Economic and Social Committee,

Having consulted the Committee of the Regions,

Acting in accordance with the procedure referred to in Article 251 of the Treaty,

Whereas:

1. Before a medicinal product for human use is placed on the market in one or more Member States, it generally has to have undergone extensive studies, including pre-clinical tests and clinical trials, to ensure that it is safe, of high quality and effective for use in the target population.
2. Such studies may not have been undertaken for use in the paediatric population and many of the medicinal products currently used to treat the paediatric population have not been studied or authorised for such use. Market forces alone have proven insufficient to stimulate adequate research into, and the development and authorisation of, medicinal products for the paediatric population.
3. Problems resulting from the absence of suitably adapted medicinal products for the paediatric population include inadequate dosage information which leads to increased risks of adverse reactions including death, ineffective treatment through under-dosage, non-availability to the paediatric population of therapeutic advances, suitable formulations and routes of administration, as well as use of magistral or officinal formulations to treat the paediatric population which may be of poor quality.
4. This Regulation aims to facilitate the development and accessibility of medicinal products for use in the paediatric population, to ensure that medicinal products used to treat the paediatric population are subject to ethical research of high quality and are appropriately authorised for use in the paediatric population, and to improve the information available on the use of medicinal products in the various paediatric populations.

   These objectives should be achieved without subjecting the paediatric population to unnecessary clinical trials and without delaying the authorisation of medicinal products for other age populations.
5. While taking into account the fact that the regulation of medicinal products must be fundamentally aimed at safeguarding public health, this aim must be achieved by means that do not impede the free movement of safe medicinal products within the Community. The differences between the national legislative, regulatory and administrative provisions on medicinal products tend to hinder intra-Community trade and therefore directly affect the operation of the internal market. Any action to promote the development and authorisation of

medicinal products for paediatric use is therefore justified with a view to preventing or eliminating these obstacles. Article 95 of the Treaty is therefore the proper legal basis.

6. The establishment of a system of both obligations and rewards and incentives has proved necessary to achieve these objectives. The precise nature of these obligations and rewards and incentives should take account of the status of the particular medicinal product concerned. This Regulation should apply to all the medicinal products required for paediatric use and therefore its scope should cover products under development and yet-to-be authorised, authorised products covered by intellectual property rights and authorised products no longer covered by intellectual property rights.
7. Any concerns about conducting trials in the paediatric population should be balanced by the ethical concerns about giving medicinal products to a population in which they have not been appropriately tested. Public health threats from the use of untested medicinal products in the paediatric population can be safely addressed through the study of medicinal products for the paediatric population, which should be carefully controlled and monitored through the specific requirements for the protection of the paediatric population who take part in clinical trials in the Community laid down in 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 use.
8. It is appropriate to create a scientific committee, the Paediatric Committee, within the European Medicines Agency, hereinafter 'the Agency', with expertise and competence in the development and assessment of all aspects of medicinal products to treat paediatric populations. The rules on scientific committees of the Agency, as laid down in Regulation (EC) No 726/2004, should apply to the Paediatric Committee. Members of the Paediatric Committee should therefore not have financial or other interests in the pharmaceutical industry which could affect their impartiality, should undertake to act in the public interest and in an independent manner, and should make an annual declaration of their financial interests. The Paediatric Committee should be primarily responsible for the scientific assessment and agreement of paediatric investigation plans and for the system of waivers and deferrals thereof; it should also be central to various support measures contained in this Regulation. In its work, the Paediatric Committee should consider the potential significant therapeutic benefits for the paediatric patients involved in the studies or the paediatric population at large including the need to avoid unnecessary studies. The Paediatric Committee should follow existing Community requirements, including Directive 2001/20/EC, as well as International Conference on Harmonisation (ICH) guideline E11 on the development of medicinal products for the paediatric population, and it should avoid any delay in the authorisation of medicinal products for other populations deriving from the requirements for studies in the paediatric population.
9. Procedures should be established for the Agency to agree and modify a paediatric investigation plan, which is the document upon which the development and authorisation of medicinal products for the paediatric population should be based. The paediatric investigation plan should include details of the timing and the measures proposed to demonstrate the quality, safety and efficacy of the medicinal product in the paediatric population. Since the paediatric population is in fact composed of a number of population subsets, the paediatric investigation plan should specify which population subsets need to be studied, by what means and by when.

10. The introduction of the paediatric investigation plan in the legal framework concerning medicinal products for human use aims at ensuring that the development of medicinal products that are potentially to be used for the paediatric population becomes an integral part of the development of medicinal products, integrated into the development programme for adults. Thus, paediatric investigation plans should be submitted early during product development, in time for studies to be conducted in the paediatric population, where appropriate, before marketing authorisation applications are submitted. It is appropriate to set a deadline for the submission of a paediatric investigation plan in order to ensure early dialogue between the sponsor and the Paediatric Committee. Furthermore, early submission of a paediatric investigation plan, combined with the submission of a deferral request as described below, will avoid delaying the authorisation for other populations. As the development of medicinal products is a dynamic process dependent on the result of ongoing studies, provision should be made for modifying an agreed plan where necessary.
11. It is necessary to introduce a requirement for new medicinal products and for authorised medicinal products covered by a patent or a supplementary protection certificate to present either the results of studies in the paediatric population in accordance with an agreed paediatric investigation plan or proof of having obtained a waiver or deferral, at the time of filing a marketing authorisation application or an application for a new indication, new pharmaceutical form or new route of administration. The paediatric investigation plan should be the basis upon which compliance with that requirement is judged. However, that requirement should not apply to generics or similar biological medicinal products and medicinal products authorised through the well-established medicinal use procedure, nor to homeopathic medicinal products and traditional herbal medicinal products authorised through the simplified registration procedures of 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.
12. Provision should be made for research into the paediatric use of medicinal products which are not protected by a patent or supplementary protection certificate to be financed under Community research programmes.
13. In order to ensure that research in the paediatric population is only conducted to meet their therapeutic needs, there is a need to establish procedures for the Agency to waive the requirement referred to in Recital (11) for specific products or for classes or part of classes of medicinal products, these waivers being then made public by the Agency. As knowledge of science and medicine evolves over time, provision should be made for the lists of waivers to be amended. However, if a waiver is revoked, that requirement should not apply for a given period in order to allow time for at least a paediatric investigation plan to be agreed and studies in the paediatric population to be initiated before an application for marketing authorisation is submitted.
14. In certain cases, the Agency should defer the initiation or completion of some or all of the measures contained in a paediatric investigation plan, with a view to ensuring that research is conducted only when safe and ethical and that the requirement for study data in the paediatric population does not block or delay the authorisation of medicinal products for other populations.
15. Free scientific advice should be provided by the Agency as an incentive to sponsors developing medicinal products for the paediatric population. To ensure scientific consistency, the Agency should manage the interface between the Paediatric Committee and the Scientific Advice Working Group of the Committee for Medicinal Products for Human Use, as well as the interaction between the Paediatric Committee and the other Community committees and working groups concerning medicinal products.

16. The existing procedures for the marketing authorisation of medicinal products for human use should not be changed. However, from the requirement referred to in Recital (11) it follows that competent authorities should check compliance with the agreed paediatric investigation plan and any waivers and deferrals at the existing validation step for marketing authorisation applications. The assessment of quality, safety and efficacy of medicinal products for the paediatric population and the granting of marketing authorisations should remain the remit of the competent authorities. Provision should be made for the Paediatric Committee to be asked for its opinion on compliance and on the quality, safety and efficacy of a medicinal product in the paediatric population.
17. To provide healthcare professionals and patients with information on the safe and effective use of medicinal products in the paediatric population and as a transparency measure, information on the results of studies in the paediatric population, as well as on the status of the paediatric investigation plans, waivers and deferrals, should be included in product information. When all the measures in the paediatric investigation plan have been complied with, that fact should be recorded in the marketing authorisation, and should then be the basis upon which companies can obtain the rewards for compliance.
18. In order to identify medicinal products authorised for use in the paediatric population and enable their prescription, provision should be made for the labels of medicinal products granted an indication for use in the paediatric population to display a symbol which will be selected by the Commission on a recommendation by the Paediatric Committee.
19. In order to establish incentives for authorised products no longer covered by intellectual property rights, it is necessary to establish a new type of marketing authorisation, the Paediatric Use Marketing Authorisation. A Paediatric Use Marketing Authorisation should be granted through existing marketing authorisation procedures but should apply specifically for medicinal products developed exclusively for use in the paediatric population. It should be possible for the name of the medicinal product that has been granted a Paediatric Use Marketing Authorisation to retain the existing brand name of the corresponding product authorised for adults, in order to capitalise on existing brand recognition, while benefiting from the data exclusivity associated with a new marketing authorisation.
20. An application for a Paediatric Use Marketing Authorisation should include the submission of data concerning use of the product in the paediatric population, collected in accordance with an agreed paediatric investigation plan. These data may be derived from the published literature or from new studies. An application for a Paediatric Use Marketing Authorisation should also be able to refer to data contained in the dossier of a medicinal product which is or has been authorised in the Community. This is intended to provide an additional incentive to encourage small and medium-sized enterprises, including generic companies, to develop off-patent medicinal products for the paediatric population.
21. This Regulation should include measures to maximise access by the Community population to new medicinal products tested and adapted for paediatric use, and to minimise the chance of Community-wide rewards and incentives being granted without sections of the Community paediatric population benefiting from the availability of a newly authorised medicine. An application for a marketing authorisation, including an application for a Paediatric Use Marketing Authorisation, which contains the results of studies conducted in compliance with an agreed paediatric investigation plan should be eligible for the Community centralised procedure set out in Articles 5 to 15 of Regulation (EC) No 726/2004.

22. When an agreed paediatric investigation plan has led to the authorisation of a paediatric indication for a product already marketed for other indications, the marketing authorisation holder should be obliged to place the product on the market, taking into account the paediatric information, within two years of the date of approval of the indication. That requirement should relate only to products already authorised, but not to medicinal products authorised via a Paediatric Use Marketing Authorisation.
23. An optional procedure should be established to make it possible to obtain a single Community-wide opinion for a nationally authorised medicinal product when data on the paediatric population following an agreed paediatric investigation plan form part of the marketing authorisation application. To achieve this, the procedure set out in Articles 32, 33 and 34 of Directive 2001/83/EC could be used. This will allow the adoption of a Community harmonised Decision on use of that medicinal product in the paediatric population and its inclusion in all national product information.
24. It is essential to ensure that pharmacovigilance mechanisms are adapted to meet the specific challenges of collecting safety data in the paediatric population, including data on possible long-term effects. Efficacy in the paediatric population may also need additional study following authorisation. Therefore, an additional requirement for applying for a marketing authorisation that includes the results of studies conducted in compliance with an agreed paediatric investigation plan should be an obligation for the applicant to indicate how he proposes to ensure the long-term follow-up of possible adverse reactions to the use of the medicinal product and efficacy in the paediatric population. Additionally, where there is a particular cause for concern, the applicant should submit and implement a risk management system and/or perform specific post-marketing studies as a condition for the granting of the marketing authorization
25. It is necessary in the interests of public health to ensure the continuing availability of safe and effective medicinal products authorised for paediatric indications developed as a result of this Regulation. If a marketing authorisation holder intends to withdraw such a medicinal product from the market then arrangements should be in place so that the paediatric population can continue to have access to the medicinal product in question. In order to help achieve this, the Agency should be informed in good time of any such intention and should make that intention public.
26. For products falling within the scope of the requirement to submit paediatric data, if all the measures included in the agreed paediatric investigation plan are complied with, if the product is authorised in all Member States and if relevant information on the results of studies is included in product information, a reward should be granted in the form of a 6-month extension of the supplementary protection certificate created by Council Regulation (EEC) No 1768/92. Any decisions by Member States' authorities as regards the setting of prices for medicinal products or their inclusion in the scope of national health insurance schemes have no bearing on the granting of this reward.
27. An application for an extension of the duration of the certificate pursuant to this Regulation should only be admissible where a certificate is granted pursuant to Regulation (EEC) No 1768/92.
28. Because the reward is for conducting studies in the paediatric population and not for demonstrating that a product is safe and effective in the paediatric population, the reward should be granted even when a paediatric indication is not authorised. However, to improve the information available on the use of medicinal products in the paediatric population, relevant information on use in paediatric populations should be included in authorised product information.

29. Under Regulation (EC) No 141/2000 of the European Parliament and of the Council of 16 December 1999 on orphan medicinal products, medicinal products designated as orphan medicinal products gain ten years of market exclusivity on the granting of a marketing authorisation for the orphan indication. As such products are frequently not patent-protected, the reward of supplementary protection certificate extension cannot be applied; when they are patent-protected, such an extension would provide a double incentive. Therefore, for orphan medicinal products, instead of an extension of the supplementary protection certificate, the ten-year period of orphan market exclusivity should be extended to twelve years if the requirement for data on use in the paediatric population is fully met.
30. The measures provided for in this Regulation should not preclude the operation of other incentives or rewards. To ensure transparency on the different measures available at Community and Member State levels, the Commission should draw up a detailed list of all the incentives available, on the basis of information provided by the Member States. The measures set out in this Regulation, including the agreement of paediatric investigation plans, should not be grounds for obtaining any other Community incentives to support research, such as the funding of research projects under the multi-annual Community Framework Programmes for Research, Technological Development and Demonstration Activities.
31. In order to increase the availability of information on the use of medicinal products in the paediatric population, and to avoid unnecessary repetition of studies in the paediatric population which do not add to the collective knowledge, the European database provided for in Article 11 of Directive 2001/20/EC should include a European register of clinical trials of medicinal products for paediatric use comprising all ongoing, prematurely terminated, and completed paediatric studies conducted both in the Community and in third countries. Part of the information concerning paediatric clinical trials entered into the database, as well as details of the results of all paediatric clinical trials submitted to the competent authorities, should be made public by the Agency.
32. An inventory of the therapeutic needs of the paediatric population should be established by the Paediatric Committee after consultation with the Commission, the Member States and interested parties, and should be regularly updated. The inventory should identify the existing medicinal products used by the paediatric population and highlight the therapeutic needs of that population and the priorities for research and development. In this way, companies should be able easily to identify opportunities for business development; the Paediatric Committee should be able better to judge the need for medicinal products and studies when assessing draft paediatric investigation plans, waivers and deferrals; and healthcare professionals and patients should have an information source available to support their decisions as to which medicinal products to choose.
33. Clinical trials in the paediatric population may require specific expertise, specific methodology and, in some cases, specific facilities and should be carried out by appropriately trained investigators. A network, which links existing national and Community initiatives and study centres in order to build up the necessary competences at Community level, and which takes account of Community and third country data, would help facilitate cooperation and avoid unnecessary duplication of studies. This network should contribute to the work of strengthening the foundations of the European Research Area in the context of Community Framework Programmes for Research, Technological Development and Demonstration Activities, benefit the paediatric population and provide a source of information and expertise for industry.

34. For certain authorised products, pharmaceutical companies may already hold data on safety or efficacy in the paediatric population. To improve the information available on the use of medicinal products in the paediatric populations, companies holding such data should be required to submit them to all competent authorities where the product is authorised. In this way the data could be assessed and, if appropriate, information should be included in the authorised product information aimed at healthcare professionals and patients.
35. Community funding should be provided to cover all aspects of the work of the Paediatric Committee and of the Agency resulting from the implementation of this Regulation, such as the assessment of paediatric investigation plans, fee waivers for scientific advice, and information and transparency measures, including the database of paediatric studies and the network.
36. The measures necessary for the implementation of this Regulation 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 Commission.
37. Regulation (EEC) No 1768/92, Directive 2001/20/EC, Directive 2001/83/EC and Regulation (EC) No 726/2004 should therefore be amended accordingly.
38. Since the objective of this Regulation, namely improving availability of medicinal products tested for paediatric use, cannot be sufficiently achieved by the Member States and can therefore be better achieved at Community level, given that this will make it possible to take advantage of the widest possible market and avoid the dispersion of limited resources, the Community may adopt measures, in accordance with the principle of subsidiarity as set out in Article 5 of the Treaty. In accordance with the principle of proportionality, as set out in that Article, this Regulation does not go beyond what is necessary in order to achieve this objective,

HAVE ADOPTED THIS REGULATION :

TITLE I - INTRODUCTORY PROVISIONS

CHAPTER 1 - Subject matter and definitions

Article 1

This Regulation lays down rules concerning the development of medicinal products for human use in order to meet the specific therapeutic needs of the paediatric population, without subjecting the paediatric population to unnecessary clinical or other trials and in compliance with Directive 2001/20/EC.

Article 2

In addition to the definitions laid down in Article 1 of Directive 2001/83/EC, the following definitions shall apply for the purposes of this Regulation:

1) 'paediatric population' means that part of the population aged between birth and 18 years;
2) 'paediatric investigation plan' means a research and development programme aimed at ensuring that the necessary data are generated determining the conditions in which a medicinal product may be authorised to treat the paediatric population;

3) ‘medicinal product authorised for a paediatric indication’ means a medicinal product which is authorised for use in part or all of the paediatric population and in respect of which the details of the authorised indication are specified in the summary of the product characteristics drawn up in accordance with Article 11 of Directive 2001/83/EC;
4) ‘paediatric use marketing authorisation’ means a marketing authorisation granted in respect of a medicinal product for human use which is not protected by a supplementary protection certificate under Regulation (EEC) No 1768/92 or by a patent which qualifies for the granting of the supplementary protection certificate, covering exclusively therapeutic indications which are relevant for use in the paediatric population, or subsets thereof, including the appropriate strength, pharmaceutical form or route of administration for that product.

CHAPTER 2 - Paediatric committee

Article 3

1. By 26 July 2007, a Paediatric Committee shall be established within the European Medicines Agency set up under Regulation (EC) No 726/2004, hereinafter ‘the Agency’. The Paediatric Committee shall be considered as established once the members referred to in Article 4(1)(a) and (b) have been appointed.
   The Agency shall fulfill the secretariat functions for the Paediatric Committee and shall provide it with technical and scientific support.
2. Save where otherwise provided for in this Regulation, Regulation (EC) No 726/2004 shall apply to the Paediatric Committee, including the provisions on the independence and impartiality of its members.
3. The Executive Director of the Agency shall ensure appropriate coordination between the Paediatric Committee and the Committee for Medicinal Products for Human Use, the Committee for Orphan Medicinal Products, their working parties and any other scientific advisory groups.
   The Agency shall draw up specific procedures for possible consultations between them.

Article 4

1. The Paediatric Committee shall be composed of the following members:
   (a) five members, with their alternates, of the Committee for Medicinal Products for Human Use, having been appointed to that Committee in accordance with Article 61(1) of Regulation (EC) No 726/2004. These five members with their alternates shall be appointed to the Paediatric Committee by the Committee for Medicinal Products for Human Use;
   (b) one member and one alternate appointed by each Member State whose national competent authority is not represented through the members appointed by the Committee for Medicinal Products for Human Use;
   (c) three members and three alternates appointed by the Commission, on the basis of a public call for expressions of interest, after consulting the European Parliament, in order to represent health professionals;

(d) three members and three alternates appointed by the Commission, on the basis of a public call for expressions of interest, after consulting the European Parliament, in order to represent patient associations.

The alternates shall represent and vote for the members in their absence.

For the purposes of points (a) and (b), Member States shall cooperate, under the coordination of the Executive Director of the Agency, in order to ensure that the final composition of the Paediatric Committee, including members and alternates, covers the scientific areas relevant to paediatric medicinal products, and including at least: pharmaceutical development, paediatric medicine, general practitioners, paediatric pharmacy, paediatric pharmacology, paediatric research, pharmacovigilance, ethics and public health.

For the purposes of points (c) and (d), the Commission shall take into account the expertise provided by the members appointed under points (a) and (b).

2. The members of the Paediatric Committee shall be appointed for a renewable period of three years. At meetings of the Paediatric Committee, they may be accompanied by experts.
3. The Paediatric Committee shall elect its Chairman from among its members for a term of three years, renewable once.
4. The names and qualifications of the members shall be made public by the Agency.

Article 5

1. When preparing its opinions, the Paediatric Committee shall use its best endeavours to reach a scientific consensus. If such a consensus cannot be reached, the Paediatric Committee shall adopt an opinion consisting of the position of the majority of the members. The opinion shall mention the divergent positions, with the grounds on which they are based. This opinion shall be made accessible to the public pursuant to Article 25(5) and (7).
2. The Paediatric Committee shall draw up its rules of procedure for the implementation of its tasks. The rules of procedure shall enter into force after receiving a favourable opinion from the Management Board of the Agency and, subsequently, from the Commission.
3. All meetings of the Paediatric Committee may be attended by representatives of the Commission, the Executive Director of the Agency or his representatives.

Article 6

1. The tasks of the Paediatric Committee shall include the following:
   (a) to assess the content of any paediatric investigation plan for a medicinal product submitted to it in accordance with this Regulation and formulate an opinion thereon;
   (b) to assess waivers and deferrals and formulate an opinion thereon;
   (c) at the request of the Committee for Medicinal Products for Human Use, a competent authority or the applicant, to assess compliance of the application for a Marketing Authorisation with the agreed paediatric investigation plan concerned and formulate an opinion thereon;
   (d) at the request of the Committee for Medicinal Products for Human Use or a competent authority, to assess any data generated in accordance with an agreed paediatric investigation plan and

formulate an opinion on the quality, safety or efficacy of the medicinal product for use in the paediatric population;

(e) to advise on the content and format of data to be collected for the survey referred to in Article 42;

(f) to support and advise the Agency on establishing the European network referred to in Article 44;

(g) to assist scientifically in the elaboration of any documents related to the fulfillment of the objectives of this Regulation;

(h) to provide advice on any question related to medicinal products for use in the paediatric population, at the request of the Executive Director of the Agency or the Commission;

(i) to establish a specific inventory of paediatric medicinal product needs and update it on a regular basis, as referred to in Article 43;

(j) to advise the Agency and the Commission regarding the communication of arrangements available for conducting research into medicinal products for use in the paediatric population;

(k) to make a recommendation to the Commission on the symbol referred to in Article 32(2).

2. When carrying out its tasks, the Paediatric Committee shall consider whether or not any proposed studies can be expected to be of significant therapeutic benefit to and/or fulfill a therapeutic need of the paediatric population. The Paediatric Committee shall take into account any information available to it, including any opinions, decisions or advice given by the competent authorities of third countries.

TITLE II - MARKETING AUTHORISATION REQUIREMENTS

CHAPTER 1 - General authorisation requirements

Article 7

1. An application for marketing authorisation under Article 6 of Directive 2001/83/EC in respect of a medicinal product for human use which is not authorised in the Community at the time of entry into force of this Regulation shall be regarded as valid only if it includes, in addition to the particulars and documents referred to in Article 8(3) of Directive 2001/83/EC, one of the following:

   (a) the results of all studies performed and details of all information collected in compliance with an agreed paediatric investigation plan;

   (b) a decision of the Agency granting a product-specific waiver;

   (c) a decision of the Agency granting a class waiver pursuant to Article 11;

   (d) a decision of the Agency granting a deferral.

   For the purposes of point (a), the decision of the Agency agreeing the paediatric investigation plan concerned shall also be included in the application.

2. The documents submitted pursuant to paragraph 1 shall, cumulatively, cover all subsets of the paediatric population.

Article 8

In the case of authorised medicinal products which are protected either by a supplementary protection certificate under Regulation (EEC) No 1768/92, or by a patent which qualifies for the granting of the supplementary protection certificate, Article 7 of this Regulation shall apply to applications for authorisation of new indications, including paediatric indications, new pharmaceutical forms and new routes of administration.

For the purposes of the first subparagraph, the documents referred to in Article 7(1) shall cover both the existing and the new indications, pharmaceutical forms and routes of administration.

Article 9

Articles 7 and 8 shall not apply to products authorised under Articles 10, 10a, 13 to 16 or 16a to 16i of Directive 2001/83/EC.

Article 10

In consultation with the Member States, the Agency and other interested parties, the Commission shall draw up the detailed arrangements concerning the format and content which applications for agreement or modification of a paediatric investigation plan and requests for waivers or deferrals must follow in order to be considered valid and concerning the operation of the compliance check referred to in Articles 23 and 28(3).

CHAPTER 2 - Waivers

Article 11

1. Production of the information referred to in point (a) of Article 7(1) shall be waived for specific medicinal products or for classes of medicinal products, if there is evidence showing any of the following:
    (a) that the specific medicinal product or class of medicinal products is likely to be ineffective or unsafe in part or all of the paediatric population;
    (b) that the disease or condition for which the specific medicinal product or class is intended occurs only in adult populations;
    (c) that the specific medicinal product does not represent a significant therapeutic benefit over existing treatments for paediatric patients.
2. The waiver provided for in paragraph 1 may be issued with reference either to one or more specified subsets of the paediatric population, or to one or more specified therapeutic indications, or to a combination of both.

Article 12

The Paediatric Committee may of its own motion adopt an opinion, on the grounds set out in Article 11(1), to the effect that a class or a product-specific waiver, as referred to in Article 11(1), should be granted.

As soon as the Paediatric Committee adopts an opinion, the procedure laid down in Article 25 shall apply. In the case of a class waiver, only paragraphs 6 and 7 of Article 25 shall apply.

Article 13

1. The applicant may, on the grounds set out in Article 11(1), apply to the Agency for a product-specific waiver.
2. Following receipt of the application, the Paediatric Committee shall appoint a rapporteur and shall within 60 days adopt an opinion as to whether or not a product-specific waiver should be granted.
   Either the applicant or the Paediatric Committee may request a meeting during that 60-day period.
   Whenever appropriate, the Paediatric Committee may request the applicant to supplement the particulars and documents submitted. Where the Paediatric Committee avails itself of this option, the 60-day time-limit shall be suspended until such time as the supplementary information requested has been provided.
3. As soon as the Paediatric Committee adopts an opinion, the procedure laid down in Article 25 shall apply.

Article 14

1. The Agency shall maintain a list of all waivers. The list shall be regularly updated (at least every year) and made available to the public.
2. The Paediatric Committee may, at any time, adopt an opinion advocating the review of a granted waiver.
   In the case of a change affecting a product-specific waiver, the procedure laid down in Article 25 shall apply.
   In the case of a change affecting a class waiver, paragraphs 6 and 7 of Article 25 shall apply.
3. If a particular product-specific or class waiver is revoked, the requirement set out in Articles 7 and 8 shall not apply for 36 months from the date of the removal from the list of waivers.

CHAPTER 3 - Paediatric investigation plan

Section 1 - Requests for agreement

Article 15

1. Where the intention is to apply for a marketing authorisation in accordance with Article 7(1)(a) or (d), Article 8 or Article 30, a paediatric investigation plan shall be drawn up and submitted to the Agency with a request for agreement.
2. The paediatric investigation plan shall specify the timing and the measures proposed to assess the quality, safety and efficacy of the medicinal product in all subsets of the paediatric population that may be concerned. In addition, it shall describe any measures to adapt the formulation of the medicinal product so as to make its use more acceptable, easier, safer or more effective for different subsets of the paediatric population.

Article 16

1. In the case of the applications for marketing authorisation referred to in Articles 7 and 8 or the applications for waiver referred to in Articles 11 and 12, the paediatric investigation plan or the application for waiver shall be submitted with a request for agreement, except in duly justified cases, not later than upon completion of the human pharmaco-kinetic studies in adults specified in Section 5.2.3 of Part I of Annex I to Directive 2001/83/EC, so as to ensure that an opinion on use in the paediatric population of the

medicinal product concerned can be given at the time of the assessment of the marketing authorisation or other application concerned.

2. Within 30 days following receipt of the request referred to in paragraph 1 and in Article 15(1), the Agency shall verify the validity of the request and prepare a summary report for the Paediatric Committee.
3. Whenever appropriate, the Agency may ask the applicant to submit additional particulars and documents, in which case the time-limit of 30 days shall be suspended until such time as the supplementary information requested has been provided.

Article 17

1. Following receipt of a proposed paediatric investigation plan which is valid in accordance with the provisions of Article 15(2), the Paediatric Committee shall appoint a rapporteur and shall within 60 days adopt an opinion as to whether or not the proposed studies will ensure the generation of the necessary data determining the conditions in which the medicinal product may be used to treat the paediatric population or subsets thereof, and as to whether or not the expected therapeutic benefits justify the studies proposed. When adopting its opinion, the Committee shall consider whether or not the measures proposed to adapt the formulation of the medicinal product for use in different subsets of the paediatric population are appropriate.

   Within the same period, either the applicant or the Paediatric Committee may request a meeting.
2. Within the 60-day period referred to in paragraph 1, the Paediatric Committee may request the applicant to propose modifications to the plan, in which case the time-limit referred to in paragraph 1 for the adoption of the final opinion shall be extended for a maximum of 60 days. In such cases, the applicant or the Paediatric Committee may request an additional meeting during this period. The time-limit shall be suspended until such time as the supplementary information requested has been provided.

Article 18

As soon as the Paediatric Committee adopts an opinion, whether positive or negative, the procedure laid down in Article 25 shall apply.

Article 19

If, having considered a paediatric investigation plan, the Paediatric Committee concludes that Article 11(1)(a), (b) or (c) applies to the medicinal product concerned, it shall adopt a negative opinion under Article 17(1).

In such cases, the Paediatric Committee shall adopt an opinion in favour of a waiver under Article 12, whereupon the procedure laid down in Article 25 shall apply.

Section 2 - Deferrals

Article 20

1. At the same time as the paediatric investigation plan is submitted under Article 16(1), a request may be made for deferral of the initiation or completion of some or all of the measures set out in that plan. Such

deferral shall be justified on scientific and technical grounds or on grounds related to public health.

In any event, a deferral shall be granted when it is appropriate to conduct studies in adults prior to initiating studies in the paediatric population or when studies in the paediatric population will take longer to conduct than studies in adults.

2. On the basis of the experience acquired as a result of the operation of this Article, the Commission may adopt provisions, in accordance with the regulatory procedure with scrutiny referred to in Article 51(2), amending or supplementing non-essential elements of this Regulation to define further the grounds for granting a deferral.

Article 21

1. At the same time as the Paediatric Committee adopts a positive opinion under Article 17(1), it shall, of its own motion or following a request submitted by the applicant under Article 20, adopt an opinion, if the conditions specified in Article 20 are met, in favour of deferring the initiation or completion of some or all of the measures in the paediatric investigation plan.

   An opinion in favour of a deferral shall specify the time-limits for initiating or completing the measures concerned.

2. As soon as the Paediatric Committee adopts an opinion in favour of deferral, as referred to in paragraph 1, the procedure laid down in Article 25 shall apply.

Section 3 - Modification of a paediatric investigation plan

Article 22

If, following the decision agreeing the paediatric investigation plan, the applicant encounters such difficulties with its implementation as to render the plan unworkable or no longer appropriate, the applicant may propose changes or request a deferral or a waiver, based on detailed grounds, to the Paediatric Committee. Within 60 days, the Paediatric Committee shall review these changes or the request for a deferral or a waiver and adopt an opinion proposing their refusal or acceptance. As soon as the Paediatric Committee adopts an opinion, whether positive or negative, the procedure laid down in Article 25 shall apply.

Section 4 - Compliance with the paediatric investigation plan

Article 23

1. The competent authority responsible for granting marketing authorisation shall verify whether an application for marketing authorisation or variation complies with the requirements laid down in Articles 7 and 8 and whether an application submitted pursuant to Article 30 complies with the agreed paediatric investigation plan.

   Where the application is submitted in accordance with the procedure set out in Articles 27 to 39 of Directive 2001/83/EC, the verification of compliance, including, as appropriate, requesting an opinion of the Paediatric Committee in accordance with paragraph 2(b) and (c) of this Article, shall be conducted by the reference Member State.

2. The Paediatric Committee may, in the following cases, be requested to give its opinion as to whether studies conducted by the applicant are in compliance with the agreed paediatric investigation plan:
    (a) by the applicant, prior to submitting an application for marketing authorisation or variation as referred to in Articles 7, 8 and 30, respectively;
    (b) by the Agency, or the national competent authority, when validating an application, as referred to in point (a), which does not include an opinion concerning compliance adopted following a request under point (a);
    (c) by the Committee for Medicinal Products for Human Use, or the national competent authority, when assessing an application, as referred to in point (a), where there is doubt concerning compliance and an opinion has not been already given following a request under points (a) or (b).
    In the case of point (a), the applicant shall not submit its application until the Paediatric Committee has adopted its opinion, and a copy thereof shall be annexed to the application.
3. If the Paediatric Committee is requested to give an opinion under paragraph 2, it shall do so within 60 days of receiving the request.
    Member States shall take account of such an opinion.

Article 24

If, when conducting the scientific assessment of a valid application for Marketing Authorisation, the competent authority concludes that the studies are not in conformity with the agreed paediatric investigation plan, the product shall not be eligible for the rewards and incentives provided for in Articles 36, 37 and 38.

CHAPTER 4 - Procedure

Article 25

1. Within ten days of its receipt, the Agency shall transmit the opinion of the Paediatric Committee to the applicant.
2. Within 30 days following receipt of the opinion of the Paediatric Committee, the applicant may submit to the Agency a written request, citing detailed grounds, for a re-examination of the opinion.
3. Within 30 days following receipt of a request for re-examination pursuant to paragraph 2, the Paediatric Committee, having appointed a new rapporteur, shall issue a new opinion confirming or revising its previous opinion. The rapporteur shall be able to question the applicant directly. The applicant may also offer to be questioned. The rapporteur shall inform the Paediatric Committee without delay in writing about details of contacts with the applicant. The opinion shall be duly reasoned and a statement of reasons for the conclusion reached shall be annexed to the new opinion, which shall become definitive.
4. If, within the 30-day period referred to in paragraph 2, the applicant does not request re-examination, the opinion of the Paediatric Committee shall become definitive.
5. The Agency shall adopt a decision within a period not exceeding 10 days following receipt of the Paediatric Committee's definitive opinion. This decision shall be communicated to the applicant in writing and shall annex the definitive opinion of the Paediatric Committee.

6. In the case of a class waiver as referred to in Article 12, the Agency shall adopt a decision within ten days following receipt of the opinion of the Paediatric Committee as referred to in Article 13(3). This decision shall annex the opinion of the Paediatric Committee.
7. Decisions of the Agency shall be made public after deletion of any information of a commercially confidential nature.

CHAPTER 5 - Miscellaneous provisions

Article 26

Any legal or natural person developing a medicinal product intended for paediatric use may, prior to the submission of a paediatric investigation plan and during its implementation, request advice from the Agency on the design and conduct of the various tests and studies necessary to demonstrate the quality, safety and efficacy of the medicinal product in the paediatric population in accordance with Article 57(1)(n) of Regulation (EC) No 726/2004.

In addition, this legal or natural person may request advice on the design and conduct of pharmacovigilance and risk management systems as referred to in Article 34.

The Agency shall provide advice under this Article free of charge.

TITLE III - MARKETING AUTHORISATION PROCEDURES

Article 27

Save where otherwise provided in this Title, marketing authorisation procedures for the marketing authorisations covered by this Title shall be governed by the provisions laid down in Regulation (EC) No 726/2004 or in Directive 2001/83/EC.

CHAPTER 1 - Marketing authorisation procedures for applications falling within the scope of Articles 7 and 8

Article 28

1. Applications may be submitted in accordance with the procedure laid down in Articles 5 to 15 of Regulation (EC) No 726/2004 for a marketing authorisation as referred to in Article 7(1) of this Regulation which includes one or more paediatric indications on the basis of studies conducted in compliance with an agreed paediatric investigation plan.

   Where authorisation is granted, the results of all those studies shall be included in the summary of product characteristics and, if appropriate, in the package leaflet of the medicinal product, provided that the competent authority deems the information to be of use to patients, whether or not all the paediatric indications concerned were approved by the competent authority.

2. Where a marketing authorisation is granted or varied, any waiver or deferral which has been granted pursuant to this Regulation shall be recorded in the summary of product characteristics and, if appropriate, in the package leaflet of the medicinal product concerned.
3. If the application complies with all the measures contained in the agreed completed paediatric investigation plan and if the summary of product characteristics reflects the results of studies conducted in compliance with that agreed paediatric investigation plan, the competent authority shall include within the marketing authorisation a statement indicating compliance of the application with the agreed completed paediatric investigation plan. For the purpose of the application of Article 45(3), this statement shall also indicate whether significant studies contained in the agreed Paediatric Investigation Plan have been completed after the entry into force of this Regulation.

Article 29

In the case of medicinal products authorised under Directive 2001/83/EC, an application as referred to in Article 8 of this Regulation may be submitted, in accordance with the procedure laid down in Articles 32, 33 and 34 of Directive 2001/83/EC, for authorisation of a new indication, including the extension of an authorisation for use in the paediatric population, a new pharmaceutical form or a new route of administration. That application shall comply with the requirement laid down in point (a) of Article 7(1).

The procedure shall be limited to the assessment of the specific sections of the summary of product characteristics to be varied.

CHAPTER 2 - Paediatric use marketing authorisation

Article 30

1. Submission of an application for a paediatric use marketing authorisation shall in no way preclude the right to apply for a marketing authorisation for other indications.
2. An application for a paediatric use marketing authorisation shall be accompanied by the particulars and documents necessary to establish quality, safety and efficacy in the paediatric population, including any specific data needed to support an appropriate strength, pharmaceutical form or route of administration for the product, in accordance with an agreed paediatric investigation plan.

   The application shall also include the decision of the Agency agreeing the paediatric investigation plan concerned.
3. Where a medicinal product is or has been authorised in a Member State or in the Community, data contained in the dossier on that product may, where appropriate, be referred to, in accordance with Article 14(11) of Regulation (EC) No 726/2004 or Article 10 of Directive 2001/83/EC, in an application for a paediatric use marketing authorisation.
4. The medicinal product in respect of which a paediatric use marketing authorisation is granted may retain the name of any medicinal product which contains the same active substance and in respect of which the same holder has been granted authorisation for use in adults.

Article 31

Without prejudice to Article 3(2) of Regulation (EC) No 726/2004, an application for a paediatric use marketing authorisation may be made in accordance with the procedure laid down in Articles 5 to 15 of Regulation (EC) No 726/2004.

CHAPTER 3 - Identification

Article 32

1. Where a medicinal product is granted a marketing authorisation for a paediatric indication, the label shall display the symbol agreed in accordance with paragraph 2. The package leaflet shall contain an explanation of the meaning of the symbol.
2. By 26 January 2008, the Commission shall select a symbol following a recommendation of the Paediatric Committee. The Commission shall make the symbol public.
3. The provisions of this Article shall also apply to medicinal products authorised before the entry into force of this Regulation, and to medicinal products authorised after the entry into force of this Regulation but before the symbol has been made public, if they are authorised for paediatric indications.
   In this case, the symbol and the explanation referred to in paragraph 1 shall be included in the labelling and package leaflet respectively of the medicinal products concerned not later than two years after the symbol has been made public.

TITLE IV - POST-AUTHORISATION REQUIREMENTS

Article 33

Where medicinal products are authorised for a paediatric indication following completion of an agreed paediatric investigation plan and those products have already been marketed with other indications, the marketing authorisation holder shall, within two years of the date on which the paediatric indication is authorised, place the product on the market taking into account the paediatric indication. A register, coordinated by the Agency, and made publicly available, shall mention these deadlines.

Article 34

1. In the following cases, the applicant shall detail the measures to ensure the follow-up of efficacy and of possible adverse reactions to the paediatric use of the medicinal product:
   (a) applications for a marketing authorisation that includes a paediatric indication;
   (b) applications to include a paediatric indication in an existing marketing authorisation;
   (c) applications for a paediatric use marketing authorisation.
2. Where there is particular cause for concern, the competent authority shall require, as a condition for granting marketing authorisation, that a risk management system be set up or that specific post-marketing studies be performed and submitted for review. The risk management system shall comprise a set of pharmacovigilance activities and interventions designed to identify, characterise, prevent or minimise risks relating to medicinal products, including the assessment of the effectiveness of those

interventions.

Assessment of the effectiveness of any risk management system and the results of any studies performed shall be included in the periodic safety update reports referred to in Article 104(6) of Directive 2001/83/EC and Article 24(3) of Regulation (EC) No 726/2004.

In addition, the competent authority may request submission of additional reports assessing the effectiveness of any risk minimisation system and the results of any such studies performed.

3. In addition to paragraphs 1 and 2, the provisions on pharmacovigilance as laid down in Regulation (EC) No 726/2004 and in Directive 2001/83/EC shall apply to marketing authorisations for medicinal products which include a paediatric indication.
4. In the case of a deferral, the marketing authorisation holder shall submit an annual report to the Agency providing an update on progress with paediatric studies in accordance with the decision of the Agency agreeing the paediatric investigation plan and granting a deferral.

   The Agency shall inform the competent authority if it is found that the marketing authorisation holder has failed to comply with the decision of the Agency agreeing the paediatric investigation plan and granting a deferral.
5. The Agency shall draw up guidelines relating to the application of this Article.

Article 35

If a medicinal product is authorised for a paediatric indication and the marketing authorisation holder has benefited from rewards or incentives under Article 36, 37 or 38, and these periods of protection have expired, and if the marketing authorisation holder intends to discontinue placing the medicinal product on the market, the marketing authorisation holder shall transfer the marketing authorisation or allow a third party, which has declared its intention to continue to place the medicinal product in question on the market, to use the pharmaceutical, pre-clinical and clinical documentation contained in the file of the medicinal product on the basis of Article 10c of Directive 2001/83/EC.

The marketing authorisation holder shall inform the Agency of its intention to discontinue the placing on the market of the product no less than six months before the discontinuation. The Agency shall make this fact public.

TITLE V - REWARDS AND INCENTIVES

Article 36

1. Where an application under Article 7 or 8 includes the results of all studies conducted in compliance with an agreed paediatric investigation plan, the holder of the patent or supplementary protection certificate shall be entitled to a six-month extension of the period referred to in Articles 13(1) and 13(2) of Regulation (EEC) No 1768/92.

   The first subparagraph shall also apply where completion of the agreed paediatric investigation plan fails to lead to the authorisation of a paediatric indication, but the results of the studies conducted are

reflected in the summary of product characteristics and, if appropriate, in the package leaflet of the medicinal product concerned.

2. The inclusion in a marketing authorisation of the statement referred to in Article 28(3) shall be used for the purposes of applying paragraph 1 of this Article.
3. Where the procedures laid down in Directive 2001/83/EC have been used, the six-month extension of the period referred to in paragraph 1 shall be granted only if the product is authorised in all Member States.
4. Paragraphs 1, 2 and 3 shall apply to products that are protected by a supplementary protection certificate under Regulation (EEC) No 1768/92, or under a patent which qualifies for the granting of the supplementary protection certificate. They shall not apply to medicinal products designated as orphan medicinal products pursuant to Regulation (EC) No 141/2000.
5. In the case of an application under Article 8 which leads to the authorisation of a new paediatric indication, paragraphs 1, 2 and 3 shall not apply if the applicant applies for, and obtains, a one-year extension of the period of marketing protection for the medicinal product concerned, on the grounds that this new paediatric indication brings a significant clinical benefit in comparison with existing therapies, in accordance with Article 14(11) of Regulation (EC) No 726/2004 or the fourth subparagraph of Article 10(1) of Directive 2001/83/EC.

Article 37

Where an application for a marketing authorisation is submitted in respect of a medicinal product designated as an orphan medicinal product pursuant to Regulation (EC) No 141/2000 and that application includes the results of all studies conducted in compliance with an agreed paediatric investigation plan, and the statement referred to in Article 28(3) of this Regulation is subsequently included in the marketing authorisation granted, the ten-year period referred to in Article 8(1) of Regulation (EC) No 141/2000 shall be extended to twelve years.

The first paragraph shall also apply where completion of the agreed paediatric investigation plan fails to lead to the authorisation of a paediatric indication, but the results of the studies conducted are reflected in the summary of product characteristics and, if appropriate, in the package leaflet of the medicinal product concerned.

Article 38

1. Where a paediatric use marketing authorisation is granted in accordance with Articles 5 to 15 of Regulation (EC) No 726/2004, the data and marketing protection periods referred to in Article 14(11) of that Regulation shall apply.
2. Where a paediatric use marketing authorisation is granted in accordance with the procedures laid down in Directive 2001/83/EC, the data and marketing protection periods referred to in Article 10(1) of that Directive shall apply.

Article 39

1. In addition to the rewards and incentives provided for in Articles 36, 37 and 38, medicinal products for paediatric use may be eligible for incentives provided by the Community or by the Member States to support research into, and the development and availability of, medicinal products for paediatric use.
2. By 26 January 2008, the Member States shall communicate to the Commission detailed information concerning any measures they have enacted to support research into, and the development and availability of, medicinal products for paediatric use. This information shall be updated regularly at the request of the Commission.
3. By 26 July 2008, the Commission shall make publicly available a detailed inventory of all rewards and incentives provided by the Community and Member States to support research into, and the development and availability of, medicinal products for paediatric use. This inventory shall be updated regularly and the updates shall also be made publicly available.

Article 40

1. Funds for research into medicinal products for the paediatric population shall be provided for in the Community budget in order to support studies relating to medicinal products or active substances not covered by a patent or a supplementary protection certificate.
2. The Community funding referred to in paragraph 1 shall be delivered through the Community Framework Programmes for Research, Technological Development and Demonstration Activities or any other Community initiatives for the funding of research.

TITLE VI - COMMUNICATION AND COORDINATION

Article 41

1. The European database created by Article 11 of Directive 2001/20/EC shall include clinical trials carried out in third countries which are contained in an agreed paediatric investigation plan, in addition to the clinical trials referred to in Articles 1 and 2 of that Directive. In the case of such clinical trials carried out in third countries, the details listed in Article 11 of that Directive shall be entered into the database by the addressee of the Agency's decision on a paediatric investigation plan.

   By way of derogation from the provisions of Article 11 of Directive 2001/20/EC, the Agency shall make public part of the information on paediatric clinical trials entered in the European database.
2. Details of the results of all the trials referred to in paragraph 1 and of any other trials submitted to competent authorities in compliance with Articles 45 and 46 shall be made public by the Agency, whether or not the trial was terminated prematurely. These results shall be submitted without delay to the Agency by the clinical trial sponsor, the addressee of the Agency's decision on a paediatric investigation plan, or by the marketing authorisation holder as appropriate.
3. In consultation with the Agency, Member States and interested parties, the Commission shall draw up guidance on the nature of the information referred to in paragraph 1 to be entered in the European database created by Article 11 of Directive 2001/20/EC, on which information shall be made accessible to

the public in application of paragraph 1, on how clinical trial results shall be submitted and be made public in application of paragraph 2, and on the Agency's responsibilities and tasks in this regard.

Article 42

Member States shall collect available data on all existing uses of medicinal products in the paediatric population and shall communicate these data to the Agency by 26 January 2009.

The Paediatric Committee shall provide guidance on the content and the format of the data to be collected by 26 October 2007.

Article 43

1. On the basis of the information referred to in Article 42 and after consulting the Commission, the Member States and the interested parties, the Paediatric Committee shall establish an inventory of therapeutic needs,

   in particular with a view to identifying research priorities.

   The Agency shall make the inventory public at the earliest by 26 January 2009 and at the latest by 26 January 2010 and shall update it regularly.
2. In establishing the inventory of therapeutic needs, account shall be taken of the prevalence of the conditions in the paediatric population, the seriousness of the conditions to be treated, the availability and suitability of alternative treatments for the conditions in the paediatric population, including the efficacy and the adverse reaction profile of those treatments, including any unique paediatric safety issues, and any data resulting from studies in third countries.

Article 44

1. The Agency shall, with the scientific support of the Paediatric Committee, develop a European network of existing national and European networks, investigators and centres with specific expertise in the performance of studies in the paediatric population.
2. The objectives of the European network shall be, inter alia, to coordinate studies relating to paediatric medicinal products, to build up the necessary scientific and administrative competences at European level, and to avoid unnecessary duplication of studies and testing in the paediatric population.
3. By 26 January 2008, the Management Board of the Agency shall, on a proposal from the Executive Director and following consultation with the Commission, the Member States and interested parties, adopt an implementing strategy for the launching and operation of the European network. This network must, where appropriate, be compatible with the work of strengthening the foundations of the European Research Area in the context of the Community Framework Programmes for Research, Technological Development and Demonstration Activities.

Article 45

1. By 26 January 2008, any paediatric studies already completed, by the date of entry into force, in respect of products authorised in the Community shall be submitted by the marketing authorisation holder for assessment to the competent authority.

The competent authority may update the summary of product characteristics and package leaflet, and may vary the marketing authorisation accordingly. Competent authorities shall exchange information regarding the studies submitted and, as appropriate, their implications for any marketing authorisations concerned.

The Agency shall coordinate the exchange of information.

2. All existing paediatric studies, as referred to in paragraph 1, and all paediatric studies initiated prior to the entry into force of this Regulation shall be eligible to be included in a paediatric investigation plan, and shall be taken into consideration by the Paediatric Committee when assessing applications for paediatric investigation plans, waivers and deferrals and by competent authorities when assessing applications submitted pursuant to Article 7, 8 or 30.
3. Without prejudice to the previous paragraph, the rewards and incentives of Articles 36, 37 and 38 shall only be granted provided that significant studies contained in an agreed Paediatric Investigation Plan are completed after the entry into force of this Regulation.
4. In consultation with the Agency, the Commission shall draw up guidelines to establish assessment criteria for the significance of studies for the purposes of applying paragraph 3.

Article 46

1. Any other marketing authorisation holder-sponsored studies which involve the use in the paediatric population of a medicinal product covered by a marketing authorisation, whether or not they are conducted in compliance with an agreed paediatric investigation plan, shall be submitted to the competent authority within six months of completion of the studies concerned.
2. Paragraph 1 shall apply independent of whether or not the marketing authorisation holder intends to apply for a marketing authorisation of a paediatric indication.
3. The competent authority may update the summary of product characteristics and package leaflet, and may vary the marketing authorisation accordingly.
4. Competent authorities shall exchange information regarding the studies submitted and, as appropriate, their implications for any marketing authorisations concerned.
5. The Agency shall coordinate the exchange of information.

TITLE VII - GENERAL AND FINAL PROVISIONS

CHAPTER 1 - General provisions

Section 1 - Fees, community funding, penalties and reports

Article 47

1. Where an application for a paediatric use marketing authorisation is submitted in accordance with the procedure laid down in Regulation (EC) No 726/2004, the amount of the reduced fees for the examination

of the application and the maintenance of the marketing authorisation shall be fixed in accordance with Article 70 of Regulation (EC) No 726/2004.

2. Council Regulation (EC) No 297/95 of 10 February 1995 on fees payable to the European Medicines Agency shall apply.
3. Assessments of the following by the Paediatric Committee shall be free of charge:
    (a) applications for waiver;
    (b) applications for deferral;
    (c) paediatric investigation plans;
    (d) compliance with the agreed paediatric investigation plan.

Article 48

The Community contribution provided for in Article 67 of Regulation (EC) No 726/2004 shall cover the work of the Paediatric Committee, including scientific support provided by experts, and of the Agency, including the assessment of paediatric investigation plans, scientific advice and any fee waivers provided for in this Regulation, and shall support the Agency's activities under Articles 41 and 44 of this Regulation.

Article 49

1. Without prejudice to the Protocol on the Privileges and Immunities of the European Communities, each Member State shall determine the penalties to be applied for infringement of the provisions of this Regulation or the implementing measures adopted pursuant to it in relation to medicinal products authorised through the procedures laid down in Directive 2001/83/EC and shall take all measures necessary for their implementation.
    The penalties shall be effective, proportionate and dissuasive.
    Member States shall inform the Commission of these provisions by 26 October 2007. They shall notify any subsequent alterations as soon as possible.
2. Member States shall inform the Commission immediately of any litigation instituted for infringement of this Regulation.
3. At the Agency's request, the Commission may impose financial penalties for infringement of the provisions of this Regulation or the implementing measures adopted pursuant to it in relation to medicinal products authorised through the procedure laid down in Regulation (EC) No 726/2004. Measures amending or supplementing non-essential elements of this Regulation concerning the maximum amounts as well as the conditions and methods for collection of those penalties shall be adopted in accordance with the regulatory procedure with scrutiny referred to in Article 51(2).
4. The Commission shall make public the names of anyone infringing the provisions of this Regulation or of any implementing measures adopted pursuant to it and the amounts of, and reasons for, the financial penalties imposed.

Article 50

1. On the basis of a report from the Agency, and at least on an annual basis, the Commission shall make public a list of the companies and of the products that have benefited from any of the rewards and

incentives in this Regulation and the companies that have failed to comply with any of the obligations in this Regulation.

The Member States shall provide this information to the Agency.

2. By 26 January 2013, the Commission shall present to the European Parliament and the Council a general report on experience acquired as a result of the application of this Regulation. This shall include in particular a detailed inventory of all medicinal products authorised for paediatric use since its entry into force.
3. By 26 January 2017, the Commission shall present a report to the European Parliament and the Council on the experience acquired as a result of the application of Articles 36, 37 and 38. The report shall include an analysis of the economic impact of the rewards and incentives, together with an analysis of the estimated consequences for public health of this Regulation, with a view to proposing any necessary amendments.
4. Provided that there are sufficient data available to allow robust analyses to be made, the provisions of paragraph 3 shall be fulfillled at the same time as the provisions of paragraph 2.

Section 2 - Standing committee

Article 51

1. The Commission shall be assisted by the Standing Committee on Medicinal Products for Human Use set up by Article 121 of Directive 2001/83/EC, hereinafter referred to as 'the Committee'.
2. Where reference is made to this paragraph, Article 5a(1) to (4) and Article 7 of Decision 1999/468/EC shall apply, having regard to the provisions of Article 8 thereof.
3. The Committee shall adopt its rules of procedure.

CHAPTER 2 - Amendments

Article 52

Regulation (EEC) No 1768/92 is hereby amended as follows:

1) in Article 1, the following definition shall be added:

'(e)"Application for an extension of the duration" means an application for an extension of the duration of the certificate pursuant to Article 13(3) of this Regulation and of Article 36 of Regulation (EC) No 1901/2006 of the European Parliament and of the Council of 12 December 2006 on medicinal products for paediatric use.'»

2) in Article 7, the following paragraphs shall be added:

'3. The application for an extension of the duration may be made when lodging the application for a certificate or when the application for the certificate is pending and the appropriate requirements of Articles 8(1)(d) or 8(1a), respectively, are fulfillled.

4. The application for an extension of the duration of a certificate already granted shall be lodged not later than two years before the expiry of the certificate.

5. Notwithstanding paragraph 4, for five years following the entry into force of Regulation (EC) No

1901/2006, the application for an extension of the duration of a certificate already granted shall be lodged not later than six months before the expiry of the certificate.';»

3) Article 8 shall be amended as follows:

(a) in paragraph 1, the following point shall be added:

'(d) where the application for a certificate includes a request for an extension of the duration:

(i) a copy of the statement indicating compliance with an agreed completed paediatric investigation plan as referred to in Article 36(1) of Regulation (EC) No 1901/2006;

(ii) where necessary, in addition to the copy of the authorisations to place the product on the market as referred to in point (b), proof that it has authorisations to place the product on the market of all other Member States, as referred to in Article 36(3) of Regulation (EC) No 1901/2006.';»

(b) the following paragraphs shall be inserted:

'1a. Where an application for a certificate is pending, an application for an extended duration in accordance with Article 7(3) shall include the particulars referred to in paragraph 1(d) and a reference to the application for a certificate already filed.

1b. The application for an extension of the duration of a certificate already granted shall contain the particulars referred to in paragraph 1(d) and a copy of the certificate already granted.';»

(c) paragraph 2 shall be replaced by the following:

'2. Member States may provide that a fee is to be payable upon application for a certificate and upon application for the extension of the duration of a certificate.';»

4) Article 9 shall be amended as follows:

(a) in paragraph 1, the following subparagraph shall be added:

'The application for an extension of the duration of a certificate shall be lodged with the competent authority of the Member State concerned.';»

(b) in paragraph 2, the following point shall be added:

'(f) where applicable, an indication that the application includes an application for an extension of the duration.';»

(c) the following paragraph shall be added:

'3. Paragraph 2 shall apply to the notification of the application for an extension of the duration of a certificate already granted or where an application for a certificate is pending. The notification shall additionally contain an indication of the application for an extended duration of the certificate.';»

5) in Article 10, the following paragraph shall be added:

'6. Paragraphs 1 to 4 shall apply mutatis mutandis to the application for an extension of the duration.';»

6) in Article 11, the following paragraph shall be added:

'3. Paragraphs 1 and 2 shall apply to the notification of the fact that an extension of the duration of a certificate has been granted or of the fact that the application for an extension has been rejected.';»

7) in Article 13, the following paragraph shall be added:

'3. The periods laid down in paragraphs 1 and 2 shall be extended by six months in the case where Article 36 of Regulation (EC) No 1901/2006 applies. In that case, the duration of the period laid down in paragraph 1 of this Article may be extended only once.';»

8) the following Article shall be inserted:

'Article 15a

Revocation of an extension of the duration

1. The extension of the duration may be revoked if it was granted contrary to the provisions of Article 36 of Regulation (EC) No 1901/2006.

2. Any person may submit an application for revocation of the extension of the duration to the body responsible under national law for the revocation of the corresponding basic patent.';»

9) Article 16 shall be amended as follows:

(a) the text of Article 16 becomes that Article's paragraph 1;

(b) the following paragraph shall be added:

'2. If the extension of the duration is revoked in accordance with Article 15a, notification thereof shall be published by the authority referred to in Article 9(1).';»

10) Article 17 shall be replaced by the following:

'Article 17

Appeals

The decisions of the authority referred to in Article 9(1) or of the bodies referred to in Articles 15(2) and 15a(2) taken under this Regulation shall be open to the same appeals as those provided for in national law against similar decisions taken in respect of national patents.'.»

Article 53

In Article 11 of Directive 2001/20/EC, the following paragraph shall be added:

'4. By way of derogation from paragraph 1, the Agency shall make public part of the information on paediatric clinical trials entered in the European database in accordance with the provisions of Regulation (EC) No 1901/2006 of the European Parliament and of the Council of 12 December 2006 on medicinal products for paediatric use.'»

Article 54

In Article 6 of Directive 2001/83/EC, the first subparagraph of paragraph 1 shall be replaced by the following:

'1. No medicinal product may be placed on the market of a Member State unless a marketing authorisation has been issued by the competent authorities of that Member State in accordance with this Directive or unless an authorisation has been granted in accordance with Regulation (EC) No 726/2004, read in conjunction with Regulation (EC) No 1901/2006 of the European Parliament and of the Council of 12 December 2006 on medicinal products for paediatric use.'»

Article 55

Regulation (EC) No 726/2004 is hereby amended as follows:

1) Article 56(1) shall be replaced by the following:

'1. The Agency shall comprise:

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

(b) the Committee for Medicinal Products for Veterinary Use, which shall be responsible for preparing the opinion of the Agency on any question relating to the evaluation of medicinal products for veterinary use;

(c) the Committee on Orphan Medicinal Products;

(d) the Committee on Herbal Medicinal Products;

(e) the Paediatric Committee;

(f) a Secretariat, which shall provide technical, scientific and administrative support for the committees and ensure appropriate coordination between them;

(g) an Executive Director, who shall exercise the responsibilities set out in Article 64;

(h) a Management Board, which shall exercise the responsibilities set out in Articles 65, 66 and 67.';»

2) in Article 57(1), the following point shall be added:

'(t) taking decisions as referred to in Article 7(1) of Regulation (EC) No 1901/2006 of the European Parliament and of the Council of 12 December 2006 on medicinal products for paediatric use.'»

3) the following Article shall be inserted:

'Article 73a

Decisions taken by the Agency under Regulation (EC) No 1901/2006 may form the subject of an action before the Court of Justice of the European Communities under the conditions laid down in Article 230 of the Treaty.'.»

CHAPTER 3 - Final provisions

Article 56

The requirement laid down in Article 7(1) shall not apply to valid applications pending at the time of entry into force of this Regulation.

Article 57

1. This Regulation shall enter into force on the thirtieth day following that of its publication in the Official Journal of the European Union.
2. Article 7 shall apply from 26 July 2008.

   Article 8 shall apply from 26 January 2009.

   Articles 30 and 31 shall apply from 26 July 2007.

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

Regulation (EC) No 1394/2007 - Advanced Therapies

REGULATION (EC) NO 1394/2007 OF THE EUROPEAN PARLIAMENT AND OF THE COUNCIL OF 13 NOVEMBER 2007ON ADVANCED THERAPY MEDICINAL PRODUCTS AND AMENDING DIRECTIVE 2001/83/EC AND REGULATION (EC) NO 726/2004

(Text with EEA relevance)

THE EUROPEAN PARLIAMENT AND THE COUNCIL OF THE EUROPEAN UNION,

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

Having regard to the proposal from the Commission,

Having regard to the Opinion of the European Economic and Social Committee,

After consulting the Committee of the Regions,

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

Whereas:

(1) New scientific progress in cellular and molecular biotechnology has led to the development of advanced therapies, such as gene therapy, somatic cell therapy, and tissue engineering. This nascent field of biomedicine offers new opportunities for the treatment of diseases and dysfunctions of the human body.

(2) Insofar as advanced therapy products are presented as having properties for treating or preventing diseases in human beings, or that they may be used in or administered to human beings with a view to restoring, correcting or modifying physiological functions by exerting principally a pharmacological, immunological or metabolic action, they are biological medicinal products within the meaning of Annex I to 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, read in conjunction with the definition of medicinal products in Article 1(2) thereof. Thus, the essential aim of any rules governing their production, distribution and use must be to safeguard public health.

(3) For reasons of clarity, complex therapeutic products require precise legal definitions. Gene therapy medicinal products and somatic cell therapy medicinal products have been defined in Annex I to Directive 2001/83/EC, but a legal definition of tissue engineered products remains to be laid down. When products are based on viable cells or tissues, the pharmacological, immunological or metabolic action should be considered as the principal mode of action. It should also be clarified that products which do not meet the definition of a medicinal product, such as products made exclusively of non-viable materials which act primarily by physical means, cannot by definition be advanced therapy medicinal products.

(4) According to Directive 2001/83/EC and the Medical Device Directives the basis for deciding which regulatory regime is applicable to combinations of medicinal products and medical devices is the principal mode of action of the combination product. However, the complexity of combined advanced therapy medicinal products containing viable cells or tissues requires a specific approach. For these products, whatever the role of the medical device, the pharmacological, immunological or metabolic action of these cells or tissues should be

considered to be the principal mode of action of the combination product. Such combination products should always be regulated under this Regulation.

(5) Because of the novelty, complexity and technical specificity of advanced therapy medicinal products, specially tailored and harmonised rules are needed to ensure the free movement of those products within the Community, and the effective operation of the internal market in the biotechnology sector.

(6) This Regulation is a lex specialis, which introduces additional provisions to those laid down in Directive 2001/83/EC. The scope of this Regulation should be to regulate advanced therapy medicinal products which are intended to be placed on the market in Member States and either prepared industrially or manufactured by a method involving an industrial process, in accordance with the general scope of the Community pharmaceutical legislation laid down in Title II of Directive 2001/83/EC. Advanced therapy medicinal products which are prepared on a non-routine basis according to specific quality standards, and used within the same Member State in a hospital under the exclusive professional responsibility of a medical practitioner, in order to comply with an individual medical prescription for a custom-made product for an individual patient, should be excluded from the scope of this Regulation whilst at the same time ensuring that relevant Community rules related to quality and safety are not undermined.

(7) The regulation of advanced therapy medicinal products at Community level should not interfere with decisions made by Member States on whether to allow the use of any specific type of human cells, such as embryonic stem cells, or animal cells. It should also not affect the application of national legislation prohibiting or restricting the sale, supply or use of medicinal products containing, consisting of or derived from these cells.

(8) This Regulation respects the fundamental rights and observes the principles reflected in the Charter of Fundamental Rights of the European Union and also takes into account the Council of Europe Convention for the Protection of Human Rights and Dignity of the Human Being with regard to the Application of Biology and Medicine: Convention on Human Rights and Biomedicine.

(9) All other modern biotechnology medicinal products currently regulated at Community level are already subject to a centralised authorisation procedure, involving a single scientific evaluation of the quality, safety and efficacy of the product, which is carried out to the highest possible standard by the European Medicines Agency as established by Regulation (EC) No 726/2004 of the European Parliament and of the Council of 31 March 2004 laying down Community procedures for the authorisation and supervision of medicinal products for human and veterinary use (hereinafter referred to as the Agency). This procedure should also be compulsory for advanced therapy medicinal products in order to overcome the scarcity of expertise in the Community, ensure a high level of scientific evaluation of these medicinal products in the Community, preserve the confidence of patients and medical professions in the evaluation and facilitate Community market access for these innovative technologies.

(10) The evaluation of advanced therapy medicinal products often requires very specific expertise, which goes beyond the traditional pharmaceutical field and covers areas bordering on other sectors such as biotechnology and medical devices. For this reason, it is appropriate to create, within the Agency, a Committee for Advanced Therapies, which should be responsible for preparing a draft opinion on the quality, safety and efficacy of each advanced therapy medicinal product for final approval by the Agency's Committee for Medicinal Products for Human Use. In addition, the Committee for Advanced Therapies should be consulted for the evaluation of any other medicinal product which requires specific expertise falling within its area of competence.

(11) The Committee for Advanced Therapies should gather the best available expertise on advanced therapy medicinal products in the Community. The composition of the Committee for Advanced Therapies should ensure appropriate coverage of the scientific areas relevant to advanced therapies, including gene therapy, cell therapy, tissue engineering, medical devices, pharmacovigilance and ethics. Patient associations and clinicians with scientific experience of advanced therapy medicinal products should also be represented.

(12) To ensure scientific consistency and the efficiency of the system, the Agency should ensure the coordination between the Committee for Advanced Therapies and its other Committees, advisory groups and working parties, notably the Committee for Medicinal Products for Human Use, the Committee on Orphan Medicinal Products, and the Scientific Advice Working Party.

(13) Advanced therapy medicinal products should be subject to the same regulatory principles as other types of biotechnology medicinal products. However, technical requirements, in particular the type and amount of quality, pre-clinical and clinical data necessary to demonstrate the quality, safety and efficacy of the product, may be highly specific. While those requirements are already laid down in Annex I to Directive 2001/83/EC for gene therapy medicinal products and somatic cell therapy medicinal products, they need to be established for tissue engineered products. This should be done through a procedure that provides for sufficient flexibility, so as to easily accommodate the rapid evolution of science and technology.

(14) Directive 2004/23/EC of the European Parliament and of the Council sets standards of quality and safety for the donation, procurement, testing, processing, preservation, storage and distribution of human tissues and cells. This Regulation should not derogate from the basic principles laid down in Directive 2004/23/EC, but should supplement them with additional requirements, where appropriate. Where an advanced therapy medicinal product contains human cells or tissues, Directive 2004/23/EC should apply only as far as donation, procurement and testing are concerned, since the further aspects are covered by this Regulation.

(15) As regards the donation of human cells or tissues, principles such as the anonymity of both donor and recipient, altruism of the donor and solidarity between donor and recipient should be respected. As a matter of principle, human cells or tissues contained in advanced therapy medicinal products should be procured from voluntary and unpaid donation. Member States should be urged to take all necessary steps to encourage a strong public and non-profit sector involvement in the procurement of human cells or tissues, as voluntary and unpaid cell and tissue donations may contribute to high safety standards for cells and tissues and therefore to the protection of human health.

(16) Clinical trials on advanced therapy medicinal products should be conducted in accordance with the overarching principles and the ethical requirements laid down in 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 use. However, Commission Directive 2005/28/EC of 8 April 2005 laying down principles and detailed guidelines for good clinical practice as regards investigational medicinal products for human use, as well as the requirements for authorisation of the manufacturing or importation of such products should be adapted by laying down rules tailored to fully take into account the specific technical characteristics of advanced therapy medicinal products.

(17) The manufacture of advanced therapy medicinal products should be in compliance with the principles of good manufacturing practice, as set out in Commission Directive 2003/94/EC of 8 October 2003 laying down the

principles and guidelines of good manufacturing practice in respect of medicinal products for human use and investigational medicinal products for human use, and adapted, where necessary, to reflect the specific nature of those products. Furthermore, guidelines specific to advanced therapy medicinal products should be drawn up, so as to properly reflect the particular nature of their manufacturing process.

(18) Advanced therapy medicinal products may incorporate medical devices or active implantable medical devices. Those devices should meet the essential requirements laid down in Council Directive 93/42/EEC of 14 June 1993 concerning medical devices and Council Directive 90/385/EEC of 20 June 1990 on the approximation of the laws of the Member States relating to active implantable medical devices, respectively, in order to ensure an appropriate level of quality and safety. The results of the assessment of the medical device part or the active implantable medical device part by a notified body in accordance with those Directives should be recognised by the Agency in the evaluation of a combined advanced therapy medicinal product carried out under this Regulation.

(19) The requirements in Directive 2001/83/EC as regards the summary of product characteristics, labelling and the package leaflet should be adapted to the technical specificities of advanced therapy medicinal products by laying down specific rules on those products. These rules should comply fully with the patient's right to know the origin of any cells or tissues used in the preparation of advanced therapy medicinal products, while respecting donor anonymity.

(20) Follow-up of efficacy and adverse reactions is a crucial aspect of the regulation of advanced therapy medicinal products. The applicant should therefore detail in its marketing authorisation application whether measures are envisaged to ensure such follow-up and, if so, what those measures are. Where justified on public health grounds, the holder of the marketing authorisation should also be required to put in place a suitable risk management system to address risks related to advanced therapy medicinal products.

(21) The operation of this Regulation requires the establishment of guidelines to be drawn up either by the Agency or by the Commission. Open consultation with all interested parties, in particular Member State authorities and the industry, should be carried out in order to allow a pooling of the limited expertise in this area and ensure proportionality. The guidelines on good clinical practice and good manufacturing practice should be laid down as soon as possible, preferably during the first year after entry into force and before the date of application of this Regulation.

(22) A system allowing complete traceability of the patient as well as of the product and its starting materials is essential to monitor the safety of advanced therapy medicinal products. The establishment and maintenance of that system should be done in such a way as to ensure coherence and compatibility with traceability requirements laid down in Directive 2004/23/EC in respect of human tissues and cells, and in 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. The traceability system should also respect the provisions laid down in Directive 95/46/EC of the European Parliament and of the Council of 24 October 1995 on the protection of individuals with regard to the processing of personal data and the free movement of such data.

(23) As science evolves very rapidly in this field, undertakings developing advanced therapy medicinal products should be enabled to request scientific advice from the Agency, including advice on post-authorisation

activities. As an incentive, the fee for that scientific advice should be kept at a minimal level for small and medium-sized enterprises, and should also be reduced for other applicants.

(24) The Agency should be empowered to give scientific recommendations on whether a given product based on genes, cells or tissues meets the scientific criteria which define advanced therapy medicinal products, in order to address, as early as possible, questions of borderline with other areas such as cosmetics or medical devices, which may arise as science develops. The Committee for Advanced Therapies, with its unique expertise, should have a prominent role in the provision of such advice.

(25) Studies necessary to demonstrate the quality and non-clinical safety of advanced therapy medicinal products are often carried out by small and medium-sized enterprises. As an incentive to conduct those studies, a system of evaluation and certification of the resulting data by the Agency, independently of any marketing authorisation application, should be introduced. Even though the certification would not be legally binding, this system should also aim at facilitating the evaluation of any future application for clinical trials and marketing authorisation application based on the same data.

(26) In order to take into account scientific and technical developments, the Commission should be empowered to adopt any necessary changes regarding the technical requirements for applications for marketing authorisation of advanced therapy medicinal products, the summary of product characteristics, labelling, and the package leaflet. The Commission should ensure that relevant information on envisaged measures is made available to interested parties without delay.

(27) Provisions should be laid down to report on the implementation of this Regulation after experience has been gained, with a particular attention to the different types of advanced therapy medicinal products authorised.

(28) The opinions of the Scientific Committee for Medicinal Products and Medical Devices concerning tissue engineering and that of the European Group on Ethics in Science and New Technologies have been taken into account, as well as international experience in this field.

(29) The measures necessary for the implementation of this Regulation 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 Commission.

(30) In particular, the Commission should be empowered to adopt amendments to Annexes I to IV to this Regulation and to Annex I to Directive 2001/83/EC. Since those measures are of general scope and are designed to amend non-essential elements of this Regulation and of Directive 2001/83/EC, they must be adopted in accordance with the regulatory procedure with scrutiny provided for in Article 5a of Decision 1999/468/EC. Those measures are essential for the proper operation of the whole regulatory framework and should therefore be adopted as soon as possible.

(31) Directive 2001/83/EC and Regulation (EC) No 726/2004 should therefore be amended accordingly,

HAVE ADOPTED THIS REGULATION:

CHAPTER 1- SUBJECT MATTER AND DEFINITIONS

Article 1 - Subject matter

This Regulation lays down specific rules concerning the authorisation, supervision and pharmacovigilance of advanced therapy medicinal products.

Article 2 - Definitions

1. In addition to the definitions laid down in Article 1 of Directive 2001/83/EC and in Article 3, points (a) to (l) and (o) to (q) of Directive 2004/23/EC, the following definitions shall apply for the purposes of this Regulation:
    (a) 'Advanced therapy medicinal product' means any of the following medicinal products for human use:
    a gene therapy medicinal product as defined in Part IV of Annex I to Directive 2001/83/EC,
    a somatic cell therapy medicinal product as defined in Part IV of Annex I to Directive 2001/83/EC,
    a tissue engineered product as defined in point (b).
    (b) 'Tissue engineered product' means a product that:
    contains or consists of engineered cells or tissues, and
    is presented as having properties for, or is used in or administered to human beings with a view to regenerating, repairing or replacing a human tissue.
        - A tissue engineered product may contain cells or tissues of human or animal origin, or both. The cells or tissues may be viable or non-viable. It may also contain additional substances, such as cellular products, bio-molecules, bio-materials, chemical substances, scaffolds or matrices.
        - Products containing or consisting exclusively of non-viable human or animal cells and/or tissues, which do not contain any viable cells or tissues and which do not act principally by pharmacological, immunological or metabolic action, shall be excluded from this definition.
    (c) Cells or tissues shall be considered 'engineered' if they fulfill at least one of the following conditions:
        - the cells or tissues have been subject to substantial manipulation, so that biological characteristics, physiological functions or structural properties relevant for the intended regeneration, repair or replacement are achieved. The manipulations listed in Annex I, in particular, shall not be considered as substantial manipulations,
        - the cells or tissues are not intended to be used for the same essential function or functions in the recipient as in the donor.
    (d) 'Combined advanced therapy medicinal product' means an advanced therapy medicinal product that fulfills the following conditions:
        - it must incorporate, as an integral part of the product, one or more medical devices within the meaning of Article 1(2)(a) of Directive 93/42/EEC or one or more active implantable medical devices within the meaning of Article 1(2)(c) of Directive 90/385/EEC, and
        - its cellular or tissue part must contain viable cells or tissues, or

- its cellular or tissue part containing non-viable cells or tissues must be liable to act upon the human body with action that can be considered as primary to that of the devices referred to.

2. Where a product contains viable cells or tissues, the pharmacological, immunological or metabolic action of those cells or tissues shall be considered as the principal mode of action of the product.
3. An advanced therapy medicinal product containing both autologous (emanating from the patient himself) and allogeneic (coming from another human being) cells or tissues shall be considered to be for allogeneic use.
4. A product which may fall within the definition of a tissue engineered product and within the definition of a somatic cell therapy medicinal product shall be considered as a tissue engineered product.
5. A product which may fall within the definition of:
   - a somatic cell therapy medicinal product or a tissue engineered product, and
   - a gene therapy medicinal product,

shall be considered as a gene therapy medicinal product.

CHAPTER 2 - MARKETING AUTHORISATION REQUIREMENTS

Article 3 - Donation, procurement and testing

Where an advanced therapy medicinal product contains human cells or tissues, the donation, procurement and testing of those cells or tissues shall be made in accordance with Directive 2004/23/EC.

Article 4 - Clinical trials

1. The rules set out in Article 6(7) and Article 9(4) and (6) of Directive 2001/20/EC in respect of gene therapy and somatic cell therapy medicinal products shall apply to tissue engineered products.
2. The Commission shall, after consulting the Agency, draw up detailed guidelines on good clinical practice specific to advanced therapy medicinal products.

Article 5 - Good manufacturing practice

The Commission shall, after consulting the Agency, draw up guidelines in line with the principles of good manufacturing practice and specific to advanced therapy medicinal products.

Article 6 - Issues specific to medical devices

1. A medical device which forms part of a combined advanced therapy medicinal product shall meet the essential requirements laid down in Annex I to Directive 93/42/EEC.
2. An active implantable medical device which forms part of a combined advanced therapy medicinal product shall meet the essential requirements laid down in Annex 1 to Directive 90/385/EEC.

Article 7 - Specific requirements for advanced therapy medicinal products containing devices

In addition to the requirements laid down in Article 6(1) of Regulation (EC) No 726/2004, applications for the authorisation of an advanced therapy medicinal product containing medical devices, bio-materials, scaffolds or

matrices shall include a description of the physical characteristics and performance of the product and a description of the product design methods, in accordance with Annex I to Directive 2001/83/EC.

CHAPTER 3 - MARKETING AUTHORISATION PROCEDURE

Article 8 - Evaluation procedure

1. The Committee for Medicinal Products for Human Use shall consult the Committee for Advanced Therapies on any scientific assessment of advanced therapy medicinal products necessary to draw up the scientific opinions referred to in Article 5(2) and (3) of Regulation (EC) No 726/2004. The Committee for Advanced Therapies shall also be consulted in the event of re-examination of the opinion pursuant to Article 9(2) of Regulation (EC) No 726/2004.
2. When preparing a draft opinion for final approval by the Committee for Medicinal Products for Human Use, the Committee for Advanced Therapies shall endeavour to reach a scientific consensus. If such consensus cannot be reached, the Committee for Advanced Therapies shall adopt the position of the majority of its members. The draft opinion shall mention the divergent positions and the grounds on which they are based.
3. The draft opinion given by the Committee for Advanced Therapies under paragraph 1 shall be sent to the Chairman of the Committee for Medicinal Products for Human Use in a timely manner so as to ensure that the deadline laid down in Article 6(3) or Article 9(2) of Regulation (EC) No 726/2004 can be met.
4. Where the scientific opinion on an advanced therapy medicinal product drawn up by the Committee for Medicinal Products for Human Use under Article 5(2) and (3) of Regulation (EC) No 726/2004 is not in accordance with the draft opinion of the Committee for Advanced Therapies, the Committee for Medicinal Products for Human Use shall annex to its opinion a detailed explanation of the scientific grounds for the differences.
5. The Agency shall draw up specific procedures for the application of paragraphs 1 to 4.

Article 9 - Combined advanced therapy medicinal products

1. Where a combined advanced therapy medicinal product is concerned, the whole product shall be subject to final evaluation by the Agency.
2. The application for a marketing authorisation for a combined advanced therapy medicinal product shall include evidence of conformity with the essential requirements referred to in Article 6.
3. The application for a marketing authorisation for a combined advanced therapy medicinal product shall include, where available, the results of the assessment by a notified body in accordance with Directive 93/42/EEC or Directive 90/385/EEC of the medical device part or active implantable medical device part.The Agency shall recognise the results of that assessment in its evaluation of the medicinal product concerned.

   The Agency may request the relevant notified body to transmit any information related to the results of its assessment. The notified body shall transmit the information within a period of one month.

   If the application does not include the results of the assessment, the Agency shall seek an opinion on the conformity of the device part with Annex I to Directive 93/42/EEC or Annex 1 to Directive 90/385/EEC from

a notified body identified in conjunction with the applicant, unless the Committee for Advanced Therapies advised by its experts for medical devices decides that involvement of a notified body is not required.

CHAPTER 4 - SUMMARY OF PRODUCT CHARACTERISTICS, LABELLING AND PACKAGE LEAFLET

Article 10 - Summary of product characteristics

By way of derogation from Article 11 of Directive 2001/83/EC, the summary of the product characteristics for advanced therapy medicinal products shall contain the information listed in Annex II to this Regulation, in the order indicated therein.

Article 11 - Labelling of outer/immediate packaging

By way of derogation from Articles 54 and 55(1) of Directive 2001/83/EC, the particulars listed in Annex III to this Regulation shall appear on the outer packaging of advanced therapy medicinal products or, where there is no outer packaging, on the immediate packaging.

Article 12 - Special immediate packaging

In addition to the particulars mentioned in Article 55(2) and (3) of Directive 2001/83/EC, the following particulars shall appear on the immediate packaging of advanced therapy medicinal products:

(a) the unique donation and product codes, as referred to in Article 8(2) of Directive 2004/23/EC;

(b) in the case of advanced therapy medicinal products for autologous use, the unique patient identifier and the statement 'For autologous use only'.

Article 13 - Package leaflet

1. By way of derogation from Article 59(1) of Directive 2001/83/EC, the package leaflet for an advanced therapy medicinal product shall be drawn up in accordance with the summary of product characteristics and shall include the information listed in Annex IV to this Regulation, in the order indicated therein.
2. The package leaflet shall reflect the results of consultations with target patient groups to ensure that it is legible, clear and easy to use.

CHAPTER 5 - POST-AUTHORISATION REQUIREMENTS

Article 14 - Post-authorisation follow-up of efficacy and adverse reactions, and risk management

1. In addition to the requirements for pharmacovigilance laid down in Articles 21 to 29 of Regulation (EC) No 726/2004, the applicant shall detail, in the marketing authorisation application, the measures envisaged to ensure the follow-up of efficacy of advanced therapy medicinal products and of adverse reactions thereto.
2. Where there is particular cause for concern, the Commission shall, on the advice of the Agency, require as part of the marketing authorisation that a risk management system designed to identify, characterise, prevent or minimise risks related to advanced therapy medicinal products, including an evaluation of the

effectiveness of that system, be set up, or that specific post-marketing studies be carried out by the holder of the marketing authorisation and submitted for review to the Agency.

In addition, the Agency may request submission of additional reports evaluating the effectiveness of any risk management system and the results of any such studies performed.

Evaluation of the effectiveness of any risk management system and the results of any studies performed shall be included in the periodic safety update reports referred to in Article 24(3) of Regulation (EC) No 726/2004.

3. The Agency shall forthwith inform the Commission if it finds that the marketing authorisation holder has failed to comply with the requirements referred to in paragraph 2.
4. The Agency shall draw up detailed guidelines relating to the application of paragraphs 1, 2 and 3.
5. If serious adverse events or reactions occur in relation to a combined advanced therapy medicinal product, the Agency shall inform the relevant national competent authorities responsible for implementing Directives 90/385/EEC, 93/42/EEC and 2004/23/EC.

Article 15 - Traceability

1. The holder of a marketing authorisation for an advanced therapy medicinal product shall establish and maintain a system ensuring that the individual product and its starting and raw materials, including all substances coming into contact with the cells or tissues it may contain, can be traced through the sourcing, manufacturing, packaging, storage, transport and delivery to the hospital, institution or private practice where the product is used.
2. The hospital, institution or private practice where the advanced therapy medicinal product is used shall establish and maintain a system for patient and product traceability. That system shall contain sufficient detail to allow linking of each product to the patient who received it and vice versa.
3. Where an advanced therapy medicinal product contains human cells or tissues, the marketing authorisation holder, as well as the hospital, institution or private practice where the product is used, shall ensure that the traceability systems established in accordance with paragraphs 1 and 2 of this Article are complementary to, and compatible with, the requirements laid down in Articles 8 and 14 of Directive 2004/23/EC as regards human cells and tissues other than blood cells, and Articles 14 and 24 of Directive 2002/98/EC as regards human blood cells.
4. The marketing authorisation holder shall keep the data referred to in paragraph 1 for a minimum of 30 years after the expiry date of the product, or longer if required by the Commission as a term of the marketing authorisation.
5. In case of bankruptcy or liquidation of the marketing authorisation holder, and in the event that the marketing authorisation is not transferred to another legal entity, the data referred to in paragraph 1 shall be transferred to the Agency.
6. In the event that the marketing authorisation is suspended, revoked or withdrawn, the holder of the marketing authorisation shall remain subject to the obligations laid down in paragraphs 1, 3 and 4.
7. The Commission shall draw up detailed guidelines relating to the application of paragraphs 1 to 6, in particular the type and amount of data referred to in paragraph 1.

CHAPTER 6 - INCENTIVES

Article 16 - Scientific advice

1. The applicant or holder of a marketing authorisation may request advice from the Agency on the design and conduct of pharmacovigilance and of the risk management system referred to in Article 14.
2. By way of derogation from Article 8(1) of Council Regulation (EC) No 297/95 of 10 February 1995 on fees payable to the European Agency for the Evaluation of Medicinal Products, a 90 % reduction for small and medium-sized enterprises and 65 % for other applicants shall apply to the fee for scientific advice payable to the Agency for any advice given in respect of advanced therapy medicinal products pursuant to paragraph 1 of this Article and Article 57(1)(n) of Regulation (EC) No 726/2004.

Article 17 - Scientific recommendation on advanced therapy classification

1. Any applicant developing a product based on genes, cells or tissues may request a scientific recommendation of the Agency with a view to determining whether the referred product falls, on scientific grounds, within the definition of an advanced therapy medicinal product. The Agency shall deliver this recommendation after consultation with the Commission and within 60 days after receipt of the request.
2. The Agency shall publish summaries of the recommendations delivered in accordance with paragraph 1, after deletion of all information of commercial confidential nature.

Article 18 - Certification of quality and non-clinical data

Small and medium-sized enterprises developing an advanced therapy medicinal product may submit to the Agency all relevant quality and, where available, non-clinical data required in accordance with modules 3 and 4 of Annex I to Directive 2001/83/EC, for scientific evaluation and certification.

The Commission shall lay down provisions for the evaluation and certification of such data, in accordance with the regulatory procedure referred to in Article 26(2).

Article 19 - Reduction of the fee for marketing authorisation

1. By way of derogation from Regulation (EC) No 297/95, the fee for marketing authorisation shall be reduced by 50 % if the applicant is a hospital or a small or medium-sized enterprise and can prove that there is a particular public health interest in the Community in the advanced therapy medicinal product concerned.
2. Paragraph 1 shall also apply to fees charged by the Agency for post-authorisation activities in the first year following the granting of the marketing authorisation for the advanced therapy medicinal product.

3. Paragraphs 1 and 2 shall apply during the transitional periods laid down in Article 29.

CHAPTER 7 - COMMITTEE FOR ADVANCED THERAPIES

Article 20 - Committee for Advanced Therapies

1. A Committee for Advanced Therapies shall be established within the Agency.

2. Save where otherwise provided in this Regulation, Regulation (EC) No 726/2004 shall apply to the Committee for Advanced Therapies.
3. 3. The Executive Director of the Agency shall ensure appropriate coordination between the Committee for Advanced Therapies and the other Committees of the Agency, in particular the Committee for Medicinal Products for Human Use, the Pharmacovigilance Risk Assessment Committee and the Committee for Orphan Medicinal Products, their working parties and any other scientific advisory groups.

Article 21 - Composition of the Committee for Advanced Therapies

1. The Committee for Advanced Therapies shall be composed of the following members:
   (a) five members or co-opted members of the Committee for Medicinal Products for Human Use from five Member States, with alternates either proposed by their respective Member State or, in the case of co-opted members of the Committee for Medicinal Products for Human Use, identified by the latter on the advice of the corresponding co-opted member. These five members with their alternates shall be appointed by the Committee for Medicinal Products for Human Use;
   (b) one member and one alternate appointed by each Member State whose national competent authority is not represented among the members and alternates appointed by the Committee for Medicinal Products for Human Use;
   (c) two members and two alternates appointed by the Commission, on the basis of a public call for expressions of interest and after consulting the European Parliament, in order to represent clinicians;
   (d) two members and two alternates appointed by the Commission, on the basis of a public call for expressions of interest and after consulting the European Parliament, in order to represent patients' associations.

   The alternates shall represent and vote for the members in their absence.
2. All members of the Committee for Advanced Therapies shall be chosen for their scientific qualification or experience in respect of advanced therapy medicinal products. For the purposes of paragraph 1(b), the Member States shall cooperate, under the coordination of the Executive Director of the Agency, in order to ensure that the final composition of the Committee for Advanced Therapies provides appropriate and balanced coverage of the scientific areas relevant to advanced therapies, including medical devices, tissue engineering, gene therapy, cell therapy, biotechnology, surgery, pharmacovigilance, risk management and ethics.

   At least two members and two alternates of the Committee for Advanced Therapies shall have scientific expertise in medical devices.
3. The members of the Committee for Advanced Therapies shall be appointed for a renewable period of three years. At meetings of the Committee for Advanced Therapies, they may be accompanied by experts.
4. The Committee for Advanced Therapies shall elect its Chairman from among its members for a term of three years, renewable once.
5. The names and scientific qualifications of all members shall be made public by the Agency, in particular on the Agency's website.

Article 22 - Conflicts of interest

In addition to the requirements laid down in Article 63 of Regulation (EC) No 726/2004, members and alternates of the Committee for Advanced Therapies shall have no financial or other interests in the biotechnology sector and medical device sector that could affect their impartiality. All indirect interests that could relate to these sectors shall be entered in the register referred to in Article 63(2) of Regulation (EC) No 726/2004.

Article 23 - Tasks of the Committee for Advanced Therapies

The Committee for Advanced Therapies shall have the following tasks:

(a) to formulate a draft opinion on the quality, safety and efficacy of an advanced therapy medicinal product for final approval by the Committee for Medicinal Products for Human Use and to advise the latter on any data generated in the development of such a product;

(b) to provide advice, pursuant to Article 17, on whether a product falls within the definition of an advanced therapy medicinal product;

(c) at the request of the Committee for Medicinal Products for Human Use, to advise on any medicinal product which may require, for the evaluation of its quality, safety or efficacy, expertise in one of the scientific areas referred to in Article 21(2);

(d) to provide advice on any question related to advanced therapy medicinal products, at the request of the Executive Director of the Agency or the Commission;

(e) to assist scientifically in the elaboration of any documents related to the fulfillment of the objectives of this Regulation;

(f) at the Commission's request, to provide scientific expertise and advice for any Community initiative related to the development of innovative medicines and therapies which requires expertise in one of the scientific areas referred to in Article 21(2);

(g) to contribute to the scientific advice procedures referred to in Article 16 of this Regulation and in Article 57(1)(n) of Regulation (EC) No 726/2004.

CHAPTER 8 - GENERAL AND FINAL PROVISIONS

Article 24 - Adaptation of Annexes

The Commission shall, after consulting the Agency and in accordance with the regulatory procedure with scrutiny referred to in Article 26(3), amend Annexes I to IV in order to adapt them to scientific and technical evolution.

Article 25 - Report and review

By 30 December 2012, the Commission shall publish a general report on the application of this Regulation, which shall include comprehensive information on the different types of advanced therapy medicinal products authorised pursuant to this Regulation.

In this report, the Commission shall assess the impact of technical progress on the application of this Regulation. It shall also review the scope of this Regulation, including in particular the regulatory framework for combined advanced therapy medicinal products.

Article 26 - Committee procedure

1. The Commission shall be assisted by the Standing Committee on Medicinal Products for Human Use set up by Article 121(1) of Directive 2001/83/EC.
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, Article 5a(1) to (4) and Article 7 of Decision 1999/468/EC shall apply, having regard to the provisions of Article 8 thereof.

Article 27 - Amendments to Regulation (EC) No 726/2004

Regulation (EC) No 726/2004 is hereby amended as follows:

1. in the first subparagraph of Article 13(1), the first sentence shall be replaced by the following:
   'Without prejudice to Article 4(4) and (5) of Directive 2001/83/EC, a marketing authorisation which has been granted in accordance with this Regulation shall be valid throughout the Community.';»
2. Article 56 shall be amended as follows:
   (a) in paragraph 1, the following point shall be inserted:
   '(da) the Committee for Advanced Therapies;'»
   (b) in the first sentence of the first subparagraph of paragraph 2, the words 'paragraph 1(a) to (d)' shall be replaced by 'paragraph 1(a) to (da)';
3. the Annex shall be amended as follows:
   (a) the following point shall be inserted:
   '1a. Advanced therapy medicinal products as defined in Article 2 of Regulation (EC) No 1394/2007 of the European Parliament and of the Council of 13 November 2007 on advanced therapy medicinal products.'»
   (b) In point 3, the second subparagraph shall be replaced by the following:
   'After 20 May 2008, the Commission, having consulted the Agency, may present any appropriate proposal to amend this point and the European Parliament and the Council shall take a decision thereon in accordance with the Treaty.'»

Article 28 - Amendments to Directive 2001/83/EC

Directive 2001/83/EC is hereby amended as follows:

1. in Article 1, the following point shall be inserted:
   '4a.Advanced therapy medicinal product:
   A product as defined in Article 2 of Regulation (EC) No 1394/2007 of the European Parliament and of the Council of 13 November 2007 on advanced therapy medicinal products.'»

2. in Article 3, the following point shall be added:
   '7. Any advanced therapy medicinal product, as defined in Regulation (EC) No 1394/2007, which is prepared on a non-routine basis according to specific quality standards, and used within the same Member State in a hospital under the exclusive professional responsibility of a medical practitioner, in order to comply with an individual medical prescription for a custom-made product for an individual patient.
   Manufacturing of these products shall be authorised by the competent authority of the Member State. Member States shall ensure that national traceability and pharmacovigilance requirements as well as the specific quality standards referred to in this paragraph are equivalent to those provided for at Community level in respect of advanced therapy medicinal products for which authorisation is required pursuant to Regulation (EC) No 726/2004 of the European Parliament and of the Council of 31 March 2004 laying down Community procedures for the authorisation and supervision of medicinal products for human and veterinary use and establishing a European Medicines Agency.'»
3. in Article 4, the following paragraph shall be added:
   '5. This Directive and all Regulations referred to therein shall not affect the application of national legislation prohibiting or restricting the use of any specific type of human or animal cells, or the sale, supply or use of medicinal products containing, consisting of or derived from these cells, on grounds not dealt with in the aforementioned Community legislation. The Member States shall communicate the national legislation concerned to the Commission. The Commission shall make this information publicly available in a register.';»
4. 4. in Article 6(1), the first subparagraph shall be replaced by the following:
   'No medicinal product may be placed on the market of a Member State unless a marketing authorisation has been issued by the competent authorities of that Member State in accordance with this Directive or an authorisation has been granted in accordance with Regulation (EC) No 726/2004, read in conjunction with Regulation (EC) No 1901/2006 of the European Parliament and of the Council of 12 December 2006 on medicinal products for paediatric use and Regulation (EC) No 1394/2007.'»

Article 29 - Transitional period

1. Advanced therapy medicinal products, other than tissue engineered products, which were legally on the Community market in accordance with national or Community legislation on 30 December 2008, shall comply with this Regulation no later than 30 December 2011.
2. Tissue engineered products which were legally on the Community market in accordance with national or Community legislation on 30 December 2008 shall comply with this Regulation no later than 30 December 2012.
3. By way of derogation from Article 3(1) of Regulation (EC) No 297/95, no fee shall be payable to the Agency in respect of applications submitted for the authorisation of the advanced therapy medicinal products mentioned in paragraphs 1 and 2 of this Article.

Article 30 - Entry into force

This Regulation shall enter into force on the 20th day following its publication in the Official Journal of the European Union.

It shall apply from 30 December 2008.

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

ANNEX I

Manipulations referred to in the first indent of Article 2(1)(c)

cutting,

grinding,

shaping,

centrifugation,

soaking in antibiotic or antimicrobial solutions,

sterilization,

irradiation,

cell separation, concentration or purification,filtering,

lyophilization,

freezing,

cryopreservation,

vitrification.

ANNEX II

Summary of product characteristics referred to in Article 10

1. Name of the medicinal product.
2. Composition of the product:
   - 2.1. general description of the product, if necessary with explanatory drawings and pictures,
   - 2.2. qualitative and quantitative composition in terms of the active substances and other constituents of the product, knowledge of which is essential for proper use, administration or implantation of the product. Where the product contains cells or tissues, a detailed description of these cells or tissues and of their specific origin, including the species of animal in cases of non-human origin, shall be provided,

     For a list of excipients, see point 6.1.
3. Pharmaceutical form.
4. Clinical particulars:
   - 4.1. therapeutic indications,
   - 4.2. posology and detailed instructions for use, application, implantation or administration for adults and, where necessary, for children or other special populations, if necessary with explanatory drawings and pictures,
   - 4.3. contra-indications,

4.4. special warnings and precautions for use, including any special precautions to be taken by persons handling such products and administering them to or implanting them in 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).

5. Pharmacological properties:

5.1. pharmacodynamic properties,

5.2. pharmacokinetic properties,

5.3. preclinical safety data.

6. Quality particulars:

6.1. list of excipients, including preservative systems,

6.2. 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 and special equipment for use, administration or implantation, if necessary with explanatory drawings and pictures,

6.6. special precautions and instructions for handling and disposal of a used advanced therapy medicinal product or waste materials derived from such product, if appropriate and, if necessary, with explanatory drawings and pictures.

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.

ANNEX III

Labelling of outer/immediate packaging referred to in Article 11

(a) The name of the medicinal product and, if appropriate, an indication of whether it is intended for babies, children or adults; the international non-proprietary name (INN) shall be included, or, if the product has no INN, the common name;

(b) A description of the active substance(s) expressed qualitatively and quantitatively, including, where the product contains cells or tissues, the statement 'This product contains cells of human/animal [as appropriate{}{] origin' together with a short description of these cells or tissues and of their specific origin, including the species of animal in cases of non-human origin;

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

(d) A list of excipients, including preservative systems;
(e) The method of use, application, administration or implantation and, if necessary, the route of administration. If applicable, 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) Any special warning necessary for the particular medicinal product;
(h) The expiry date in clear terms (month and year; and day if applicable);
(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) Marketing authorisation number(s);
(m) The manufacturer's batch number and the unique donation and product codes referred to in Article 8(2) of Directive 2004/23/EC;
(n) In the case of advanced therapy medicinal products for autologous use, the unique patient identifier and the statement 'For autologous use only'.

ANNEX IV
Package leaflet referred to in Article 13

(a) For the identification of the advanced therapy medicinal product:
    i) the name of the advanced therapy medicinal product and, if appropriate, an indication of whether it is intended for babies, children or adults. The common name shall be included;
    ii) the therapeutic group or type of activity in terms easily understandable for the patient;
    iii) where the product contains cells or tissues, a description of those cells or tissues and of their specific origin, including the species of animal in cases of non-human origin;
    iv) where the product contains medical devices or active implantable medical devices, a description of those devices and their specific origin;
(b) The therapeutic indications;
(c) A list of information which is necessary before the medicinal product is taken or used, including:
    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;
    v) if appropriate, possible effects on the ability to drive vehicles or to operate machinery;
    vi) the 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 of Directive 2001/83/EC.

The list shall also take into account the particular condition of certain categories of users, such as children, pregnant or breastfeeding women, the elderly, persons with specific pathological conditions;

(d) The necessary and usual instructions for proper use, and in particular:
    i) the posology;
    ii) the method of use, application, administration or implantation and, if necessary, the route of administration;
    and, as appropriate, depending on the nature of the product:
    iii) the frequency of administration, specifying if necessary the appropriate time at which the medicinal product may or must be administered;
    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) information on what to do when one or more doses have not been taken;
    vii) 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 and quantitative composition;
    v) the name and address of the marketing authorisation holder and, where applicable, the name of his appointed representatives in the Member States;
    vi) the name and address of the manufacturer;

(g) The date on which the package leaflet was last revised.

COMMISSION REGULATION (EC) NO 1234/2008 OF 24 NOVEMBER 2008 CONCERNING THE EXAMINATION OF VARIATIONS TO THE TERMS OF MARKETING AUTHORISATIONS FOR MEDICINAL PRODUCTS FOR HUMAN USE AND VETERINARY MEDICINAL PRODUCTS

(Text with EEA relevance)

THE COMMISSION OF THE EUROPEAN COMMUNITIES,

Having regard to the Treaty establishing the European Community,

Having regard to Directive 2001/82/EC of the European Parliament and of the Council of 6 November 2001 on the Community code relating to veterinary medicinal products, and in particular Article 39(1) thereof,

Having regard to 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, and in particular Article 35(1) thereof,

Having regard to Regulation (EC) No 726/2004 of the European Parliament and of the Council of 31 March 2004 laying down Community procedures for the authorisation and supervision of medicinal products for human and veterinary use and establishing a European Medicines Agency, and in particular of Article 16(4) and Article 41(6) thereof,

Whereas:

1. The Community legal framework regarding variations to the terms of marketing authorisations is laid down in Commission Regulation (EC) No 1084/2003 of 3 June 2003 concerning the examination of variations to the terms of a marketing authorisation for medicinal products for human use and veterinary medicinal products granted by a competent authority of a Member State and Commission Regulation (EC) No 1085/2003 of 3 June 2003 concerning the examination of variations to the terms of a marketing authorisation for medicinal products for human use and veterinary medicinal products falling within the scope of Council Regulation (EEC) No 2309/93. In the light of practical experience in the application of those two Regulations, it is appropriate to proceed to their review in order to establish a simpler, clearer and more flexible legal framework, while guaranteeing the same level of public and animal health protection.
2. The procedures laid down in Regulations (EC) No 1084/2003 and (EC) No 1085/2003 should therefore be adjusted, without departing from the general principles on which those procedures are based. For reasons of proportionality, homeopathic and traditional herbal medicinal products which have not been granted a marketing authorisation but are subject to a simplified registration procedure should remain excluded from the scope of the Regulation.
3. Variations to medicinal products can be classified in different categories, depending on the level of risk to public or animal health and the impact on the quality, safety and efficacy of the medicinal product concerned. Definitions for each of those categories should therefore be laid down. In order to bring further predictability, guidelines on the details of the various categories of variations should be established and regularly updated in the light of scientific and technical progress, taking in particular account of developments regarding

international harmonisation. The European Medicines Agency (hereinafter the Agency) and the Member States should also be empowered to give recommendations on the classification of unforeseen variations.

4. It should be clarified that certain changes which have the highest potential impact on the quality, safety or efficacy of medicinal products require a complete scientific assessment, in the same way as for the evaluation of new marketing authorisation applications.
5. In order to further reduce the overall number of variations procedures and to enable competent authorities to focus on those variations that have a genuine impact on quality, safety or efficacy, an annual reporting system should be introduced for certain minor variations. Such variations should not require any prior approval and should be notified within 12 months following implementation. However, other types of minor variations whose immediate reporting is necessary for the continuous supervision of the medicinal product concerned should not be subject to the annual reporting system.
6. Each variation should require a separate submission. Grouping of variations should nevertheless be allowed in certain cases, in order to facilitate the review of the variations and reduce the administrative burden. Grouping of variations to the terms of several marketing authorisations from the same marketing authorisation holder should be allowed only insofar as all concerned marketing authorisations are affected by the exact same group of variations.
7. In order to avoid duplication of work in the evaluation of variations to the terms of several marketing authorisations, a worksharing procedure should be established under which one authority, chosen amongst the competent authorities of the Member States and the Agency, should examine the variation on behalf of the other concerned authorities.
8. Provisions should be established reflecting those laid down in Directive 2001/82/EC and Directive 2001/83/EC as regards the role of the coordination groups established under Article 31 of Directive 2001/82/EC and Article 27 of Directive 2001/83/EC, to increase cooperation between Member States and allow for the settlement of disagreements in the evaluation of certain variations.
9. This Regulation should clarify when the holder of a marketing authorisation is allowed to implement a given variation as such clarification is essential for economic operators.
10. A transitional period should be established in order to give all interested parties, in particular Member States authorities and the industry, time to adapt to the new legal framework.
11. The measures provided for in this Regulation are in accordance with the opinions of the Standing Committee on Medicinal Products for Human Use and the Standing Committee on Veterinary Medicinal Products,

HAS ADOPTED THIS REGULATION:

CHAPTER I - GENERAL PROVISIONS

Article 1 - Subject matter and scope

1. This Regulation lays down provisions concerning the examination of variations to the terms of all marketing authorisations for medicinal products for human use and veterinary medicinal products granted in accordance with Regulation (EC) No 726/2004, Directive 2001/83/EC, Directive 2001/82/EC, and Council Directive 87/22/EEC.

2. This Regulation shall not apply to transfers of a marketing authorisation from one marketing authorisation holder (hereinafter holder) to another.
3. Chapter II shall apply only to variations to the terms of marketing authorisations granted in accordance with Directive 87/22/EEC, Chapter 4 of Directive 2001/82/EC or Chapter 4 of Directive 2001/83/EC.
(3a). Chapter IIa shall apply only to variations to the terms of purely national marketing authorisations.
4. Chapter III shall apply only to variations to the terms of marketing authorisations granted in accordance with Regulation (EC) No 726/2004 (hereinafter centralised marketing authorisations).

Article 2 - Definitions

For the purposes of this Regulation, the following definitions shall apply:

1. 'Variation to the terms of a marketing authorisation' or 'variation' means any amendment to:
    (a) the information referred to in Articles 12(3) to 14 of Directive 2001/82/EC and Annex I thereto, Articles 8(3) to 11 of Directive 2001/83/EC and Annex I thereto, Articles 6(2) and 31(2) of Regulation (EC) No 726/2004, or Article 7 of Regulation (EC) No 1394/2007;
    (b) the terms of the decision granting the marketing authorisation for a medicinal product for human use, including the summary of the product characteristics and any conditions, obligations, or restrictions affecting the marketing authorisation, or changes to the labelling or the package leaflet connected with changes to the summary of the product characteristics;
    (c) the terms of the decision granting the marketing authorisation for a veterinary medicinal product, including the summary of the product characteristics and any conditions, obligations, or restrictions affecting the marketing authorisation, or changes to the labelling or the package leaflet.
2. 'Minor variation of type IA' means a variation which has only a minimal impact, or no impact at all, on the quality, safety or efficacy of the medicinal product concerned;
3. 'Major variation of type II' means a variation which is not an extension and which may have a significant impact on the quality, safety or efficacy of the medicinal product concerned;
4. 'Extension of a marketing authorisation' or 'extension' means a variation which is listed in Annex I and fulfills the conditions laid down therein;
5. 'Minor variation of type IB' means a variation which is neither a minor variation of type IA nor a major variation of type II nor an extension;
6. 'Member State concerned' means a Member State whose competent authority has granted a marketing authorisation for the medicinal product in question;
7. 'Relevant authority' means:
    (a) the competent authority of each Member State concerned;
    (b) in the case of centralised marketing authorisations, the Agency;
8. 'Urgent safety restriction' means an interim change in the terms of the marketing authorisation due to new information having a bearing on the safe use of the medicinal product;
9. 'Purely national marketing authorisation' means any marketing authorisation granted by a Member State in accordance with the acquis outside the mutual recognition or decentralised procedure and that has not been subject to a complete harmonisation following a referral procedure.

Article 3 - Classification of variations

1. In relation to any variation which is not an extension the classification laid down in Annex II shall apply.
2. A variation which is not an extension and whose classification is undetermined after application of the rules provided for in this Regulation, taking into account the guidelines referred to in Article 4(1) and, where relevant, any recommendations delivered pursuant to Article 5, shall by default be considered a minor variation of type IB.
3. By way of derogation from paragraph 2, a variation which is not an extension and whose classification is undetermined after application of the rules provided for in this Regulation shall be considered a major variation of type II in the following cases:
    (a) upon request from the holder when submitting the variation;
    (b) where the competent authority of the reference Member State as referred to in Article 32 of Directive 2001/82/EC and Article 28 of Directive 2001/83/EC (hereinafter 'the reference Member State'), in consultation with the other Member States concerned, or the Agency in the case of a centralised marketing authorisation, or the competent authority in the case of a purely national marketing authorisation, concludes, following the assessment of validity of a notification in accordance with Article 9(1), Article 13b(1), or Article 15(1) and taking into account the recommendations delivered pursuant to Article 5, that the variation may have a significant impact on the quality, safety or efficacy of the medicinal product concerned.

Article 4 - Guidelines

1. The Commission shall, after consulting the Member States and the Agency, draw up guidelines on the details of the various categories of variations, on the operation of the procedures laid down in Chapters II, IIa, III and IV of this Regulation, and on the documentation to be submitted pursuant to those procedures.
2. The guidelines referred to in paragraph 1 shall be regularly updated.

Article 5 - Recommendation on unforeseen variations

1. Prior to the submission of a variation whose classification is not provided for in this Regulation, a holder may request a recommendation on the classification of the variation as follows:
    (a) to the Agency, where the variation refers to a marketing authorisation granted under Regulation (EC) No 726/2004;
    (b) to the competent authority of the Member State concerned, where the variation refers to a purely national marketing authorisation;
    (c) to the competent authority of the reference Member State, in the other cases.

    The recommendation referred to in the first subparagraph shall be consistent with the guidelines referred to in Article 4(1). It shall be delivered within 45 days following receipt of the request and sent to the holder, the Agency, and the coordination group referred to in Article 31 of Directive 2001/82/EC or in Article 27 of Directive 2001/83/EC.

    The 45-day period referred to in the second subparagraph may be extended by 25 days where the relevant authority deems it necessary to consult with the coordination group.

1a. Prior to the examination of a variation whose classification is not provided for in this Regulation, a competent authority of a Member State may request a recommendation on the classification of the variation to the coordination group.

The recommendation referred to in the first subparagraph shall be consistent with the guidelines referred to in Article 4(1). It shall be delivered within 45 days following receipt of the request and sent to the holder, the Agency, and the competent authorities of all Member States.

2. The Agency and the two coordination groups referred to in paragraph 1 shall cooperate to ensure the coherence of the recommendations delivered in accordance with that paragraph and publish those recommendations after deletion of all information of commercial confidential nature.

Article 6 - Variations leading to the revision of product information

Where a variation leads to the revision of the summary of product characteristics, labelling or package leaflet, this revision shall be considered as part of that variation.

Article 7 - Grouping of variations

1. Where several variations are notified or applied for, a separate notification or application in accordance with Chapters II, III, or Article 19 as appropriate shall be submitted in respect of each variation sought.
2. By way of derogation from paragraph 1, the following shall apply:
    (a) where the same minor variation(s) of type IA to the terms of one or more marketing authorisations owned by the same holder are notified at the same time to the same relevant authority, a single notification as referred to in Article 8 or 14 may cover all such variations;
    (b) where several variations to the terms of the same marketing authorisation are submitted at the same time, a single submission may cover all such variations provided that the variations concerned fall within one of the cases listed in Annex III;
    (c) where several variations to the terms of the same marketing authorisation are submitted at the same time and the variations do not fall within one of the cases listed in Annex III, a single submission may cover all such variations provided that the competent authority of the reference Member State in consultation with the competent authorities of the Member States concerned or, in the case of a centralised marketing authorisation, the Agency agrees to such single submission.

    The submission referred to in subparagraphs (b) and (c) shall be made simultaneously to all relevant authorities by means of the following:
    (i) a single notification in accordance with Article 9 or 15 where at least one of the variations is a minor variation of type IB and the remaining variations are minor variations;
    (ii) a single application in accordance with Article 10 or 16 where at least one of the variations is a major variation of type II and none of the variations is an extension;
    (iii) a single application in accordance with Article 19 where at least one of the variations is an extension.

CHAPTER II - VARIATIONS TO MARKETING AUTHORISATIONS GRANTED IN ACCORDANCE WITH DIRECTIVE 87/22/EEC, CHAPTER 4 OF DIRECTIVE 2001/82/EC OR CHAPTER 4 OF DIRECTIVE 2001/83/EC

Article 8 - Notification procedure for minor variations of type IA

1. Where a minor variation of type IA is made, the holder shall submit simultaneously to all relevant authorities a notification containing the elements listed in Annex IV. This notification shall be submitted within 12 months following the implementation of the variation.

   However, the notification shall be submitted immediately after the implementation of the variation in the case of minor variations requiring immediate notification for the continuous supervision of the medicinal product concerned.
2. Within 30 days following receipt of the notification, the measures provided for in Article 11 shall be taken.

Article 9 - Notification procedure for minor variations of type IB

1. The holder shall submit simultaneously to all relevant authorities a notification containing the elements listed in Annex IV.

   If the notification fulfills the requirement laid down in the first subparagraph, the competent authority of the reference Member State shall, after consulting the other Member States concerned, acknowledge receipt of a valid notification.
2. If within 30 days following the acknowledgement of receipt of a valid notification, the competent authority of the reference Member State has not sent the holder an unfavourable opinion, the notification shall be deemed accepted by all relevant authorities.

   Where the notification is accepted by the competent authority of the reference Member State, the measures provided for in Article 11 shall be taken.
3. Where the competent authority of the reference Member State is of the opinion that the notification cannot be accepted, it shall inform the holder and the other relevant authorities, stating the grounds on which its unfavourable opinion is based.

   Within 30 days following the receipt of the unfavourable opinion, the holder may submit to all relevant authorities an amended notification in order to take due account of the grounds laid down in that opinion.

   If the holder does not amend the notification in accordance with the second subparagraph, the notification shall be deemed rejected by all relevant authorities and the measures provided for in Article 11 shall be taken.
4. Where an amended notification has been submitted, the competent authority of the reference Member State shall assess it within 30 days following its receipt and the measures provided for in Article 11 shall be taken.
5. This Article shall not apply where a type IB variation request is submitted in a grouping that includes a variation type II and does not contain an extension. In such case, the prior approval procedure in Article 10 shall apply.

   This Article shall not apply where a type IB variation request is submitted in a grouping that includes an extension. In such case, the procedure in Article 19 shall apply.

Article 10 - 'Prior Approval' procedure for major variations of type II

1. The holder shall submit simultaneously to all relevant authorities an application containing the elements listed in Annex IV.

   If the application fulfills the requirements laid down in the first subparagraph, the competent authority of the reference Member State shall acknowledge receipt of a valid application and inform the holder and the other relevant authorities that the procedure starts from the date of such acknowledgement.
2. Within 60 days following the acknowledgement of receipt of a valid application, the competent authority of the reference Member State shall prepare an assessment report and a decision on the application, which shall be communicated to the other relevant authorities.

   The competent authority of the reference Member State may reduce the period referred to in the first subparagraph, having regard to the urgency of the matter, or extend it to 90 days for variations listed in Part 1 of Annex V or for grouping of variations in accordance with Article 7(2)(c).

   The period referred to in the first subparagraph shall be 90 days for variations listed in Part 2 of Annex V.
3. Within the period referred to in paragraph 2, the competent authority of the reference Member State may request the holder to provide supplementary information within a time limit set by that competent authority. In this case:
   (a) the competent authority of the reference Member State shall inform the other competent authorities concerned of its request for supplementary information;
   (b) the procedure shall be suspended until such supplementary information has been provided;
   (c) the competent authority of the reference Member State may extend the period referred to in paragraph 2.
4. Without prejudice to Article 13 and within 30 days following receipt of the decision and of the assessment report referred to in paragraph 2, the relevant authorities shall recognise the decision and inform the competent authority of the reference Member State accordingly.

   If, within the period referred to in the first subparagraph, a relevant authority has not expressed its disagreement in accordance with Article 13, the decision shall be deemed recognised by that relevant authority.
5. Where the decision referred to in paragraph 2 has been recognised by all relevant authorities in accordance with paragraph 4, the measures provided for in Article 11 shall be taken.
6. This Article shall not apply where a type II variation request is submitted in a grouping that includes an extension. In such case, the procedure in Article 19 shall apply.

Article 11 - Measures to close the procedures of Articles 8 to 10

1. Where reference is made to this Article, the competent authority of the reference Member State shall take the following measures:
   (a) it shall inform the holder and the other relevant authorities as to whether the variation is accepted or rejected;
   (b) where the variation is rejected, it shall inform the holder and the other relevant authorities of the grounds for the rejection;

(c) it shall inform the holder and the other relevant authorities as to whether the variation requires any amendment to the decision granting the marketing authorisation.

2. Where reference is made to this Article, each relevant authority shall, where necessary and within the time limit laid down in paragraph 1 of Article 23, amend the decision granting the marketing authorisation in accordance with the accepted variation.

Article 12 - Human influenza vaccines

1. By way of derogation from Article 10, the procedure laid down in paragraphs 2 to 5 shall apply to the examination of variations concerning changes to the active substance for the purposes of the annual update of a human influenza vaccine.
2. The holder shall submit simultaneously to all relevant authorities an application containing the elements listed in Annex IV.

   If the application fulfills the requirements laid down in the first subparagraph, the competent authority of the reference Member State shall acknowledge receipt of a valid application and inform the holder and the other relevant authorities that the procedure starts from the date of such acknowledgement.
3. The competent authority of the reference Member State shall assess the application submitted. Where deemed necessary, the competent authority of the reference Member State may request additional data to the holder in order to complete its assessment.
4. The competent authority shall prepare a decision and an assessment report within 45 days from the receipt of a valid application.

   The 45-day period referred to in the first subparagraph shall be suspended from the moment when the additional data referred to in paragraph 3 is requested until the data is submitted.
5. Within 12 days from the receipt of the decision and the assessment report of the competent authority of the reference Member State, the relevant authorities shall adopt a decision accordingly and inform the competent authority of the reference Member State and the holder thereof.

Article 13 - Coordination group and arbitration

1. Where recognition of a decision in accordance with Article 10(4) or approval of an opinion in accordance with point (b) of Article 20(8) is not possible on grounds of a potential serious risk to public health in the case of medicinal products for human use or, in the case of veterinary medicinal products, on grounds of a potential serious risk to human or animal health or to the environment, a relevant authority shall request that the matter of disagreement be forthwith referred to the coordination group.

   The party in disagreement shall give a detailed statement of the reasons for its position to all Member States concerned and to the applicant.
2. Article 33(3), (4) and (5) of Directive 2001/82/EC or Article 29(3), (4) and (5) of Directive 2001/83/EC shall apply to the matter of disagreement referred to in paragraph 1.

CHAPTER IIa - VARIATIONS TO PURELY NATIONAL MARKETING AUTHORISATIONS

Article 13a - Notification procedure for minor variations of type IA

1. Where a minor variation of type IA is made, the holder shall submit to the competent authority a notification containing the elements listed in Annex IV. This notification shall be submitted within 12 months following the implementation of the variation.
   However, the notification shall be submitted immediately after the implementation of the variation in the case of minor variations requiring immediate notification for the continuous supervision of the medicinal product concerned.
2. Within 30 days following receipt of the notification, the measures provided for in Article 13e shall be taken.

Article 13b - Notification procedure for minor variations of type IB

1. The holder shall submit to the competent authority a notification containing the elements listed in Annex IV.
   If the notification fulfills the requirement laid down in the first subparagraph, the competent authority shall acknowledge receipt of a valid notification.
2. If within 30 days following the acknowledgement of receipt of a valid notification, the competent authority has not sent the holder an unfavourable opinion, the notification shall be deemed accepted by the competent authority.
   Where the notification is accepted by the competent authority, the measures provided for in Article 13e shall be taken.
3. Where the competent authority is of the opinion that the notification cannot be accepted, it shall inform the holder, stating the grounds on which its unfavourable opinion is based.
   Within 30 days following the receipt of the unfavourable opinion, the holder may submit to the competent authority an amended notification in order to take due account of the grounds laid down in that opinion.
   If the holder does not amend the notification in accordance with the second subparagraph, the notification shall be deemed rejected.
4. Where an amended notification has been submitted, the competent authority shall assess it within 30 days following its receipt and the measures provided for in Article 13e shall be taken.
5. This Article shall not apply where a type IB variation request is submitted in a grouping that includes a variation type II and does not contain an extension. In such case, the prior approval procedure in Article 13c shall apply.
   This Article shall not apply where a type IB variation request is submitted in a grouping that includes an extension. In such case, the procedure in Article 19 shall apply.

Article 13c - 'Prior Approval' procedure for major variations of type II

1. The holder shall submit to the competent authority an application containing the elements listed in Annex IV.
   If the application fulfills the requirements laid down in the first subparagraph, the competent authority shall acknowledge receipt of a valid application.
2. Within 60 days following the acknowledgement of receipt of a valid application, the competent authority shall conclude the assessment.

The competent authority may reduce the period referred to in the first subparagraph, having regard to the urgency of the matter, or extend it to 90 days for variations listed in Part 1 of Annex V or for grouping of variations in accordance with Article 13d(2)(c).

The period referred to in the first subparagraph shall be 90 days for variations listed in Part 2 of Annex V.

3. Within the periods referred to in paragraph 2, the competent authority may request the holder to provide supplementary information within a time limit set by the competent authority. In this case the procedure shall be suspended until such supplementary information has been provided and the competent authority may extend the period referred to in paragraph 2.
4. Within 30 days after the conclusion of the assessment, the measures provided for in Article 13e shall be taken.
5. This Article shall not apply where a type II variation request is submitted in a grouping that includes an extension. In such case, the procedure in Article 19 shall apply.

Article 13d - Grouping of variations to purely national marketing authorisations

1. Where several variations are notified or applied for, a separate notification or application in accordance with Articles 13a, 13b, 13c, or 19 as appropriate shall be submitted to the competent authority in respect of each variation sought.
2. By way of derogation from paragraph 1 the following shall apply:
    (a) where the same minor variation(s) of type IA to the terms of one or more marketing authorisations owned by the same holder are notified at the same time to the same competent authority, a single notification as referred to in Article 13a may cover all such variations;
    (b) where several variations to the terms of the same marketing authorisation are submitted at the same time to the same competent authority, a single submission may cover all such variations provided that the variations concerned fall within one of the cases listed in Annex III;
    (c) here the same variation(s) to the terms of one or more marketing authorisations owned by the same holder are submitted at the same time to the same competent authority and they are not covered under subparagraph (a) or (b), a single submission may cover all such variations provided that the competent authority agrees to such single submission.

    The submission referred to in points (b) and (c) shall be made by means of the following:

    (i) a single notification in accordance with Article 13b where at least one of the variations is a minor variation of type IB and the remaining variations are minor variations;
    (ii) a single application in accordance with Article 13c where at least one of the variations is a major variation of type II and none of the variations is an extension;
    (iii) a single application in accordance with Article 19 where at least one of the variations is an extension.

Article 13e - Measures to close the procedures of Articles 13a to 13c

Where reference is made to this Article, the competent authority shall take the following measures:

(a) it shall inform the holder as to whether the variation is accepted or rejected;
(b) where the variation is rejected, it shall inform the holder of the grounds for the rejection;

(c) where necessary, it shall amend the decision granting the marketing authorisation in accordance with the accepted variation within the time limit laid down in paragraph 1 of Article 23.

Article 13f - Human influenza vaccines

1. By way of derogation from Article 13c, the procedure laid down in paragraphs 2 to 4 shall apply to the examination of variations concerning changes to the active substance for the purposes of the annual update of a human influenza vaccine.
2. The holder shall submit to the competent authority an application containing the elements listed in Annex IV.

   If the application fulfills the requirements laid down in the first subparagraph, the competent authority shall acknowledge receipt of a valid application.
3. The competent authority shall assess the application submitted. Where deemed necessary, the competent authority may request additional data to the holder in order to complete its assessment.
4. The competent authority shall adopt a decision within 45 days from the receipt of a valid application and shall take the measures provided for in Article 13e.

   The 45-day period referred to in the first subparagraph shall be suspended from the moment when the additional data referred to in paragraph 3 is requested until the data is submitted.

CHAPTER III - VARIATIONS TO CENTRALISED MARKETING AUTHORISATIONS

Article 14 - Notification procedure for minor variations of type IA

1. Where a minor variation of type IA is made, the holder shall submit to the Agency a notification containing the elements listed in Annex IV. This notification shall be submitted within 12 months following implementation of the variation.

   However, the notification shall be submitted immediately after the implementation of the variation in the case of minor variations requiring immediate notification for the continuous supervision of the medicinal product concerned.
2. Within 30 days following receipt of the notification, the measures provided for in Article 17 shall be taken.

Article 15 - Notification procedure for minor variations of type IB

1. The holder shall submit to the Agency a notification containing the elements listed in Annex IV.

   If the notification fulfills the requirement laid down in the first subparagraph, the Agency shall acknowledge receipt of a valid notification.
2. If within 30 days following the acknowledgement of receipt of a valid notification the Agency has not sent the holder an unfavourable opinion, its opinion shall be deemed favourable.

   Where the opinion of the Agency on the notification is favourable, the measures provided for in Article 17 shall be taken.
3. Where the Agency is of the opinion that the notification cannot be accepted, it shall inform the holder, stating the grounds on which its unfavourable opinion is based.

   Within 30 days of receipt of the unfavourable opinion, the holder may submit to the Agency an amended

notification in order to take due account of the grounds laid down in that opinion.

If the holder does not amend the notification in accordance with the second subparagraph, the notification shall be deemed rejected.

4. Where an amended notification has been submitted, the Agency shall assess it within 30 days following its receipt and the measures provided for in Article 17 shall be taken.
5. This Article shall not apply where a type IB variation request is submitted in a grouping that includes a variation type II and does not contain an extension. In such case, the prior approval procedure in Article 16 shall apply.

   This Article shall not apply where a type IB variation request is submitted in a grouping that includes an extension. In such case, the procedure in Article 19 shall apply.

Article 16 - 'Prior Approval' procedure for major variations of type II

1. The holder shall submit to the Agency an application containing the elements listed in Annex IV.

   If the application fulfills the requirements laid down in the first subparagraph, the Agency shall acknowledge receipt of a valid application.
2. The Agency shall issue an opinion on the valid application referred to in paragraph 1 within 60 days following its receipt.

   The Agency may reduce the period referred to in the first subparagraph, having regard to the urgency of the matter, or extend it to 90 days for variations listed in Part 1 of Annex V or for grouping of variations in accordance with Article 7(2)(c).

   The period referred to in the first subparagraph shall be 90 days for variations listed in Part 2 of Annex V.
3. Within the period referred to in paragraph 2, the Agency may request the holder to provide supplementary information within a time limit set by the Agency. The procedure shall be suspended until such time as the supplementary information has been provided. In this case the Agency may extend the period referred to in paragraph 2.
4. Article 9(1) and (2) and Article 34(1) and (2) of Regulation (EC) No 726/2004 shall apply to the opinion on the valid application.

   Within 15 days from the adoption of the final opinion on the valid application, the measures provided for in Article 17 shall be taken.
5. This Article shall not apply where a type II variation request is submitted in a grouping that includes an extension. In such case, the procedure in Article 19 shall apply.

Article 17 - Measures to close the procedures of Articles 14 to 16

1. Where reference is made to this Article, the Agency shall take the following measures:
   (a) it shall inform the holder of the outcome of the assessment;
   (b) where the variation is rejected, it shall inform the holder of the grounds for the rejection;
   (c) where the outcome of the assessment is favourable and the variation affects the terms of the Commission decision granting the marketing authorisation, the Agency shall transmit to the Commission its opinion and the grounds for its opinion as well as the revised versions of the

documents referred to in Article 9(4) or Article 34(4) of Regulation (EC) No 726/2004 as appropriate.

2. In the cases identified under paragraph 1(c), the Commission, having regard to the opinion from the Agency and within the time limit foreseen in Article 23(1a), shall amend where necessary the decision granting the marketing authorisation. The Community Register of Medicinal Products provided for in Article 13(1) and Article 38(1) of Regulation (EC) No 726/2004 shall be updated accordingly.

Article 18 - Human influenza vaccines

1. By way of derogation from Article 16, the procedure laid down in paragraphs 2 to 6 shall apply to the examination of variations concerning changes to the active substance for the purposes of the annual update of a human influenza vaccine.
2. The holder shall submit to the Agency an application containing the elements listed in Annex IV.
   If the application fulfills the requirements laid down in the first subparagraph, the Agency shall acknowledge receipt of a valid application and inform the holder that the procedure starts from the date of such acknowledgement.
3. The Agency shall assess the application submitted. Where deemed necessary, the Agency may request additional data to complete its assessment.
4. Within 55 days from the receipt of a valid application, the Agency shall adopt an opinion. The Agency's opinion on the application shall be transmitted to the applicant. Where the Agency's opinion is favourable, the Agency shall also transmit to the Commission its opinion and the grounds for its opinion as well as the revised versions of the documents referred in Article 9(4) of Regulation (EC) No 726/2004.
5. The 55-day period referred to in paragraph 4 shall be suspended from the moment when the additional data referred to in paragraph 3 is requested until the data is submitted.
6. Having regard to the favourable opinion of the Agency, the Commission shall amend where necessary the decision granting the marketing authorisation. The Community Register of Medicinal Products provided for in Article 13(1) of Regulation (EC) No 726/2004 shall be updated accordingly.

CHAPTER IV

SECTION 1 - Special procedures

Article 19 - Extensions of marketing authorisations

1. An application for an extension of a marketing authorisation shall be evaluated in accordance with the same procedure as for the initial marketing authorisation to which it relates.
2. An extension shall either be granted a marketing authorisation in accordance with the same procedure as for the granting of the initial marketing authorisation to which it relates or be included in that marketing authorisation.

Article 20 - Worksharing procedure

1. By way of derogation from Articles 7(1), 9, 10, 13b, 13c, 13d, 15 and 16 the holder of a marketing authorisation may choose to follow the worksharing procedure laid down in paragraphs 3 to 9 in the following cases:
    (a) for marketing authorisations referred to in Chapters II and III, where a minor variation of type IB, a major variation of type II, or a group of variations as provided for in Article 7(2)(b) or (c) that does not contain any extension relates to several marketing authorisations owned by the same holder;
    (b) for purely national marketing authorisations referred to in Chapter IIa, where a minor variation of type IB, a major variation of type II, or a group of variations as provided for in Article 13d(2)(b) or (c) that does not contain any extension relates to several marketing authorisations owned by the same holder;
    (c) for purely national marketing authorisations referred to in Chapter IIa, where a minor variation of type IB, a major variation of type II, or a group of variations as provided for in Article 13d(2)(b) or (c) that does not contain any extension relates to one marketing authorisation that is owned by the same holder in more than one Member State.

    Variations covered under (a), (b) or (c) may be subject to the same worksharing procedure.

    The reference authority or, in the case of purely national marketing authorisations, the competent authority may refuse to process a submission under the worksharing procedure where the same change(s) to different marketing authorisations require the submission of individual supportive data for each medicinal product concerned or a separate product-specific assessment.
2. For the purposes of this Article, 'reference authority' shall mean one of the following:
    (a) the Agency where at least one of the marketing authorisations referred to paragraph 1 is a centralised marketing authorisation;
    (b) the competent authority of a Member State concerned chosen by the coordination group, taking into account a recommendation of the holder, in the other cases.
3. The holder shall submit to all relevant authorities an application containing the elements listed in Annex IV, with an indication of the preferred reference authority.

    The coordination group shall choose a reference authority. If the application fulfills the requirements laid down in the first subparagraph, that reference authority shall acknowledge receipt of a valid application.

    Where the chosen reference authority is the competent authority of a Member State which has not granted a marketing authorisation for all the medicinal products affected by the application, the coordination group may request another relevant authority to assist the reference authority in the evaluation of that application.
4. The reference authority shall issue an opinion on a valid application as referred to in paragraph 3 within one of the following periods:
    (a) a period of 60 days following acknowledgement of receipt of a valid application in the case of minor variations of type IB or major variations of type II;
    (b) a period of 90 days following acknowledgement of receipt of a valid application in the case of variations listed in Part 2 of Annex V.

5. The reference authority may reduce the period referred to in point (a) of paragraph 4, having regard to the urgency of the matter, or extend it to 90 days for variations listed in Part 1 of Annex V or for grouping of variations in accordance with Article 7(2)(c) or Article 13d(2)©.
6. Within the period referred to in paragraph 4, the reference authority may request the holder to provide supplementary information within a time limit set by the reference authority. In this case:
    (a) the reference authority shall inform the other relevant authorities of its request for supplementary information;
    (b) the procedure shall be suspended until such supplementary information has been provided;
    (c) the reference authority may extend the period referred to in point (a) of paragraph 4.
7. Where the reference authority is the Agency, Article 9(1) and (2) and Article 34(1) and (2) of Regulation (EC) No 726/2004 shall apply to the opinion referred to in paragraph 4.

    The Agency's opinion on the application shall be transmitted to the applicant and the Member States, together with the assessment report. Where the outcome of the assessment is favourable and the variation affects the terms of the Commission decision granting the marketing authorisation, the Agency shall also transmit to the Commission its opinion and the grounds for its opinion as well as the revised versions of the documents referred in Article 9(4) of Regulation (EC) No 726/2004.

    Where the Agency issues a favourable opinion, the following shall apply:
    (a) if the opinion recommends the variation to the terms of a Commission decision granting the marketing authorisation, the Commission shall, having regard to the final opinion and within the time limits foreseen in Article 23(1a), amend the decision(s) accordingly, provided that the revised versions of the documents referred to in Article 9(4) or Article 34(4) of Regulation (EC) No 726/2004 have been received. The Community Register of Medicinal Products provided for in Article 13(1) and Article 38(1) of Regulation (EC) No 726/2004 shall be updated accordingly;
    (b) the Member States concerned shall, within 60 days following receipt of the final opinion of the Agency, approve that final opinion, inform the Agency thereof and, where necessary, amend the marketing authorisations concerned accordingly, provided that the documents necessary for the amendment of the marketing authorisation have been transmitted to the Member States concerned.
8. Where the reference authority is the competent authority of a Member State:
    (a) it shall send its opinion to the holder and to all relevant authorities;
    (b) without prejudice to Article 13 and within 30 days following receipt of the opinion, the relevant authorities shall approve that opinion and inform the reference authority;
    (c) the concerned marketing authorisations shall be amended accordingly within 30 days following the approval of the opinion, provided that the documents necessary for the amendment of the marketing authorisation have been transmitted to the Member States concerned.
9. Upon request from the reference authority, the Member States concerned shall provide information related to the marketing authorisations affected by the variation for the purpose of verifying the validity of the application and of issuing the opinion on the valid application.
10. Where harmonisation of a section of the summary of product characteristics of a purely national marketing authorisation has been achieved through a worksharing procedure, any subsequent variation

submission affecting the harmonised section shall be transmitted simultaneously to all Member States concerned.

Article 21 - Pandemic situation with respect to human influenza

1. By way of derogation from Chapters I, II, IIa and III, where a pandemic situation with respect to human influenza is duly recognised by the World Health Organisation or by the Union in the framework of Decision 2119/98/EC of the European Parliament and of the Council, the relevant authorities or, in the case of centralised marketing authorisations, the Commission may exceptionally and temporarily accept a variation to the terms of a marketing authorisation for a human influenza vaccine, where certain non-clinical or clinical data are missing.
2. Where a variation is accepted pursuant to paragraph 1, the holder shall submit the missing non-clinical and clinical data within a time limit set by the relevant authority.

Article 22 - Urgent safety restrictions

1. Where, in the event of a risk to public health in the case of medicinal products for human use or, in the case of veterinary medicinal products, in the event of a risk to human or animal health or to the environment, the holder takes urgent safety restrictions on its own initiative, it shall forthwith inform all relevant authorities and, in the case of a centralised marketing authorisation, the Agency.
   If the relevant authority or, in the case of a centralised marketing authorisation, the Agency has not raised objections within 24 hours following receipt of that information, the urgent safety restrictions shall be deemed accepted.
2. In the event of a risk to public health in the case of medicinal products for human use or, in the case of veterinary medicinal products, in the event of a risk to human or animal health or to the environment, relevant authorities or, in the case of centralised marketing authorisations, the Commission may impose urgent safety restrictions on the holder.
3. Where an urgent safety restriction is taken by the holder or imposed by a relevant authority or the Commission, the holder shall submit the corresponding application for variation within 15 days following the initiation of that restriction.

SECTION 2 - Amendments to the decision granting the marketing authorisation and implementation

Article 23 - Amendments to the decision granting the marketing authorisation

1. Amendments to the decision granting the marketing authorisation resulting from the procedures laid down in Chapters II and IIa shall be made:
   (a) in the case of major variations of type II, within two months following receipt of the information referred to in Article 11(1)(c) and Article 13e(a), provided that the documents necessary for the amendment of the marketing authorisation have been transmitted to the Member States concerned;

(b) in the other cases, within six months following receipt of the information referred to in Article 11(1)(c) and Article 13e(a), provided that the documents necessary for the amendment of the marketing authorisation have been transmi tted to the Member States concerned.

1a. Amendments to the decision granting the marketing authorisation resulting from the procedures laid down in Chapter III shall be made:

(a) within two months following receipt of the information referred to in Article 17(1)(c) for the following variations:
   (i) variations related to the addition of a new therapeutic indication or to the modification of an existing one;
   (ii) variations related to the addition of a new contraindication;
   (iii) variations related to a change in posology;
   (iv) variations related to the addition of a non-food producing target species or the modification of an existing one for veterinary medicinal products;
   (v) variations concerning the replacement or addition of a serotype, strain, antigen or combination of serotypes, strains or antigens for a veterinary vaccine;
   (vi) variations related to changes to the active substance of a seasonal, pre-pandemic or pandemic vaccine against human influenza;
   (vii) variations related to changes to the withdrawal period for a veterinary medicinal product;
   (viii) other type II variations that are intended to implement changes to the decision granting the marketing authorisation due to a significant public health concern or significant animal health or environmental concern in the case of veterinary medicinal products;
(b) within 12 months following receipt of the information referred to in Article 17(1)(c) in the other cases.

   The Agency shall determine the variations referred to in point (a)(viii) and provide reasons for such determination.

2. Where the decision granting a marketing authorisation is amended as a result of one of the procedures laid down in Chapters II, IIa, III and IV, the relevant authority or, in the case of centralised marketing authorisations, the Commission shall notify the amended decision without delay to the holder.

Article 23a

The statement indicating compliance with the agreed completed paediatric investigation plan provided for under Article 28(3) of Regulation (EC) No 1901/2006 shall be included within the technical dossier of the marketing authorisation.

The relevant authority shall provide the holder with a confirmation that the statement is included in the technical dossier within 30 days after the relevant assessment has been concluded.

Article 24 - Implementation of variations

1. Minor variations of type IA may be implemented any time before completion of the procedures laid down in Articles 8, 13a and 14.

   Where a notification concerning one or several minor variations of type IA is rejected, the holder shall

cease to apply the concerned variation(s) immediately after receipt of the information referred to in Articles 11(1)(a), 13e(a), and 17(1)(a).

2. Minor variations of type IB may only be implemented in the following cases:
   (a) for variations submitted in accordance with the procedures laid down in Chapter II, after the competent authority of the reference Member State has informed the holder that it has accepted the notification pursuant to Article 9, or after the notification is deemed accepted pursuant to Article 9(2);
   (b) for variations submitted in accordance with the procedures laid down in Chapter IIa, after the relevant authority has informed the holder that it has accepted the notification pursuant to Article 13b, or after the notification is deemed accepted pursuant to Article 13b(2);
   (c) for variations submitted in accordance with the procedures laid down in Chapter III, after the Agency has informed the holder that its opinion referred to in Article 15 is favourable, or after that opinion is deemed favourable pursuant to Article 15(2);
   (d) for variations submitted in accordance with the procedure laid down in Article 20, after the reference authority has informed the holder that its opinion is favourable.
3. Major variations of type II may only be implemented in the following cases:
   (a) for variations submitted in accordance with the procedures laid down in Chapter II, 30 days after the competent authority of the reference Member State has informed the holder that it has accepted the variation pursuant to Article 10, under the condition that the documents necessary for the amendment to the marketing authorisation have been provided to the Member States concerned. Where an arbitration procedure has been initiated in accordance with Article 13, the holder shall not implement the variation until the arbitration procedure has concluded that the variation is accepted;
   (b) for variations submitted in accordance with the procedures laid down in Chapter IIa, after the competent authority has informed the holder that it has accepted the variation pursuant to Article 13c;
   (c) for variations submitted in accordance with the procedures laid down in Chapter III, after the Agency has informed the holder that its opinion referred to in Article 16 is favourable, unless the variation is one referred to in Article 23(1a)(a).

   Variations referred to in Article 23(1a)(a) may only be implemented after the Commission has amended the decision granting the marketing authorisation and notified the holder thereof;
   (d) for variations submitted in accordance with the procedure laid down in Article 20, 30 days after the reference authority has informed the holder that its opinion is favourable, under the condition that the documents necessary for the amendment to the marketing authorisation have been provided to the Member States concerned; unless an arbitration procedure has been initiated in accordance with Article 13, or unless the procedure concerns a variation to a centralised marketing authorisation as referred to in Article 23(1a)(a).

   Where an arbitration procedure has been initiated in accordance with Article 13, or where the worksharing procedure concerns a variation to a centralised marketing authorisation as referred to in Article 23(1a)(a), the holder shall not implement the variation until the arbitration procedure

has concluded that the variation is accepted, or until the Commission Decision amending the decision granting the marketing authorisation has been adopted.

4. An extension may only be implemented after the relevant authority or, in the case of extensions to a centralised marketing authorisation, the Commission has amended the decision granting the marketing authorisation and notified the holder accordingly.
5. Urgent safety restrictions and variations which are related to safety issues shall be implemented within a time frame agreed by the holder and the relevant authority and, in the case of a centralised marketing authorisation, the Agency.

   By way of derogation from the first subparagraph, urgent safety restrictions and variations related to safety issues which concern marketing authorisations granted in accordance with Chapter 4 of Directive 2001/82/EC or Chapter 4 of Directive 2001/83/EC shall be implemented within a time frame agreed by the holder and the competent authority of the reference Member State, in consultation with the other relevant authorities.

Article 24a - Application of national provisions on variations to purely national marketing authorisations

Member States that, in accordance with Article 23b(4) of Directive 2001/83/EC, may continue to apply their national provisions on variations to certain purely national marketing authorisations are listed in Annex VI to this Regulation.

CHAPTER V - FINAL PROVISIONS

Article 25 - Continuous monitoring

Where requested by a relevant authority, the holder shall supply without delay any information related to the implementation of a given variation.

Article 26 - Review

By two years from the date referred to in the second subparagraph of Article 28, the Commission services shall assess the application of this Regulation as regards the classification of variations, with a view to proposing any necessary amendments to adapt Annexes I, II and V to take account of scientific and technical progress.

Article 27 - Repeal and transitional provision

1. Regulations (EC) No 1084/2003 and (EC) No 1085/2003 are hereby repealed.

   References to the repealed Regulations shall be construed as references to this Regulation.
2. By way of derogation from paragraph 1, Regulations (EC) Nos 1084/2003 and 1085/2003 shall continue to apply to valid notifications or applications for variations which are pending at the date referred to in the second subparagraph of Article 28.

Article 28 - Entry into force

This Regulation shall enter into force on the 20th day following its publication in the Official Journal of the European Union.

It shall apply from 1 January 2010.

By way of derogation from the second subparagraph, the recommendations on unforeseen variations provided for in Article 5 may be requested, delivered and published from the date of entry into force referred to in the first subparagraph.

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

ANNEX I - Extensions of marketing authorizations

1. Changes to the active substance(s):
    (a) replacement of a chemical active substance by a different salt/ester complex/derivative, with the same therapeutic moiety, where the efficacy/safety characteristics are not significantly different;
    (b) replacement by a different isomer, a different mixture of isomers, of a mixture by an isolated isomer (e.g. racemate by a single enantiomer), where the efficacy/safety characteristics are not significantly different;
    (c) replacement of a biological active substance with one of a slightly different molecular structure where the efficacy/safety characteristics are not significantly different, with the exception of:
        - changes to the active substance of a seasonal, pre-pandemic or pandemic vaccine against human influenza;
        - replacement or addition of a serotype, strain, antigen or combination of serotypes, strains or antigens for a veterinary vaccine against avian influenza, foot-and-mouth disease or bluetongue;
        - replacement of a strain for a veterinary vaccine against equine influenza;
    (d) modification of the vector used to produce the antigen or the source material, including a new master cell bank from a different source, where the efficacy/safety characteristics are not significantly different;
    (e) a new ligand or coupling mechanism for a radiopharmaceutical, where the efficacy/safety characteristics are not significantly different;
    (f) change to the extraction solvent or the ratio of herbal drug to herbal drug preparation where the efficacy/safety characteristics are not significantly different.
2. Changes to strength, pharmaceutical form and route of administration:
    (a) change of bioavailability;
    (b) change of pharmacokinetics e.g. change in rate of release;
    (c) change or addition of a new strength/potency;
    (d) change or addition of a new pharmaceutical form;
    (e) change or addition of a new route of administration.
3. Other changes specific to veterinary medicinal products to be administered to food-producing animals: change or addition of target species.

ANNEX II - Classification of variations

1. The following variations shall be classified as minor variations of type IA:
    (a) variations of purely administrative nature that are related to the identity and contact details of:
        - the holder;
        - the manufacturer or supplier of any starting material, reagent, intermediate, active substance used in the manufacturing process or finished product;
    (b) variations related to the deletion of any manufacturing site, including for an active substance, intermediate or finished product, packaging site, manufacturer responsible for batch release, site where batch control takes place;
    (c) variations related to minor changes to an approved physico-chemical test procedure, where the updated procedure is demonstrated to be at least equivalent to the former test procedure, appropriate validation studies have been performed and the results show that the updated test procedure is at least equivalent to the former;
    (d) variations related to changes made to the specifications of the active substance or of an excipient in order to comply with an update of the relevant monograph of the European Pharmacopoeia or of the national pharmacopoeia of a Member State, where the change is made exclusively to comply with the pharmacopoeia and the specifications for product specific properties are unchanged;
    (e) variations related to changes in the packaging material not in contact with the finished product, which do not affect the delivery, use, safety or stability of the medicinal product;
    (f) variations related to the tightening of specification limits, where the change is not a consequence of any commitment from previous assessment to review specification limits and does not result from unexpected events arising during manufacture.
2. The following variations shall be classified as major variations of type II:
    (a) variations related to the addition of a new therapeutic indication or to the modification of an existing one;
    (b) variations related to significant modifications of the summary of product characteristics due in particular to new quality, pre-clinical, clinical or pharmacovigilance findings;
    (c) variations related to changes outside the range of approved specifications, limits or acceptance criteria;
    (d) variations related to substantial changes to the manufacturing process, formulation, specifications or impurity profile of the active substance or finished medicinal product which may have a significant impact on the quality, safety or efficacy of the medicinal product;
    (e) variations related to modifications in the manufacturing process or sites of the active substance for a biological medicinal product;
    (f) variations related to the introduction of a new design space or the extension of an approved one, where the design space has been developed in accordance with the relevant European and international scientific guidelines;

(g) variations concerning a change to or addition of a non-food producing target species;

(h) variations concerning the replacement or addition of a serotype, strain, antigen or combination of serotypes, strains or antigens for a veterinary vaccine against avian influenza, foot-and-mouth disease or bluetongue;

(i) variations concerning the replacement of a strain for a veterinary vaccine against equine influenza;

(j) variations related to changes to the active substance of a seasonal, pre-pandemic or pandemic vaccine against human influenza;

(k) variations related to changes to the withdrawal period for a veterinary medicinal product.

ANNEX III - Cases for grouping variations referred to in Article 7(2)(b) and Article 13d(2)(b)

1. One of the variations in the group is an extension of the marketing authorisation.
2. One of the variations in the group is a major variation of type II; all other variations in the group are variations which are consequential to this major variation of type II.
3. One of the variations in the group is a minor variation of type IB; all other variations in the group are minor variations which are consequential to this minor variation of type IB.
4. All variations in the group relate solely to changes of administrative nature to the summary of product characteristics, labelling and package leaflet or insert.
5. All variations in the group are changes to an Active Substance Master File, Vaccine Antigen Master File or Plasma Master File.
6. All variations in the group relate to a project intended to improve the manufacturing process and the quality of the medicinal product concerned or its active substance(s).
7. All variations in the group are changes affecting the quality of a human pandemic influenza vaccine.
8. All variations in the group are changes to the pharmacovigilance system referred to in points (ia) and (n) of Article 8(3) of Directive 2001/83/EC or points (k) and (o) of Article 12(3) of Directive 2001/82/EC.
9. All variations in the group are consequential to a given urgent safety restriction and submitted in accordance with Article 22.
10. All variations in the group relate to the implementation of a given class labelling.
11. All variations in the group are consequential to the assessment of a given periodic safety update report.
12. All variations in the group are consequential to a given post-authorisation study conducted under the supervision of the holder.
13. All variations in the group are consequential to a specific obligation carried out pursuant to Article 14(7) of Regulation (EC) No 726/2004.
14. All variations in the group are consequential to a specific procedure or condition carried out pursuant to Articles 14(8) or 39(7) of Regulation (EC) No 726/2004, Article 22 of Directive 2001/83/EC or Article 26(3) of Directive 2001/82/EC.

ANNEX IV - Elements to be submitted

1. A list of all the marketing authorisations affected by the notification or application.
2. A description of all the variations submitted, including:
    (a) in the case of minor variations of type IA, the date of implementation for each variation described;
    (b) in the case of minor variations of type IA which do not require immediate notification, a description of all minor variations of type IA made in the last 12 months to the terms of the concerned marketing authorisation(s) and which have not been already notified.
3. All necessary documents as listed in the guidelines referred to in point (b) of Article 4(1).
4. Where a variation leads to or is the consequence of other variations to the terms of the same marketing authorisation, a description of the relation between these variations.
5. In the case of variations to centralised marketing authorisations, the relevant fee provided for in Council Regulation (EC) No 297/95.
6. In the case of variations to marketing authorisations granted by the competent authorities of Member States:
    (a) a list of those Member States with an indication of the reference Member State if applicable;
    (b) the relevant fees provided for in the applicable national rules in the Member States concerned.

ANNEX V

PART 1

Variations concerning a change to or addition of therapeutic indications.

PART 2

1. Variations concerning a change to or addition of a non-food producing target species.
2. Variations concerning the replacement or addition of a serotype, strain, antigen or combination of serotypes, strains or antigens for a veterinary vaccine against avian influenza, foot-and-mouth disease or bluetongue.
3. Variations concerning the replacement of a strain for a veterinary vaccine against equine influenza.

ANNEX VI - List of Member States referred in Article 24a

the Republic of Bulgaria,

the Federal Republic of Germany.

COMMISSION IMPLEMENTING REGULATION (EU) NO 520/2012 OF 19 JUNE 2012 ON THE PERFORMANCE OF PHARMACOVIGILANCE ACTIVITIES PROVIDED FOR IN REGULATION (EC) NO 726/2004 OF THE EUROPEAN PARLIAMENT AND OF THE COUNCIL AND DIRECTIVE 2001/83/EC OF THE EUROPEAN PARLIAMENT AND OF THE COUNCIL

(Text with EEA relevance)

THE EUROPEAN COMMISSION,

Having regard to the Treaty on the Functioning of the European Union,

Having regard to Regulation (EC) No 726/2004 of the European Parliament and of the Council of 31 March 2004 laying down Community procedures for the authorisation and supervision of medicinal products for human and veterinary use and establishing a European Medicines Agency (1), and in particular Article 87a thereof,

Having regard to 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 (2), and in particular Article 108 thereof,

Whereas:

(1) Regulation (EU) No 1235/2010 of the European Parliament and of the Council of 15 December 2010 amending, as regards pharmacovigilance of medicinal products for human use, Regulation (EC) No 726/2004 laying down Community procedures for the authorisation and supervision of medicinal products for human and veterinary use and establishing a European Medicines Agency, and Regulation (EC) No 1394/2007 on advanced therapy medicinal products (3) strengthened and rationalised the monitoring of the safety of medicines that have been placed on the market in the Union. Similar provisions were introduced by Directive 2010/84/EU of the European Parliament and of the Council of 15 December 2010 amending, as regards pharmacovigilance, Directive 2001/83/EC on the Community code relating to medicinal products for human use (4) into Directive 2001/83/EC.

(2) Pharmacovigilance activities cover the whole life-cycle management of medicinal products for human use in relation to safety.

(3) Regulation (EU) No 1235/2010 and Directive 2010/84/EU introduced the concept of the pharmacovigilance system master file. In order to accurately reflect the pharmacovigilance system used by the marketing authorisation holder, the pharmacovigilance system master file should contain key information and documents covering all aspects of pharmacovigilance activities, including information on tasks that have been subcontracted. It should contribute to the appropriate planning and conduct of audits by the marketing authorisation holder and the supervision of pharmacovigilance activities by the qualified person responsible for pharmacovigilance. At the same time it should enable national competent authorities to verify compliance concerning all aspects of the system.

(4) The information contained in the pharmacovigilance system master file should be maintained so as to reflect any modifications that have been made and ensure easy accessibility and availability by national competent authorities for the purpose of inspections.

(5) Quality systems should form an integral part of the pharmacovigilance system. The minimum requirements for the quality system for the performance of pharmacovigilance activities should ensure that marketing authorisation holders, national competent authorities and the European Medicines Agency (hereinafter 'the Agency') establish an adequate and effective quality system, which provides for an effective monitoring of compliance and the accurate and proper documentation of all measures taken. They should also ensure that marketing authorisation holders, national competent authorities and the Agency have at their disposal sufficient competent, appropriately qualified and trained staff.

(6) Adherence to a well-defined quality system should ensure that all pharmacovigilance activities are conducted in such a way that they are likely to produce the desired results or quality objectives for the fulfillment of pharmacovigilance tasks.

(7) As part of their quality system, national competent authorities and the Agency should establish contact points to facilitate interaction between national competent authorities, the Agency, the Commission, marketing authorisation holders and persons reporting information on the risks of medicinal products, as referred to in the second subparagraph of Article 101(1) of Directive 2001/83/EC.

(8) If marketing authorisation holders, national competent authorities and the Agency use performance indicators to monitor the good performance of pharmacovigilance activities, those indicators should be documented.

(9) Pharmacovigilance activities rely increasingly on the periodic monitoring of large databases, such as the Eudravigilance database. Whereas the Eudravigilance database is expected to be a major source of pharmacovigilance information, account should also be taken of pharmacovigilance information coming from other sources.

(10) Marketing authorisation holders, national competent authorities and the Agency should continuously monitor the data in the Eudravigilance database to determine whether there are new risks or whether risks have changed and whether those risks have an impact on the risk-benefit balance of the medicinal product. They should validate and confirm signals, as appropriate, based on an examination of individual case safety reports, aggregated data from active surveillance systems or studies, literature information or other data sources. It is therefore necessary to establish common requirements for signal detection, to clarify the respective monitoring roles of marketing authorisation holders, national competent authorities and the Agency, to clarify how signals are validated and confirmed where appropriate and to specify the signal management process.

(11) As a general principle, signal detection should follow a recognised methodology. However, the methodology may vary depending on the type of medicinal product it is intended to cover.

(12) The use of internationally agreed terminology, format and standards should facilitate the interoperability of systems used for the performance of pharmacovigilance activities and avoids the duplication of encoding activities concerning the same information. It should also allow for an easier information exchange between regulatory authorities on an international level.

(13) In order to simplify the reporting of suspected adverse reactions, the marketing authorisation holder and the Member States should report those reactions only to the Eudravigilance database. The Eudravigilance database should be equipped to immediately forward reports on suspected adverse reactions received from

marketing authorisation holders to the Member States on whose territory the reaction occurred. It is therefore necessary to establish a common electronic format for the transmission of suspected adverse reaction reports by marketing authorisation holders and Member States to the Eudravigilance database.

(14) Periodic safety update reports are an important instrument to monitor the development of the safety profile of a medicinal product after it has been placed on the Union market, including an integrated (re-)evaluation of the risk-benefit balance. In order to facilitate their processing and evaluation, common format and content requirements should be established.

(15) Risk management plans are required for all new marketing authorisation applications. They contain a detailed description of the risk management system used by the marketing authorisation holder. In order to facilitate the production of risk management plans and their evaluation by the competent authorities, common format and content requirements should be established.

(16) Where competent authorities have concerns as to the safety of a medicinal product, they should be able to impose on marketing authorisation holders the obligation to conduct post-authorisation safety studies. The marketing authorisation holder should submit a draft protocol before those studies are conducted. Moreover, the marketing authorisation holder should provide, at the appropriate stage, a study abstract and a final study report. It is appropriate to provide that the protocol, the abstract and the final study report follow a common format in order to facilitate the approval and oversight of those studies by the Pharmacovigilance Risk Assessment Committee or the competent authorities in case of studies to be conducted in only one Member State that requests the study according to Article 22a of Directive 2001/83/EC.

(17) This Regulation should apply without prejudice to Directive 95/46/EC of the European Parliament and of the Council of 24 October 1995 on the protection of individuals with regard to the processing of personal data and on the free movement of such data (5) and Regulation (EC) No 45/2001 of the European Parliament and of the Council of 18 December 2000 on the protection of individuals with regard to the processing of personal data by the Community institutions and bodies and on the free movement of such data (6). The fundamental right to protection of personal data should be fully and effectively guaranteed in all pharmacovigilance activities. The purpose of safeguarding public health constitutes a substantial public interest and consequently the processing of personal data should be justified if identifiable personal data are processed only where necessary and only where the parties involved assess this necessity at every stage of the pharmacovigilance process. National competent authorities and marketing authorisation holders may apply pseudonymisation where appropriate, thereby replacing identifiable personal data with pseudonyms.

(18) The measures provided for in this Regulation are in accordance with the opinion of the Standing Committee for Medicinal Products for Human Use,

HAS ADOPTED THIS REGULATION:

CHAPTER I - Pharmacovigilance system master file

Article 1 - Structure of the pharmacovigilance system master file

1. The information in the pharmacovigilance system master file shall be accurate and reflect the pharmacovigilance system in place.

2. The marketing authorisation holder may, where appropriate, use separate pharmacovigilance systems for different categories of medicinal products. Each such system shall be described in a separate pharmacovigilance system master file.

   All medicinal products for which the marketing authorisation holder obtained a marketing authorisation in accordance with Directive 2001/83/EC or Regulation (EC) No 726/2004 shall be covered by a pharmacovigilance system master file.

Article 2 - Content of the pharmacovigilance system master file

The pharmacovigilance system master file shall contain at least all of the following elements:

1. the following information relating to the qualified person responsible for pharmacovigilance:
   (a) a description of the responsibilities demonstrating that the qualified person responsible for pharmacovigilance has sufficient authority over the pharmacovigilance system in order to promote, maintain and improve compliance with pharmacovigilance tasks and responsibilities;
   (b) a summary curriculum vitae of the qualified person responsible for pharmacovigilance, including proof of registration with the Eudravigilance database;
   (c) contact details of the qualified person responsible for pharmacovigilance;
   (d) details of back-up arrangements to apply in the absence of the qualified person responsible for pharmacovigilance;
   (e) responsibilities of the contact person for pharmacovigilance issues where such a person has been nominated at national level in accordance with Article 104(4) of Directive 2001/83/EC, including contact details;
2. a description of the organisational structure of the marketing authorisation holder, including the list of the site(s) where the following pharmacovigilance activities are undertaken: individual case safety report collection, evaluation, safety database case entry, periodic safety update report production, signal detection and analysis, risk management plan management, pre- and post-authorisation study management, and management of safety variations to the terms of a marketing authorisation;
3. a description of the location of, functionality of and operational responsibility for computerised systems and databases used to receive, collate, record and report safety information and an assessment of their fitness for purpose;
4. a description of data handling and recording and of the process used for each of the following pharmacovigilance activities:
   (a) the continuous monitoring of the risk-benefit balance of the medicinal product(s), the result of that monitoring and the decision-making process for taking appropriate measures;
   (b) operation of the risk management system(s) and of the monitoring of the outcome of risk minimisation measures;
   (c) collection, assessment and reporting of individual case safety reports;
   (d) drafting and submission of periodic safety update reports;
   (e) procedures for communicating safety concerns and safety variations to the summary of product characteristics and package leaflet to healthcare professionals and the general public;

5. a description of the quality system for the performance of pharmacovigilance activities, including all of the following elements:
    (a) a description of the management of human resources referred to in Article 10 containing the following elements: a description of the organisational structure for the performance of pharmacovigilance activities with a reference to the location of qualification records of the personnel; a summary description of the training concept, including a reference to the location of training files; instructions on critical processes;
    (b) a description of the record management system referred to in Article 12, including the location of the documents used for pharmacovigilance activities;
    (c) a description of the system for monitoring the performance of the pharmacovigilance system and for the compliance with Article 11;
6. where applicable, a description of the activities and/or services subcontracted by the marketing authorisation holder in accordance with Article 6(1).

Article 3 - Content of the Annex to the pharmacovigilance system master file

The pharmacovigilance system master file shall have an Annex containing the following documents:

1. a list of medicinal products covered by the pharmacovigilance system master file, including the name of the medicinal product, the international non-proprietary name (INN) of the active substance(s), and the Member State(s) in which the authorisation is valid;
2. a list of written policies and procedures for the purpose of complying with Article 11(1);
3. the list of subcontracts referred to in Article 6(2);
4. a list of the tasks that have been delegated by the qualified person for pharmacovigilance;
5. a list of all scheduled and completed audits;
6. where applicable, a list of the performance indicators referred to in Article 9;
7. where applicable, a list of other pharmacovigilance system master files held by the same marketing authorisation holder;
8. logbook containing the information referred to in Article 5(4).

Article 4 - Maintenance

1. The marketing authorisation holder shall keep the pharmacovigilance system master file up to date and, where necessary, revise it to take account of experience gained, of technical and scientific progress and of amendments to Directive 2001/83/EC and Regulation (EC) No 726/2004.
2. The pharmacovigilance system master file and its Annex shall be subject to version control and shall indicate the date when it was last updated by the marketing authorisation holder.
3. Any deviations from the pharmacovigilance procedures, their impact and their management shall be documented in the pharmacovigilance system master file until resolved.
4. Without prejudice to the requirements set out in Commission Regulation (EC) No 1234/2008 of 24 November 2008 concerning the examination of variations to the terms of marketing authorisations for medicinal products for human use and veterinary medicinal products (7), the marketing authorisation holder shall notify immediately the Agency of any change in the location of the pharmacovigilance system

master file or changes to the contact details and name of the qualified person responsible for pharmacovigilance. The Agency shall update the Eudravigilance database referred to in Article 24(1) of Regulation (EC) No 726/2004 and, where necessary, the European medicines web-portal referred to in Article 26(1) of Regulation (EC) No 726/2004 accordingly.

Article 5 - Form of the documents contained in the pharmacovigilance system master file

1. Pharmacovigilance system master file documents shall be complete and legible. Where appropriate, information may be provided in the form of charts or flow diagrams. All documents shall be indexed and archived so as to ensure their accurate and ready retrieval throughout the period for record-keeping.
2. The particulars and documents of the pharmacovigilance system master file may be presented in modules in accordance with the system delineated in detail in the guidance on good pharmacovigilance practices.
3. The pharmacovigilance system master file may be stored in electronic form provided that the media used for storage remain readable over time and a clearly arranged printed copy can be made available for audits and inspections.
4. The marketing authorisation holder shall record in the logbook referred to in point 8 of Article 3 any alteration of the content of the pharmacovigilance system master file made within the last five years, with the exception of the information referred to in point 1(b) to (e) of Article 2 and in Article 3. The marketing authorisation holder shall indicate in the logbook the date, the person responsible for the alteration and, where appropriate, the reason for the alteration.

Article 6 - Subcontracting

1. The marketing authorisation holder may subcontract certain activities of the pharmacovigilance system to third parties. It shall nevertheless retain full responsibility for the completeness and accuracy of the pharmacovigilance system master file.
2. The marketing authorisation holder shall draw up a list of its existing subcontracts between it and the third parties referred to in paragraph 1, specifying the product(s) and territory(ies) concerned.

Article 7 - Availability and location of the pharmacovigilance system master file

1. The pharmacovigilance system master file shall be located either at the site in the Union where the main pharmacovigilance activities of the marketing authorisation holder are performed or at the site in the Union where the qualified person responsible for pharmacovigilance operates.
2. The marketing authorisation holder shall ensure that the qualified person for pharmacovigilance has permanent access to the pharmacovigilance system master file.
3. The pharmacovigilance system master file shall be permanently and immediately available for inspection at the site where it is kept.

Where the pharmacovigilance system master file is kept in electronic form in accordance with Article 5(3), it is sufficient for the purposes of this Article that the data stored in electronic form is directly available at the site where the pharmacovigilance system master file is kept.

4. For the purposes of Article 23(4) of Directive 2001/83/EC, the national competent authority may limit its request to specific parts or modules of the pharmacovigilance system master file and the marketing authorisation holder shall bear the costs of submitting the copy of the pharmacovigilance system master file.
5. The national competent authority and the Agency may request the marketing authorisation holder to submit a copy of the logbook referred to in point 8 of Article 3 at regular intervals.

CHAPTER II - Minimum requirements for the quality systems for the performance of pharmacovigilance activities

Section 1 - General provisions

Article 8 - Quality system

1. Marketing authorisation holders, the national competent authorities and the Agency shall establish and use a quality system that is adequate and effective for the performance of their pharmacovigilance activities.
2. The quality system shall cover organisational structure, responsibilities, procedures, processes and resources, appropriate resource management, compliance management and record management.
3. The quality system shall be based on all of the following activities:
    (a) quality planning: establishing structures and planning integrated and consistent processes;
    (b) quality adherence: carrying out tasks and responsibilities in accordance with quality requirements;
    (c) quality control and assurance: monitoring and evaluating how effectively the structures and processes have been established and how effectively the processes are being carried out;
    (d) quality improvements: correcting and improving the structures and processes where necessary.
4. All elements, requirements and provisions adopted for the quality system shall be documented in a systematic and orderly manner in the form of written policies and procedures, such as quality plans, quality manuals and quality records.
5. All persons involved in the procedures and processes of the quality systems established by the national competent authorities and the Agency for the performance of pharmacovigilance activities shall be responsible for the good functioning of those quality systems and shall ensure a systematic approach towards quality and towards the implementation and maintenance of the quality system.

Article 9 - Performance indicators

1. The marketing authorisation holder, national competent authorities and the Agency may use performance indicators to continuously monitor the good performance of pharmacovigilance activities.
2. The Agency may publish a list of performance indicators on the basis of a recommendation of the Pharmacovigilance Risk Assessment Committee.

Section 2 - Minimum requirements for the quality systems for the performance of pharmacovigilance activities by marketing authorisation holders

Article 10 - Management of human resources

1. The marketing authorisation holder shall have sufficient competent and appropriately qualified and trained personnel available for the performance of pharmacovigilance activities.

   For the purposes of the first subparagraph, the market authorisation holder shall ensure that the qualified person responsible for pharmacovigilance has acquired adequate theoretical and practical knowledge for the performance of pharmacovigilance activities. Where the qualified person has not completed basic medical training in accordance with Article 24 of Directive 2005/36/EC of the European Parliament and of the Council of 7 September 2005 on the recognition of professional qualifications (8), the market authorisation holder shall ensure that the qualified person responsible for pharmacovigilance is assisted by a medically trained person. This assistance shall be duly documented.
2. The duties of the managerial and supervisory staff, including the qualified person responsible for pharmacovigilance, shall be defined in job descriptions. Their hierarchical relationships shall be defined in an organisational chart. The marketing authorisation holder shall ensure that the qualified person responsible for pharmacovigilance has sufficient authority to influence the performance of the quality system and the pharmacovigilance activities of the marketing authorisation holder.
3. All personnel involved in the performance of pharmacovigilance activities shall receive initial and continued training in relation to their role and responsibilities. The marketing authorisation holder shall keep training plans and records for documenting, maintaining and developing the competences of personnel and make them available for audit or inspection.
4. The marketing authorisation holder shall provide appropriate instructions on the processes to be used in case of urgency, including business continuity.

Article 11 - Compliance management

1. Specific quality system procedures and processes shall be in place in order to ensure the following:
   (a) the continuous monitoring of pharmacovigilance data, the examination of options for risk minimisation and prevention and appropriate measures are taken by the marketing authorisation holder;
   (b) the scientific evaluation by the marketing authorisation holder of all information on the risks of medicinal products, as referred to in the second subparagraph of Article 101(1) of Directive 2001/83/EC;
   (c) the submission of accurate and verifiable data on serious and non-serious adverse reactions to the Eudravigilance database within the time limits provided for in the first and second subparagraphs respectively of Article 107(3) of Directive 2001/83/EC;
   (d) the quality, integrity and completeness of the information submitted on the risks of medicinal products, including processes to avoid duplicate submissions and to validate signals in accordance with Article 21(2);
   (e) effective communication by the marketing authorisation holder with the national competent authorities and the Agency, including communication on new risks or changed risks, the

pharmacovigilance system master file, risk management systems, risk minimisation measures, periodic safety update reports, corrective and preventive actions, and post-authorisation studies;

(f) the update of product information by the marketing authorisation holder in the light of scientific knowledge, including the assessments and recommendations made public via the European medicines web-portal, and on the basis of a continuous monitoring by the marketing authorisation holder of information published on the European medicines web-portal;

(g) appropriate communication by the marketing authorisation holder of relevant safety information to healthcare professionals and patients.

2. Where a marketing authorisation holder has subcontracted some of its pharmacovigilance tasks, it shall retain responsibility for ensuring that an effective quality system is applied in relation to those tasks.

Article 12 - Record management and data retention

1. Marketing authorisation holders shall record all pharmacovigilance information and ensure that it is handled and stored so as to allow for accurate reporting, interpretation and verification of that information.

   Marketing authorisation holders shall put in place a record management system for all documents used for pharmacovigilance activities that ensures the retrievability of those documents as well as the traceability of the measures taken to investigate safety concerns, of the timelines for those investigations and of decisions on safety concerns, including their date and the decision-making process.

   Marketing authorisation holders shall establish mechanisms enabling the traceability and follow-up of adverse reaction reports.

2. Marketing authorisation holders shall arrange for the elements referred to in Article 2 to be kept for at least five years after the system as described in the pharmacovigilance system master file has been formally terminated by the marketing authorisation holder.

   Pharmacovigilance data and documents relating to individual authorised medicinal products shall be retained as long as the product is authorised and for at least 10 years after the marketing authorisation has ceased to exist. However, the documents shall be retained for a longer period where Union law or national law so requires.

Article 13 - Audit

1. Risk-based audits of the quality system shall be performed at regular intervals to ensure that the quality system complies with the quality system requirements set out in Articles 8, 10, 11 and 12 and to determine its effectiveness. Those audits shall be conducted by individuals who have no direct involvement in or responsibility for the matters or processes being audited.

2. Corrective action(s), including a follow-up audit of deficiencies, shall be taken where necessary. A report on the results of the audit shall be drawn up for each audit and follow-up audit. The audit report shall be sent to the management responsible for the matters audited. The dates and results of audits and follow-up audits shall be documented in accordance with the second subparagraph of Article 104(2) of Directive 2001/83/EC.

Section 3 - Minimum requirements for the quality systems for the performance of pharmacovigilance activities by national competent authorities and the Agency

Article 14 - Management of human resources

1. The national competent authorities and the Agency shall have sufficient competent and appropriately qualified and trained personnel available for the performance of pharmacovigilance activities.
   The organisational structures and the distribution of tasks and responsibilities shall be clear and, to the extent necessary, accessible. Contact points shall be established.
2. All personnel involved in the performance of pharmacovigilance activities shall receive initial and continued training. The national competent authorities and the Agency shall keep training plans and records for documenting, maintaining and developing the competences of personnel and shall make them available for audit.
3. Appropriate instructions on the processes to be used in case of urgency, including business continuity, shall be provided by the national competent authorities and by the Agency to their personnel.

Article 15 - Compliance management

1. The national competent authorities and the Agency shall establish specific procedures and processes in order to achieve all of the following objectives:
   (a) ensuring the evaluation of the quality, including completeness, of pharmacovigilance data submitted;
   (b) ensuring the assessment of pharmacovigilance data and its processing within the timelines provided by Directive 2001/83/EC and Regulation (EC) No 726/2004;
   (c) ensuring independence in the performance of pharmacovigilance activities;
   (d) ensuring effective communication among national competent authorities and between the national competent authorities and the Agency as well as with patients, healthcare professionals, marketing authorisation holders and the general public;
   (e) guaranteeing that the national competent authorities and the Agency inform each other and the Commission of their intention to make announcements relating to the safety of a medicinal product authorised in several Member States or an active substance contained in such a medicinal product in accordance with Article 106a of Directive 2001/83/EC;
   (f) conducting inspections, including pre-authorisation inspections.
2. In addition to the procedures referred to in paragraph 1, national competent authorities shall establish procedures for collecting and recording all suspected adverse reactions that occur in their territory.
3. The Agency shall establish procedures for the monitoring of medical literature in accordance with Article 27 of Regulation (EC) No 726/2004.

Article 16 - Record management and data retention

1. The national competent authorities and the Agency shall record all pharmacovigilance information and ensure that it is handled and stored so as to allow for accurate reporting, interpretation and verification of that information.

They shall put in place a record management system for all documents used for pharmacovigilance activities that ensures the retrievability of those documents as well as the traceability of the measures taken to investigate safety concerns, of the timelines for those investigations and of decisions on safety concerns, including their date and the decision-making process.

2. The national competent authorities and the Agency shall arrange for the essential documents describing their pharmacovigilance system to be kept for at least five years after the system has been formally terminated.

   Pharmacovigilance data and documents relating to individual authorised medicinal products shall be retained as long as the product is authorised and for at least 10 years after the marketing authorisation has expired. However, the documents shall be retained for a longer period where Union law or national law so requires.

Article 17 - Audit

1. Risk-based audits of the quality system shall be performed at regular intervals according to a common methodology to ensure that the quality system complies with the requirements set out in Articles 8, 14, 15 and 16 and to ensure its effectiveness.
2. Corrective action, including a follow-up audit of deficiencies, shall be taken where necessary. The audit report shall be sent to the management responsible for the matters audited. The dates and results of audits and follow-up audits shall be documented.

CHAPTER III - Minimum requirements for the monitoring of data in the Eudravigilance database

Article 18 - General requirements

1. The Agency and national competent authorities shall cooperate in the monitoring of the data available in the Eudravigilance database.
2. Marketing authorisation holders shall monitor the data available in the Eudravigilance database to the extent that they have access to that database.
3. Marketing authorisation holders, the national competent authorities and the Agency shall ensure the continuous monitoring of the Eudravigilance database with a frequency proportionate to the identified risk, the potential risks and the need for additional information.
4. The competent authority of each Member State shall be responsible for monitoring the data originating in the territory of that Member State.

Article 19 - Identification of changed risks and new risks

1. The identification of new risks or changed risks shall be based on the detection and analysis of the signals concerning a medicinal product or an active substance.

   For the purposes of this chapter, ‘signal’ means information arising from one or multiple sources, including observations and experiments, which suggests a new potentially causal association, or a new aspect of a known association between an intervention and an event or set of related events, either adverse or

beneficial, which is judged to be of sufficient likelihood to justify verificatory action.

For the purpose of monitoring data in the Eudravigilance database, only signals related to an adverse reaction shall be considered.

2. The detection of a signal shall be based on a multidisciplinary approach. Signal detection within the Eudravigilance database shall be complemented by statistical analysis, where appropriate. After consultation with the Pharmacovigilance Risk Assessment Committee, the Agency may publish a list of medical events that have to be taken into account for the detection of a signal.

Article 20 - Methodology for determining the evidentiary value of a signal

1. National competent authorities, marketing authorisation holders and the Agency shall determine the evidentiary value of a signal by using a recognised methodology taking into account the clinical relevance, quantitative strength of the association, the consistency of the data, the exposure–response relationship, the biological plausibility, experimental findings, possible analogies and the nature and quality of the data.
2. Different types of factors may be taken into account for the prioritisation of signals, in particular whether the association or medicinal product is new, factors related to the strength of the association, factors related to the seriousness of the reaction involved and factors related to the documentation of reports to the Eudravigilance database.
3. The Pharmacovigilance Risk Assessment Committee shall regularly review the methodology(ies) used and publish recommendations, as appropriate.

Article 21 - Signal management process

1. The signal management process shall include the following activities: signal detection, signal validation, signal confirmation, signal analysis and prioritisation, signal assessment, and recommendation for action.

   For the purposes of this Article, 'signal validation' means the process of evaluating the data supporting the detected signal in order to verify that the available documentation contains sufficient evidence demonstrating the existence of a new potentially causal association, or a new aspect of a known association, and therefore justifies further analysis of the signal.
2. Where a marketing authorisation holder detects a new signal when monitoring the Eudravigilance database, it shall validate it and shall forthwith inform the Agency and national competent authorities.
3. Where it is considered that a validated signal requires further analysis, it shall be confirmed as soon as possible and no later than 30 days from its receipt as follows:
   (a) where the signal concerns a product authorised in accordance with Directive 2001/83/EC, it shall be confirmed by the competent authority of a Member State in which the medicinal product is marketed or of any lead Member State or co-leader appointed in accordance with Article 22(1);
   (b) where the signal concerns a product authorised in accordance with Regulation (EC) No 726/2004, it shall be confirmed by the Agency in collaboration with the Member States.

   When analysing the validated signal, national competent authorities and the Agency may take into account other information available on the medicinal product.

Where the validity of the signal is not confirmed, special attention shall be paid to non-confirmed signals concerning a medicinal product where those signals are subsequently followed by new signals concerning the same medicinal product.

4. Without prejudice to paragraphs 2 and 3, national competent authorities and the Agency shall validate and confirm any signal that they have detected during their continuous monitoring of the Eudravigilance database.
5. Any confirmed signal shall be entered in the tracking system administered by the Agency and shall be transmitted to the Pharmacovigilance Risk Assessment Committee for the initial analysis and prioritisation of signals in accordance with Article 107h(2) of Directive 2001/83/EC and Article 28a(2) of Regulation (EC) No 726/2004.
6. The Agency shall inform forthwith the marketing authorisation holder(s) concerned of the conclusions of the Pharmacovigilance Risk Assessment Committee of the assessment of any confirmed signal.

Article 22 - Worksharing for signal management

1. For medicinal products authorised in accordance with Directive 2001/83/EC in more than one Member State and for active substances contained in several medicinal products where at least one marketing authorisation has been granted in accordance with Directive 2001/83/EC, Member States may agree within the coordination group provided for by Article 27 of Directive 2001/83/EC to appoint a lead Member State and, where appropriate, a co-leader. Any such appointment shall be reviewed at least every four years.

   The lead Member State shall monitor the Eudravigilance database and shall validate and confirm signals in accordance with Article 21(3) and (4) on behalf of the other Member States. The Member State appointed as co-leader shall assist the lead Member State in the fulfillment of its tasks.
2. When appointing a lead Member State and as appropriate a co-leader, the coordination group may take into account whether any Member State is acting as reference Member State in accordance with Article 28(1) of Directive 2001/83/EC or as a rapporteur for the assessment of periodic safety update reports in accordance with Article 107e of that Directive.
3. The Agency shall publish on the European medicines web-portal a list of the active substances that are subject to worksharing in accordance with this Article and the lead Member State and co-leader appointed for monitoring those substances in the Eudravigilance database.
4. Without prejudice to paragraph 1, all Member States shall remain responsible for monitoring the data in the Eudravigilance database in accordance with Article 107h(1)(c) and Article 107h(3) of Directive 2001/83/EC.
5. For medicinal products authorised in accordance with Regulation (EC) No 726/2004, the Agency shall be assisted in the monitoring of data in the Eudravigilance database by the rapporteur appointed by the Pharmacovigilance Risk Assessment Committee in accordance with Article 62(1) of Regulation (EC) No 726/2004.

Article 23 - Signal detection support

The Agency shall support the monitoring of the Eudravigilance database by providing national competent authorities with access to the following information:

(a) data outputs and statistical reports allowing a review of all adverse reactions reported to the Eudravigilance database in relation to an active substance or a medicinal product;

(b) customised queries supporting the evaluation of individual case safety reports and case series;

(c) grouping and stratification of data enabling the identification of patient groups with a higher risk of occurrence of adverse reactions or with a risk of a more severe adverse reaction;

(d) statistical signal detection methods.

The Agency shall also ensure appropriate support for the monitoring of the Eudravigilance database by marketing authorisation holders.

Article 24 - Signal detection audit trail

1. The national competent authorities and the Agency shall keep an audit trail of their signal detection activities conducted in the Eudravigilance database and of the relevant queries and their results.
2. The audit trail shall allow traceability of how signals have been detected and of how validated and confirmed signals have been assessed.

CHAPTER IV - Use of terminology, formats and standards

Article 25 - Use of internationally agreed terminology

1. For the classification, retrieval, presentation, risk-benefit evaluation and assessment, electronic exchange and communication of pharmacovigilance and medicinal product information, Member States, marketing authorisation holders and the Agency shall apply the following terminology:

(a) the Medical Dictionary for Regulatory Activities (MedDRA) as developed by the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH), multidisciplinary topic M1;

(b) the lists of Standard Terms published by the European Pharmacopoeia Commission;

(c) the terminology set out in EN ISO 11615:2012, Health Informatics, Identification of Medicinal Products (IDMP) standard, 'Data elements and structures for unique identification and exchange of regulated medicinal product information' (ISO/FDIS 11615:2012);

(d) the terminology set out in EN ISO 11616:2012 Health Informatics, Identification of Medicinal Products (IDMP) standard, 'Data elements and structures for unique identification and exchange of regulated pharmaceutical product information' (ISO/FDIS 11616:2012);

(e) the terminology set out in EN ISO 11238:2012 Health Informatics, Identification of Medicinal Products (IDMP) standard, 'Data elements and structures for unique identification and exchange of regulated information on substances' (ISO/FDIS 11238:2012);

(f) the terminology set out in EN ISO 11239:2012 Health Informatics, Identification of Medicinal Products (IDMP) standard, 'Data elements and structures for unique identification and exchange of regulated information on pharmaceutical dose forms, units of presentation and routes of administration' (ISO/FDIS 11239:2012);

(g) the terminology set out in EN ISO 11240:2012 Health Informatics, Identification of Medicinal Products (IDMP) standard, 'Data elements and structures for unique identification and exchange of units of measurement' (ISO/FDIS 11240:2012).

2. Member States, national competent authorities or marketing authorisation holders shall request the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use, the European Pharmacopoeia Commission, the European Committee for Standardisation or the International Organisation for Standardisation to add a new term to the terminology referred to in paragraph 1, where necessary. In such a case, they shall inform the Agency accordingly.
3. Member States, marketing authorisation holders and the Agency shall monitor the use of the terminology referred to in paragraph 1 either systematically or by regular random evaluation.

Article 26 - Use of internationally agreed formats and standards

1. For the description, retrieval, presentation, risk-benefit evaluation and assessment, electronic exchange and communication of pharmacovigilance and medicinal product information, national competent authorities, marketing authorisation holders and the Agency shall apply the following formats and standards:
    (a) the Extended Eudravigilance Medicinal Product Report Message (XEVPRM), which is the format for the electronic submission of information on all medicinal products for human use authorised in the Union in accordance with the second subparagraph of Article 57(2) of Regulation (EC) No 726/2004, as published by the Agency;
    (b) ICH E2B(R2) 'Maintenance of the ICH guideline on clinical safety data management: data elements for transmission of Individual Case Safety Reports';
    (c) ICH M2 standard 'Electronic Transmission of Individual Case Safety Reports Message Specification'.
2. For the purpose of paragraph 1 national competent authorities, marketing authorisation holders and the Agency may also apply the following formats and standards:
    (a) EN ISO 27953-2:2011 Health Informatics, Individual case safety reports (ICSRs) in pharmacovigilance — Part 2: Human pharmaceutical reporting requirements for ICSR (ISO 27953-2:2011);
    (b) EN ISO 11615:2012, Health Informatics, Identification of Medicinal Products (IDMP) standard, 'Data elements and structures for unique identification and exchange of regulated medicinal product information' (ISO/FDIS 11615:2012);
    (c) EN ISO 11616:2012, Health Informatics, Identification of Medicinal Products (IDMP) standard 'Data elements and structures for unique identification and exchange of regulated pharmaceutical product information' (ISO/FDIS 11616:2012);
    (d) EN ISO 11238:2012, Health Informatics, Identification of Medicinal Products (IDMP) standard, 'Data elements and structures for unique identification and exchange of regulated information on substances' (ISO/FDIS 11238:2012);
    (e) EN ISO 11239:2012, Health Informatics, Identification of Medicinal Products (IDMP) standard, 'Data elements and structures for unique identification and exchange of regulated information on

pharmaceutical dose forms, units of presentation and routes of administration' (ISO/FDIS 11239:2012);

(f) EN ISO 11240:2012, Health Informatics, Identification of Medicinal Products (IDMP) standard, 'Data elements and structures for unique identification and exchange of units of measurement' (ISO/FDIS 11240:2012).

CHAPTER V - Transmission of reports of suspected adverse reactions

Article 27 - Individual case safety reports

Individual case safety reports shall be used for reporting to the Eudravigilance database suspected adverse reactions to a medicinal product that occur in a single patient at a specific point in time.

Article 28 - Content of the individual case safety report

1. Member States and marketing authorisation holders shall ensure that individual case safety reports are as complete as possible and shall communicate the updates of those reports to the Eudravigilance database in an accurate and reliable manner.

   In the case of expedited reporting, the individual case safety report shall include at least an identifiable reporter, an identifiable patient, one suspected adverse reaction and the medicinal product(s) concerned.
2. Member States and marketing authorisation holders shall record the details necessary for obtaining follow-up information on individual case safety reports. The follow-up of reports shall be adequately documented.
3. When reporting suspected adverse reactions, Member States and marketing authorisation holders shall provide all available information on each individual case, including the following:
   (a) administrative information: report type, date and a worldwide unique case identification number as well as unique sender identification and sender type; the date on which the report was first received from the source and the date of receipt of the most recent information, using a precise date; other case identifiers and their sources, as well as references to additional available documents held by the sender of the individual case safety report, where applicable;
   (b) literature reference in accordance with the 'Vancouver style' as developed by the International Committee of Medical Journal Editors (9) for adverse reactions reported in the worldwide literature, including a comprehensive English summary of the article;
   (c) study type, study name and the sponsor's study number or study registration number for reports from studies not covered by 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 use (10);
   (d) information on the primary source(s): information identifying the reporter, including Member State of residence and professional qualifications;
   (e) information identifying the patient (and parent in the case of a parent-child report), including age at the time of the onset of the first reaction, age group, gestation period when reaction/event was

observed in the foetus, weight, height or gender, last menstrual date and/or gestation period at time of exposure;

(f) relevant medical history and concurrent conditions;

(g) the name, as defined in Article 1(20) of Directive 2001/83/EC, of the medicinal product(s) suspected to be related to the occurrence of the adverse reaction, including interacting medicinal products or, where the name is not known, the active substance(s) and any other characteristics that allow for the identification of the medicinal product(s), including the name of the marketing authorisation holder, marketing authorisation number, country of marketing authorisation, pharmaceutical form and (parent) route(s) of administration, indication(s) for use in the case, dose administered, start date and end date of administration, actions taken with the medicinal product(s), effect of the dechallenge and rechallenge for suspect medicinal products;

(h) for biological medicinal product(s), the batch number(s);

(i) concomitant medicinal products, identified in accordance with point (g), which are not suspected to be related to the occurrence of the adverse reaction and past-medical drug therapy for the patient (and for the parent), where applicable;

(j) information on the suspected adverse reaction(s): start date and end date of the suspected adverse reaction(s) or duration, seriousness, outcome of the suspected adverse reaction(s) at the time of last observation, time intervals between suspect medicinal product administration and start of adverse reaction, the original reporter's words or short phrases used to describe the reaction(s) and Member State or third-country of occurrence of the suspected adverse reaction;

(k) results of tests and procedures relevant to the investigation of the patient;

(l) date and reported cause of death, including autopsy-determined causes, in the event of death of the patient;

(m) a case narrative, where possible, providing all relevant information for individual cases with the exception of non-serious adverse reactions;

(n) reasons for nullifying or amending an individual case safety report.

For the purposes of point (b), upon request of the Agency, the marketing authorisation holder that transmitted the initial report shall provide a copy of the relevant article taking into account copyright restrictions, and a full translation of that article into English.

For the purposes of point (h), a follow-up procedure shall be in place to obtain the batch number where it is not indicated in the initial report.

For the purposes of point (m), the information shall be presented in a logical time sequence, in the chronology of the patient's experience including clinical course, therapeutic measures, outcome and follow-up information obtained; any relevant autopsy or post-mortem findings shall also be summarised in the narrative.

4. Where suspected adverse reactions are reported in narrative and textual descriptions in an official language of the Union other than English, the original verbatim text and a summary thereof in English shall be provided by the marketing authorisation holder.

Member States may report case narratives in their official language(s). For those reports, case translations shall be provided where requested by the Agency or other Member States for the evaluation of potential

signals.

English shall be used for the reporting of suspected adverse reactions originating outside the Union.

Article 29 - Format of electronic transmission of suspected adverse reactions

Member States and marketing authorisation holders shall use the formats provided for in Article 26 and the terminology provided for in Article 25 for the electronic transmission of suspected adverse reactions.

CHAPTER VI - Risk management plans

Article 30 - Content of the risk management plan

1. The risk management plan established by the marketing authorisation holder shall contain the following elements:
   (a) an identification or characterisation of the safety profile of the medicinal product(s) concerned;
   (b) an indication of how to characterise further the safety profile of the medicinal product(s) concerned;
   (c) a documentation of measures to prevent or minimise the risks associated with the medicinal product, including an assessment of the effectiveness of those interventions;
   (d) a documentation of post-authorisation obligations that have been imposed as a condition of the marketing authorisation.
2. Products containing the same active substance and belonging to the same marketing authorisation holder may be subject, where appropriate, to the same risk management plan.
3. Where a risk management plan refers to post-authorisation studies, it shall indicate whether those studies are initiated, managed or financed by the marketing authorisation holder voluntarily or pursuant to obligations imposed by the national competent authorities, the Agency or the Commission. All post-authorisation obligations shall be listed in the summary of the risk management plan together with a timeframe.

Article 31 - Summary of the risk management plan

1. The summary of the risk management plan to be made publicly available in accordance with point (c) of Article 106 of Directive 2001/83/EC and Article 26(1)(c) of Regulation (EC) No 726/2004 shall include key elements of the risk management plan with a specific focus on risk minimisation activities and, with regard to the safety specification of the medicinal product concerned, important information on potential and identified risks as well as missing information.
2. Where a risk management plan concerns more than one medicinal product, a separate summary of the risk management plan shall be provided for each medicinal product.

Article 32 - Updates of the risk management plan

1. Where the marketing authorisation holder updates a risk management plan, it shall submit the updated risk management plan to the national competent authorities or the Agency as appropriate. After agreement with the national competent authorities or the Agency as appropriate, the marketing

authorisation holder may submit only the modules concerned by the update. If necessary, the marketing authorisation holder shall provide the competent authorities or the Agency with an updated summary of the risk management plan.

2. Each submission of the risk management plan shall have a distinct version number and shall be dated.

Article 33 - Format of the risk management plan

The risk management plan shall be in the format set out in Annex I.

CHAPTER VII - Periodic safety update reports

Article 34 - Content of periodic safety update reports

1. The periodic safety` update report shall be based on all available data and shall focus on new information which has emerged since the data lock point of the last periodic safety update report.
2. The periodic safety update report shall provide an accurate estimate of the population exposed to the medicinal product, including all data relating to the volume of sales and volume of prescriptions. This estimate of exposure shall be accompanied by a qualitative and quantitative analysis of actual use, which shall indicate, where appropriate, how actual use differs from the indicated use based on all data available to the marketing authorisation holder, including the results of observational or drug utilisation studies.
3. The periodic safety update report shall contain the results of assessments of the effectiveness of risk minimisation activities relevant to the risk–benefit assessment.
4. Marketing authorisation holders shall not be required to include systematically detailed listings of individual cases, including case narratives, in the periodic safety update report. However, they shall provide case narratives in the relevant risk evaluation section of the periodic safety update report where integral to the scientific analysis of a signal or safety concern in the relevant risk evaluation section.
5. Based on the evaluation of the cumulative safety data and the risk-benefit analysis, the marketing authorisation holder shall draw conclusions in the periodic safety update report as to the need for changes and/or actions, including implications for the approved summary of product characteristics for the product(s) for which the periodic safety update report is submitted.
6. Unless otherwise specified in the list of Union reference dates and frequency of submission referred to in Article 107c of Directive 2001/83/EC or agreed with the national competent authorities or the Agency, as appropriate, a single periodic safety update report shall be prepared for all medicinal products containing the same active substance and authorised for one marketing authorisation holder. The periodic safety update report shall cover all indications, routes of administration, dosage forms and dosing regimens, irrespective of whether authorised under different names and through separate procedures. Where relevant, data relating to a particular indication, dosage form, route of administration or dosing regimen shall be presented in a separate section of the periodic safety update report and any safety concerns shall be addressed accordingly.
7. Unless otherwise specified in the list of Union reference dates and frequency of submission referred to in Article 107c of Directive 2001/83/EC, if the substance that is the subject of the periodic safety update report is also authorised as a component of a fixed combination medicinal product, the marketing

authorisation holder shall either submit a separate periodic safety update report for the combination of active substances authorised for the same marketing authorisation holder, with cross-references to the single-substance periodic safety update report(s), or provide the combination data within one of the single-substance periodic safety update reports.

Article 35 - Format of periodic safety update reports

1. Electronic periodic safety update reports shall be submitted in the format set out in Annex II.
2. The Agency may publish templates for the modules set out in Annex II.

CHAPTER VIII - Post-authorisation safety studies

Article 36 - Scope

1. This chapter applies to non-interventional post-authorisation safety studies initiated, managed or financed by a marketing authorisation holder under obligations imposed by a national competent authority, the Agency or the Commission in accordance with Articles 21a and 22a of Directive 2001/83/EC and Articles 10 and 10a of Regulation (EC) No 726/2004.
2. The marketing authorisation holder shall submit the study protocol, the abstract of the final study report and the final study report which have been provided in accordance with Articles 107n and 107p of Directive 2001/83/EC in English except for studies to be conducted in only one Member State that requests the study according to Article 22a of Directive 2001/83/EC. For the latter studies the marketing authorisation holder shall provide an English translation of the title and abstract of the study protocol as well as an English translation of the abstract of the final study report.
3. The marketing authorisation holder shall ensure that all study information is handled and stored so as to allow for accurate reporting, interpretation and verification of that information and shall ensure that the confidentiality of the records of the study subjects remains protected. The marketing authorisation holder shall ensure that the analytical dataset and statistical programmes used for generating the data included in the final study report are kept in electronic format and are available for auditing and inspection.
4. The Agency may publish appropriate templates for the protocol, abstract and final study report.

Article 37 - Definitions

For the purposes of this chapter, the following definitions shall apply:

(1) 'Start of data collection' means the date from which information on the first study subject is first recorded in the study dataset or, in the case of the secondary use of data, the date from which data extraction starts;

(2) 'End of data collection' means the date from which the analytical dataset is completely available.

Article 38 - Format of post-authorisation safety studies

Protocols, abstracts and final study reports for non-interventional post-authorisation safety studies shall be submitted in the format set out in Annex III.

CHAPTER IX - Final provisions

Article 39 - Data protection

This Regulation shall apply without prejudice to the obligations of national competent authorities and marketing authorisation holders relating to their processing of personal data under Directive 95/46/EC or the obligations of the Agency relating to its processing of personal data under Regulation (EC) No 45/2001.

Article 40 - Transitional provisions

1. The obligation on the part of marketing authorisation holders, national competent authorities and the Agency to use the terminology provided for in points (c) to (g) of Article 25 shall apply from 1 July 2016.
2. Article 26(2) shall apply from 1 July 2016.
3. The obligation on the part of the marketing authorisation holder to comply with the format and content as provided for in Articles 29 to 38 shall apply from 10 January 2013.

Article 41 - Entry into force and application

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

It shall apply from 10 July 2012.

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

Done at Brussels, 19 June 2012.

For the Commission

The President

José Manuel BARROSO

(1) OJ L 136, 30.4.2004, p. 1.
(2) OJ L 311, 28.11.2001, p. 67.
(3) OJ L 348, 31.12.2010, p. 1.
(4) OJ L 348, 31.12.2010, p. 74.
(5) OJ L 281, 23.11.1995, p. 31.
(6) OJ L 8, 12.1.2001, p. 1.
(7) OJ L 334, 24.11.2008, p. 7.
(8) OJ L 255, 30.9.2005, p. 22.
(9) International Committee of Medical Journal Editors. Uniform requirements for manuscripts submitted to biomedical journals. N Engl J Med 1997; 336:309-15.
(10) OJ L 121, 1.5.2001, p. 34.

ANNEX I - Risk management plans

Format of the risk management plan

The risk management plan shall consist of the following modules:

Part I: Product(s) overview

Part II: Safety specification

Module SI:
Epidemiology of the indication(s) and target population(s)

Module SII:
Non-clinical part of the safety specification

Module SIII:
Clinical trial exposure

Module SIV:
Populations not studied in clinical trials

Module SV:
Post-authorisation experience

Module SVI:
Additional EU requirements for the safety specification

Module SVII:
Identified and potential risks

Module SVIII:
Summary of the safety concerns

Part III: Pharmacovigilance plan (including post-authorisation safety studies)

Part IV: Plans for post-authorisation efficacy studies

Part V: Risk minimisation measures (including evaluation of the effectiveness of risk minimisation activities)

Part VI: Summary of the risk management plan

Part VII: Annexes

ANNEX II - Format of the electronic periodic safety update reports

The periodic safety update report shall consist of the following modules:

Part I Title page including signature

Part II Executive Summary

Part III Table of contents

1. Introduction
2. Worldwide marketing authorisation status
3. Actions taken in the reporting interval for safety reasons
4. Changes to reference safety information
5. Estimated exposure and use patterns
   - 5.1. Cumulative subject exposure in clinical trials
   - 5.2. Cumulative and interval patient exposure from marketing experience
6. Data in summary tabulations
   - 6.1. Reference information
   - 6.2. Cumulative summary tabulations of serious adverse events from clinical trials
   - 6.3. Cumulative and interval summary tabulations from post-marketing data sources
7. Summaries of significant findings from clinical trials during the reporting interval
   - 7.1. Completed clinical trials
   - 7.2. Ongoing clinical trials
   - 7.3. Long-term follow-up
   - 7.4. Other therapeutic use of medicinal product
   - 7.5. New safety data related to fixed combination therapies
8. Findings from non-interventional studies
9. Information from other clinical trials and sources
10. Non-clinical data
11. Literature
12. Other periodic reports
13. Lack of efficacy in controlled clinical trials
14. Late-breaking information
15. Overview on signals: New, ongoing or closed
16. Signal and risk evaluation
    - 16.1.Summaries of safety concerns
    - 16.2.Signal evaluation
    - 16.3.Evaluation of risks and new information

16.4. Characterisation of risks
16.5. Effectiveness of risk minimisation (if applicable)

17. Benefit evaluation
    17.1. Important baseline efficacy and effectiveness information
    17.2. Newly identified information on efficacy and effectiveness
    17.3. Characterisation of benefits
18. Integrated benefit-risk analysis for authorised indications
    18.1. Benefit-risk context — Medical need and important alternatives
    18.2. Benefit-risk analysis evaluation
19. Conclusions and actions
20. Appendices to the periodic safety update report

ANNEX III - Protocols, abstracts and final study reports for post-authorisation safety studies

1. Format of the study protocol

1. Title: informative title including a commonly used term indicating the study design and the medicinal product, substance or drug class concerned, and a sub-title with a version identifier and the date of the last version.
2. Marketing authorisation holder.
3. Responsible parties including a list of all collaborating institutions and other relevant study sites.
4. Abstract: stand-alone summary of the study protocol, including the following subsections:
    (a) title with subtitles including version and date of the protocol and name and affiliation of the main author;
    (b) rationale and background;
    (c) research question and objectives;
    (d) study design;
    (e) population;
    (f) variables;
    (g) data sources;
    (h) study size;
    (i) data analysis;
    (j) milestones.
5. Amendments and updates: any substantial amendment and update to the study protocol after the start of data collection, including a justification for the amendment or update, the date of the change, and a reference to the section of the protocol where the change has been made.
6. Milestones: table with planned dates for the following milestones:
    (a) start of data collection;
    (b) end of data collection;
    (c) study progress report(s) as referred to in Article 107m(5) of Directive 2001/83/EC;

(d) interim report(s) of study results, if applicable;

(e) final report of study results.

7. Rationale and background: description of the safety hazard(s), the safety profile or the risk management measures that led to the study being imposed as an obligation for a marketing authorisation.
8. Research question and objectives in accordance with the decision of the national competent authority that imposed the study as an obligation.
9. Research methods: description of the research methods, including:
    (a) study design;
    (b) setting: study population defined in terms of persons, place, time period, and selection criteria, including the rationale for any inclusion and exclusion criteria. Where any sampling from a source population is undertaken, a description of the source population and details of sampling methods shall be provided. Where the study design is a systematic review or a meta-analysis, the criteria for the selection and eligibility of studies shall be explained;
    (c) variables;
    (d) data sources: strategies and data sources for determining exposures, outcomes and all other variables relevant to the study objectives. Where the study will use an existing data source, such as electronic health records, any information on the validity of the recording and coding of the data shall be reported. In the case of a systematic review or meta-analysis, the search strategy and processes and any methods for confirming data from investigators shall be described;
    (e) study size: any projected study size, precision sought for study estimates and any calculation of the study size that can minimally detect a pre-specified risk with a pre-specified interpretative power;
    (f) data management;
    (g) data analysis;
    (h) quality control;
    (i) limitations of the research methods.
10. Protection of human subjects: safeguards in order to comply with national and Union requirements for ensuring the well-being and rights of participants in non-interventional post-authorisation safety studies.
11. Management and reporting of adverse events/adverse reactions and other medically important events while the study is being conducted.
12. Plans for disseminating and communicating study results.
13. References.

2. Format of the abstract of the final study report

1. Title, with subtitles including date of the abstract and name and affiliation of main author.
2. Keywords (not more than five keywords indicating the main study characteristics).
3. Rationale and background.
4. Research question and objectives.
5. Study design.
6. Setting.
7. Subjects and study size, including dropouts.

8. Variables and data sources.
9. Results.
10. Discussion (including, where relevant, an evaluation of the impact of study results on the risk–benefit balance of the product).
11. Marketing authorisation holder.
12. Names and affiliations of principal investigators.

3. Format of the final study report

1. Title: title including a commonly used term indicating the study design; sub-titles with date of final report and name and affiliation of the main author.
2. Abstract: stand-alone summary referred to in Section 2 of this Annex.
3. Marketing authorisation holder: name and address of the marketing authorisation holder.
4. Investigators: names, titles, degrees, addresses and affiliations of the principal investigator and all co-investigators, and list of all collaborating primary institutions and other relevant study sites.
5. Milestones: dates for the following milestones:
    (a) start of data collection (planned and actual dates);
    (b) end of data collection (planned and actual dates);
    (c) study progress reports;
    (d) interim reports of study results, where applicable;
    (e) final report of study results (planned and actual date);
    (f) any other important milestone applicable to the study, including date of study registration in the electronic study register.
6. Rationale and background: description of the safety concerns that led to the study being initiated, and critical review of relevant published and unpublished data evaluating pertinent information and gaps in knowledge that the study is intended to fill.
7. Research question and objectives.
8. Amendments and updates to the protocol: list of any substantial amendments and updates to the initial study protocol after the start of data collection, including a justification for each amendment or update.
9. Research methods
    9.1. Study design: key elements of the study design and rationale for this choice.
    9.2. Setting: setting, locations, and relevant dates for the study, including periods of recruitment, follow-up, and data collection. In the case of a systematic review or meta-analysis, study characteristics used as criteria for eligibility, with rationale.
    9.3. Subjects: any source population and eligibility criteria for study subjects. Sources and methods for selection of participants shall be provided, including, where relevant, methods for case ascertainment, as well as number of and reasons for dropouts.
    9.4. Variables: all outcomes, exposures, predictors, potential confounders, and effect modifiers, including operational definitions. Diagnostic criteria shall be provided, where applicable.
    9.5. Data sources and measurement: for each variable of interest, sources of data and details of methods of assessment and measurement. If the study has used an existing data source, such as electronic health

records, any information on the validity of the recording and coding of the data shall be reported. In the case of a systematic review or meta-analysis, description of all information sources, search strategy, methods for selecting studies, methods of data extraction and any processes for obtaining or confirming data from investigators.

9.6. Bias.

9.7. Study size: study size, rationale for any study size calculation and any method for attaining projected study size.

9.8. Data transformation: transformations, calculations or operations on the data, including how quantitative data were handled in the analyses and which groupings were chosen and why.

9.9. Statistical methods: description of the following items:

(a) main summary measures;

(b) all statistical methods applied to the study;

(c) any methods used to examine subgroups and interactions;

(d) how missing data were addressed;

(e) any sensitivity analyses;

(f) any amendment to the plan of data analysis included in the study protocol, with rationale for the change.

9.10. Quality control: mechanisms to ensure data quality and integrity.

10. Results: comprising the following subsections:

10.1. Participants: numbers of study subjects at each stage of study. In the case of a systematic review or meta-analysis, number of studies screened, assessed for eligibility and included in the review with reasons for exclusion at each stage.

10.2. Descriptive data: characteristics of study participants, information on exposures and potential confounders and number of participants with missing data. In the case of a systematic review or meta-analysis, characteristics of each study from which data were extracted.

10.3. Outcome data: numbers of study subjects across categories of main outcomes.

10.4. Main results: unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision. Where relevant, estimates of relative risk shall be translated into absolute risk for a meaningful time period.

10.5. Other analyses.

10.6. Adverse events and adverse reactions.

11. Discussion

11.1. Key results: key results with reference to the study objectives, prior research in support of and conflicting with the findings of the completed post-authorisation safety study, and, where relevant, the impact of the results on the risk–benefit balance of the product.

11.2. Limitations: limitations of the study taking into account circumstances that may have affected the quality or integrity of the data, limitations of the study approach and methods used to address them, sources of potential bias and imprecision, and validation of the events. Both the direction and magnitude of potential biases shall be discussed.

11.3. Interpretation: interpretation of results, considering objectives, limitations, multiplicity of analyses, results from similar studies and other relevant evidence.

11.4. Generalisability.

12. References.

TABLE DES MATIÈRES

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May 2015

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