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►B 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

(OJ L 311, 28.11.2001, p. 67)

Amended by:

		Official Journal		
		No	page	date
►M1	Directive 2002/98/EC of the European Parliament and of the Council of 27 January 2003	L 33	30	8.2.2003
►M2	Commission directive 2003/63/EC of 25 June 2003	L 159	46	27.6.2003
►M3	Directive 2004/24/EC of the European Parliament and of the Council of 31 March 2004	L 136	85	30.4.2004
►M4	Directive 2004/27/EC of the European Parliament and of the Council of 31 March 2004	L 136	34	30.4.2004
►M5	Regulation (EC) No 1901/2006 of the European Parliament and of the Council of 12 December 2006	L 378	1	27.12.2006
►M6	Regulation (EC) No 1394/2007 of the European Parliament and of the Council of 13 November 2007	L 324	121	10.12.2007
►M7	Directive 2008/29/EC of the European Parliament and of the Council of 11 March 2008	L 81	51	20.3.2008
►M8	Directive 2009/53/EC of the European Parliament and of the Council of 18 June 2009	L 168	33	30.6.2009
►M9	Commission Directive 2009/120/EC of 14 September 2009	L 242	3	15.9.2009
►M10	Directive 2010/84/EU of the European Parliament and of the Council of 15 December 2010	L 348	74	31.12.2010
►M11	Directive 2011/62/EU of the European Parliament and of the Council of 8 June 2011	L 174	74	1.7.2011
►M12	Directive 2012/26/EU of the European Parliament and of the Council of 25 October 2012	L 299	1	27.10.2012
►M13	Regulation (EU) 2017/745 of the European Parliament and of the Council of 5 April 2017	L 117	1	5.5.2017
►M14	Regulation (EU) 2019/5 of the European Parliament and of the Council of 11 December 2018	L 4	24	7.1.2019
►M15	Regulation (EU) 2019/1243 of the European Parliament and of the Council of 20 June 2019	L 198	241	25.7.2019
►M16	Directive (EU) 2022/642 of the European Parliament and of the Council of 12 April 2022	L 118	4	20.4.2022

Corrected by:

►C1 Corrigendum, OJ L 87, 31.3.2009, p. 174 (1394/2007)

►C2 Corrigendum, OJ L 276, 21.10.2011, p. 63 (2010/84/EU)

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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

TITLE I

DEFINITIONS

Article 1

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

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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.

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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.

▼M11

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.

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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.

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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 ([1]).

▼M4

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.

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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. ►M4 *Kit* ◄*:*

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

([1]) OJ L 324, 10.12.2007, p. 121.

▼B

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.

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11. *Adverse reaction:*

A response to a medicinal product which is noxious and unintended.

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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.

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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.

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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.

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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.

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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.

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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.

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19. *Medicinal Prescription:*

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

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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.

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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.

▼B

26. *Package leaflet:*

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

▼M14

26a. *Variation or variation to the terms of a marketing authorisation:*

An amendment to the contents of the particulars and documents referred to in:

(a) Article 8(3) and Articles 9 to 11 of this Directive and Annex I thereto, Article 6(2) of Regulation (EC) No 726/2004 and in Article 7 of Regulation (EC) No 1394/2007; and

(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 related to changes to the summary of the product characteristics.

▼M4

27. *Agency:*

The European Medicines Agency established by Regulation (EC) No 726/2004 ([1]).

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.

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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 fulfil 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.

([1]) OJ L 136, 30.4.2004, p. 1.

▼**M10**

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.

▼**M3**

29. *Traditional herbal medicinal product:*

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

30. *Herbal medicinal product:*

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

31. *Herbal substances:*

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

32. *Herbal preparations:*

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

▼**M11**

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.

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TITLE II

SCOPE

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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.

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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.

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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).

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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 ([1]).

▼B

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

5. Any radionuclides in the form of sealed sources.

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

([1]) OJ L 121, 1.5.2001, p. 34.

▼M6

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 ([1]).

▼B

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 ([2]).

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.

▼M6

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.

([1]) 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).
([2]) OJ L 207, 30.7.1986, p. 1.

▼M4

Article 5

1. A Member State may, in accordance with legislation in force and to fulfil special needs, exclude from the provisions of this Directive medicinal products supplied in response to a bona fide unsolicited order, formulated in accordance with the specifications of an authorised health-care professional and for use by an individual patient under his direct personal responsibility.

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 ([1]), shall not be affected by paragraph 3.

▼M16

Article 5a

By way of derogation from Article 6, the competent authorities of the United Kingdom in respect of Northern Ireland may temporarily authorise the supply to patients in Northern Ireland of a medicinal product belonging to the categories referred to in Article 3(1) and (2) of Regulation (EC) No 726/2004 provided that all of the following conditions are fulfilled:

(a) the medicinal product concerned has been granted a marketing authorisation by the competent authority of the United Kingdom for parts of the United Kingdom other than Northern Ireland;

(b) the medicinal product concerned is only made available to patients or end-consumers in the territory of Northern Ireland and is not made available in any Member State.

The maximum validity of the temporary authorisation shall be six months. Notwithstanding the specified validity, the temporary authorisation shall cease to be valid if the medicinal product concerned has been granted a marketing authorisation in accordance with Article 10 of Regulation (EC) No 726/2004, or if such marketing authorisation has been refused in accordance with that Article.

([1]) 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).

▼B

TITLE III

PLACING ON THE MARKET

CHAPTER 1

Marketing authorization

Article 6

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1. ►M6 ►C1 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 ([1]) and Regulation (EC) No 1394/2007. ◄ ◄

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

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

▼B

2. The authorisation referred to in paragraph 1 shall also be required for radionuclide generators, ►M4 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, ►M4 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.

([1]) OJ L 378, 27.12.2006, p. 1.

▼M16

2a. By way of derogation from paragraph 2, marketing authorisations may be granted by the competent authorities of the United Kingdom in respect of Northern Ireland to applicants established in parts of the United Kingdom other than Northern Ireland.

2b. By way of derogation from paragraph 2, marketing authorisations may be granted by the competent authorities of the United Kingdom in respect of Northern Ireland and, until 31 December 2024, by the competent authorities of Cyprus, Ireland and Malta, in accordance with the mutual recognition or the decentralised procedure laid down in Chapter 4 of this Title, to marketing authorisation holders established in parts of the United Kingdom other than Northern Ireland.

The competent authorities of the United Kingdom in respect of Northern Ireland and, until 31 December 2024, the competent authorities of Cyprus, Ireland and Malta may extend marketing authorisations already granted prior to 20 April 2022 to marketing authorisation holders established in parts of the United Kingdom other than Northern Ireland.

The marketing authorisations granted or extended by the competent authorities of Cyprus, Ireland or Malta in accordance with the first and second subparagraph shall cease to be valid at the latest on 31 December 2026.

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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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(b) Name of the medicinal product.

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

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

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(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.

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(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.

▼M11

(ha) 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.

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(i) Results of:

— pharmaceutical (physico-chemical, biological or microbiological) tests,

— pre-clinical (toxicological and pharmacological) tests,

— clinical trials.

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(ia) 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 fulfil 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.

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

▼M4

(ib) 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.

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

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(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.

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

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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.

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The risk management system referred to in point (iaa) 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.

▼B

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.

[1] OJ L 18, 22.1.2000, p. 1.

▼M4

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.

▼M4

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.

▼**M4**

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).

▼M4

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.

▼M10

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.

▼M10

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).

▼M4

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.

▼B

CHAPTER 2

Specific provisions applicable to homeopathic medicinal products

▼M4

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.

▼B

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,

▼B

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

▼M15

The Commission is empowered to adopt delegated acts in accordance with Article 121a amending the third indent of the first subparagraph if new scientific evidence so warrants.

▼B

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.

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▼B

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,

▼M4

— 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,

▼B

— 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,

▼M4

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

▼B

— data concerning the stability of the medicinal product.

▼B

Article 16

1. Homeopathic medicinal products other than those referred to in Article 14(1) shall be authorized and labelled in accordance with ►M4 Articles 8, 10, 10a, 10b, 10c and 11 ◄.

2. A Member State may introduce or retain in its territory specific rules for the ►M4 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 practised in that Member State.

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

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

▼M3

CHAPTER 2a

Specific provisions applicable to traditional herbal medicinal products

Article 16a

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

(a) they have indications exclusively appropriate to traditional herbal medicinal products which, by virtue of their composition and purpose, are intended and designed for use without the supervision of a medical practitioner for diagnostic purposes or for prescription or monitoring of treatment;

(b) they are exclusively for administration in accordance with a specified strength and posology;

(c) they are an oral, external and/or inhalation preparation;

(d) the period of traditional use as laid down in Article 16c(1)(c) has elapsed;

(e) the data on the traditional use of the medicinal product are sufficient; in particular the product proves not to be harmful in the specified conditions of use and the pharmacological effects or efficacy of the medicinal product are plausible on the basis of long-standing use and experience.

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

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

▼**M3**

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.

▼M3

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

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

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

Article 16d

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

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

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

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

Article 16e

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

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

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

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

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

▼M3

(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

▼M10

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 [1] shall apply, by analogy, to traditional-use registration granted under this Chapter.

▼M3

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

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

▼M3

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

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

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

Article 16h

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

(a) as regards simplified registrations, to:

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

— perform the tasks arising from Article 16d,

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

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

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

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

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

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

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

▼M3

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 fulfil further responsibilities conferred upon it by provisions of this chapter and other Community law.

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

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

The herbal monographs shall be published.

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

▼M3

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.

▼B

CHAPTER 3

Procedures relevant to the marketing authorization

▼M4

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 ►M10 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 ►M10 Articles 28 ◄ to 39 apply.

Article 18

Where a Member State is informed in accordance with Article 8(3)(1) that another Member State has authorised a medicinal product which is the subject of a marketing authorisation application in the Member State concerned, it shall reject the application unless it was submitted in compliance with ►M10 Articles 28 ◄ to 39.

▼M16

Article 18a

1. By way of derogation from Article 17(1), second subparagraph, Article 17(2) and Article 18, if an application for marketing authorisation is submitted in one or more Member States and in the United Kingdom in respect of Northern Ireland, or if an application for marketing authorisation is submitted in the United Kingdom in respect of Northern Ireland for a medicinal product which is already being examined or has already been authorised in a Member State, the application regarding the United Kingdom in respect of Northern Ireland shall not have to be submitted in accordance with Articles 28 to 39 provided that all of the following conditions are fulfilled:

(a) the marketing authorisation for the United Kingdom in respect of Northern Ireland is granted by the competent authority for the United Kingdom in respect of Northern Ireland in compliance with Union law, and such compliance with Union law is ensured during the period of validity of that marketing authorisation;

(b) the medicinal products authorised by the competent authority for the United Kingdom in respect of Northern Ireland are made available to patients or end-consumers only in the territory of Northern Ireland, and they are not made available in any Member State.

▼M16

2. The marketing authorisation holder of a medicinal product for which a marketing authorisation has already been granted for the United Kingdom in respect of Northern Ireland in accordance with Articles 28 to 39 before 20 April 2022 shall be allowed to withdraw the marketing authorisation for the United Kingdom in respect of Northern Ireland from the mutual recognition or the decentralised procedure and to submit an application for a marketing authorisation for that medicinal product to the competent authorities of the United Kingdom with respect to Northern Ireland in accordance with paragraph 1.

▼B

Article 19

In order to examine the application submitted in accordance with ►M4 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 ►M4 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 ►M4 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 ►M4 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, ►M4 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.

▼M16

With regard to quality control testing carried out in parts of the United Kingdom other than Northern Ireland regarding medicinal products included in the list referred to in Article 127d other than those authorised by the Commission, the competent authorities of the United Kingdom in respect of Northern Ireland and, until 31 December 2024, the competent authorities of Cyprus, Ireland and Malta may consider that there is a justifiable case within the meaning of point (b) of the first paragraph, without carrying out a case-by-case assessment provided that:

(a) each batch of the medicinal products concerned is released by a qualified person on a site in the Union or in Northern Ireland or by a qualified person on a site in parts of the United Kingdom other than Northern Ireland applying quality standards that are equivalent to those laid down in Article 51;

(b) the establishment designated by the third party conducting the quality control testing is supervised by the competent authority of the United Kingdom, including by performing on-the-spot checks;

(c) where the batch release is carried out by a qualified person who resides and operates in parts of the United Kingdom other than Northern Ireland, the manufacturing authorisation holder declares that it does not have at its disposal a qualified person who resides and operates in the Union on 20 April 2022.

▼B

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.

▼M10

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 fulfilment 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.

▼**M10**

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 fulfilment 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.

▼**M10**

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.

▼M10

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.

▼M4

Article 23a

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

▼M12

If the product ceases to be placed on the market of a Member State, either temporarily or permanently, the marketing authorisation holder shall notify the competent authority of that Member State. 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 competent authority of the reasons for such action in accordance with Article 123(2).

▼M4

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

▼M8

Article 23b

▼M14

1. Variations shall be classified in different categories depending on the level of risk to public health and the potential impact on the quality, safety and efficacy of the medicinal product concerned. Those categories shall range from changes to terms of the marketing authorisation that have the highest potential impact on the quality, safety or efficacy of the medicinal product, to changes that have no or minimal impact thereon.

2. The procedures for examination of applications for variations shall be proportionate to the risk and impact involved. Those procedures shall range from procedures that allow implementation only after approval based on a complete scientific assessment to procedures that allow immediate implementation and subsequent notification by the marketing authorisation holder to the competent authority.

2a. The Commission is empowered to adopt delegated acts in accordance with Article 121a in order to supplement this Directive by:

(a) specifying the categories in which variations shall be classified; and

(b) establishing procedures for the examination of applications for variations to the terms of marketing authorisations.

3. When adopting the delegated acts referred to in this Article, the Commission shall endeavour to make possible the submission of a single application for one or more identical changes made to the terms of different marketing authorisations.

4. A Member State may continue to apply national provisions on variations applicable at the time of entry into force of Commission Regulation (EC) No 1234/2008 ([1]) 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, Regulation (EC) No 1234/2008 shall apply to that medicinal product from that date.

([1]) 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 (OJ L 334, 12.12.2008, p. 7).

▼M8

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, ►M14 Regulation (EC) No 1234/2008 ◄ shall apply.

▼M4

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.

▼M10

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.

▼M4

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.

▼B

Article 25

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

▼M4

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.

▼M4

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.

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▼M4

Article 27

▼M10

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 fulfilment 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 fulfilment 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.

▼M4

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.

▼M10

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

▼M4

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.

▼M4

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.

▼M4

Article 30

1. If two or more applications submitted in accordance with Articles 8, 10, 10a, 10b, 10c and 11 have been made for marketing authorisation for a particular medicinal product, and if Member States have adopted divergent decisions concerning the authorisation of the medicinal product or its suspension or revocation, a Member State, the Commission or the applicant or the marketing authorisation holder may refer the matter to the Committee for Medicinal Products for Human Use, hereinafter referred to as 'the Committee', for the application of the procedure laid down in Articles 32, 33 and 34.

2. In order to promote harmonisation of authorisations for medicinal products authorised in the Community, Member States shall, each year, forward to the coordination group a list of medicinal products for which a harmonised summary of product characteristics should be drawn up.

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

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

Article 31

1. ►M10 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. ◄

▼M10

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.

▼M12

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

▼M4

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.

▼M12

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.

▼M4

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.

▼M4

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

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

4. The Agency shall forthwith inform the applicant or the marketing authorisation holder where the opinion of the Committee is that:

(a) the application does not satisfy the criteria for authorisation; or

(b) the summary of the product characteristics proposed by the applicant or the marketing authorisation holder in accordance with Article 11 should be amended; or

(c) the authorisation should be granted subject to certain conditions, in view of conditions considered essential for the safe and effective use of the medicinal product including pharmacovigilance; or

(d) a marketing authorisation should be suspended, varied or revoked.

Within 15 days after receipt of the opinion, the applicant or the marketing authorisation holder may notify the Agency in writing of his intention to request a re-examination of the opinion. In that case, he shall forward to the Agency the detailed grounds for the request within 60 days after receipt of the opinion.

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

5. Within 15 days after its adoption, the Agency shall forward the final opinion of the Committee to the Member States, to the Commission and to the applicant or the marketing authorisation holder, together with a report describing the assessment of the medicinal product and stating the reasons for its conclusions.

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

(a) a draft summary of the product characteristics, as referred to in Article 11;

(b) any conditions affecting the authorisation within the meaning of paragraph 4(c);

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

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

▼B

Article 33

Within ►M4 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 ►M4 Article 32(5), second subparagraph ◄ shall be annexed.

▼B

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 ►M4 or the marketing authorisation holder ◄.

▼M4

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.

▼M12

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.

▼B

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.

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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.

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▼B

Article 37

►M12 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.

▼M4

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).

▼B

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.

▼M16

1a. By way of derogation from paragraph 1 of this Article, the competent authorities of the United Kingdom in respect of Northern Ireland and, until 31 December 2024, the competent authorities of Cyprus, Ireland and Malta shall allow medicinal products to be imported from parts of the United Kingdom other than Northern Ireland by holders of a wholesale distribution authorisation as referred to in Article 77(1) that are not in possession of a relevant manufacturing authorisation provided that all of the following conditions are fulfilled:

▼M16

(a) the medicinal products have undergone quality control testing either in the Union, as provided for in Article 51(3), or in parts of the United Kingdom other than Northern Ireland in compliance with Article 20, first paragraph, point (b);

(b) the medicinal products have been subject to batch release by a qualified person in the Union in accordance with Article 51(1) or, for medicinal products authorised by the competent authorities of Cyprus, Ireland, Malta and the United Kingdom in respect of Northern Ireland, in parts of the United Kingdom other than Northern Ireland applying quality standards that are equivalent to those laid down in Article 51(1);

(c) the marketing authorisation for the medicinal product concerned has been granted in accordance with Union law, by the competent authority of a Member State or by the Commission or, as regards medicinal products placed on the market in Northern Ireland, by the competent authority of the United Kingdom in respect of Northern Ireland;

(d) medicinal products are only made available to patients or end-consumers in the Member State into which the medicinal products are imported, or, if imported into Northern Ireland, are only made available to patients or end-consumers in Northern Ireland;

(e) the medicinal products bear the safety features referred to in Article 54, point (o).

Article 80, first subparagraph, point (b), shall not apply to imports that fulfil the conditions laid down in the first subparagraph of this paragraph.

▼B

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.

▼M16

3a. For batches of medicinal products which are exported to parts of the United Kingdom other than Northern Ireland from a Member State and subsequently imported into Northern Ireland or, until 31 December 2024, into Cyprus, Ireland or Malta, the controls upon importation referred to Article 51(1), first and second subparagraphs, shall not be required, provided that those batches have undergone such controls in a Member State prior to being exported to parts of the United Kingdom other than Northern Ireland and that they are accompanied by the control reports referred to in Article 51(1), third subparagraph.

▼M11

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).

▼B

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.

▼B

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;

▼M11

(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;

▼M11

(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.

▼M4

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.

▼M15

2. The Commission is empowered to adopt delegated acts in accordance with Article 121a to amend paragraph 1 to take account of scientific and technical progress.

▼M11

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

▼M11

(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.

▼B

Article 47

▼M15

The Commission is empowered to adopt delegated acts in accordance with Article 121a in order to supplement this Directive by specifying the principles and guidelines of good manufacturing practices for medicinal products referred to in Article 46(f).

▼B

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

▼M11

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;

▼M11

(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.

▼B

Article 48

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

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

▼M16

3. Where the manufacturing authorisation is granted by the competent authority of the United Kingdom in respect of Northern Ireland, the qualified person referred to in paragraph 1 may reside and operate in parts of the United Kingdom other than Northern Ireland. This paragraph shall not apply where the manufacturing authorisation holder already has at its disposal a qualified person who resides and operates in the Union on 20 April 2022.

▼B

Article 49

1. Member States shall ensure that the qualified person referred to in Article 48 fulfils the ►M4 ———— ◄ 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.

▼B

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:

— ►M4 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.

▼B

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 ►M4 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;

▼M4

(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.

▼M11

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.

▼B

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.

▼B

2. In the case of medicinal products imported from a third country, where appropriate arrangements have been made by the Community with the exporting country to ensure that the manufacturer of the medicinal product applies standards of good manufacturing practice at least equivalent to those laid down by the Community, and to ensure that the controls referred to under point (b) of the first subparagraph of paragraph 1 have been carried out in the exporting country, the qualified person may be relieved of responsibility for carrying out those controls.

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

Article 52

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

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

▼M11

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.

▼M11

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.

▼B

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:

▼M4

(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

(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 ►M4 detailed guidance ◄ published pursuant to Article 65. However, if the product is injectable, or a topical or eye preparation, all excipients must be stated;

▼M4

(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;

▼B

(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;

▼M4

(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;

▼B

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

(m) the manufacturer's batch number;

▼M4

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

▼M11

(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.

▼**M11**

Article 54a

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;

▼M11

(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.

▼B

Article 55

1. The particulars laid down ►M4 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.

▼M4

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

▼B

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

— the expiry date,

— the batch number.

▼B

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:

▼M4

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

▼B

— 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.

▼M4

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.

▼B

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,

▼M11

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

▼M4

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.

▼B

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.

▼M4

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;

▼M10

(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;

▼M4

(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.

▼M10

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).

▼M4

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.

▼M4

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.

▼M10

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.

▼B

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

▼M4

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.

▼B

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 ►M4 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 ►M4 for the patient ◄, to the exclusion of any element of a promotional nature.

▼B

Article 63

▼M12

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.

▼B

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.

▼M4

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.

▼M12

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.

▼M4

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.

▼M12

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.

▼B

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.

▼M4

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;

▼M4

(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.

▼B

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,

▼M4

— the name and address of the manufacturer,

▼B

— 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.

▼B

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:

▼M4

— 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,

▼B

— 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’,

▼M4

— a warning advising the user to consult a doctor if the symptoms persist.

▼B

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.

▼B

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:

▼M4

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

▼B

(b) medicinal products subject to special medical prescription;

▼M4

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

▼B

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,

▼B

— 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.

▼M4

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.

▼B

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

▼M11

WHOLESALE DISTRIBUTION AND BROKERING OF MEDICINAL PRODUCTS

▼B

Article 76

►M4 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.

▼M4

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.

▼M11

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.

▼B

Article 77

▼M11

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.

▼B

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.

▼B

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.

▼M11

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.

▼B

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

(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;

▼M11

(ca) 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);

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(d) they must have an emergency plan which ensures effective implementation of any recall from the market ordered by the competent authorities or carried out in cooperation with the manufacturer or marketing authorization holder for the medicinal product concerned;

▼M11

(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;

▼B

(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;

▼M11

(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.

▼M4

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.

▼B

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,

▼M4

— the name and pharmaceutical form of the medicinal product,

▼B

— the quantity supplied,

— the name and address of the supplier and consignor,

▼M11

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

▼B

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.

▼M4

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 ([1]).

Article 85

This Title shall apply to homeopathic medicinal products.

▼M12

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.

([1]) OJ L 147, 9.6.1975, p. 23.

▼M11

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.

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 ([1]) 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;

([1]) OJ L 204, 21.7.1998, p. 37.

▼M11

(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;

(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) ([1]), 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;

([1]) OJ L 178, 17.7.2000, p. 1.

▼M11

(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;

(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.

▼B

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,

▼M4

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

▼B

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.

▼B

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.

▼M4

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.

▼M4

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.

▼B

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.

▼M4

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.

▼B

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;

▼B

(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.

▼M4

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▼B

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.

▼M4

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.

▼B

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.

▼B

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.

▼M4

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.

▼B

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.

▼M4

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.

▼B

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

(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;

▼M4

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

▼B

(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.

▼B

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.

▼M4

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.

▼B

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.

▼M4

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.

▼M10

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;

▼M10

(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.

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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.

▼M16

By way of derogation from the second subparagraph, where the marketing authorisation is granted by the competent authority of United Kingdom in respect of Northern Ireland, the qualified person referred to in point (a) of the first subparagraph may reside and operate in parts of the United Kingdom other than Northern Ireland. This subparagraph shall not apply where the marketing authorisation holder already has at its disposal a qualified person who resides and operates in the Union on 20 April 2022.

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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.

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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.

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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 public 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.

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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.

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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.

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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.

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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.

▼**M10**

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.

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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.

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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.

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Section 4

Urgent Union procedure

Article 107i

▼M12

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.

1a. 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.

1b. 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.

▼**M10**

2. Without prejudice to the provisions of ►**M12** 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 ►**M12** 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 ►**M12** 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 ►**M12** 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.

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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.

▼**M10**

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.

▼M10

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.

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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.

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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.

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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.

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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.

▼B

TITLE X

SPECIAL PROVISIONS ON MEDICINAL PRODUCTS DERIVED FROM HUMAN BLOOD AND PLASMA

▼M1

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 [1] shall apply.

▼B

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.

[1] OJ L 33, 8.2.2003, p. 30.

▼B

TITLE XI

SUPERVISION AND SANCTIONS

Article 111

▼M11

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.

1a. Manufacturers, located in the Union or in third countries, and wholesale distributors of medicinal products shall be subject to repeated inspections.

1b. 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:

(a) manufacturers or distributors of active substances located in third countries;

(b) manufacturers or importers of excipients.

1c. 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.

1d. Inspections may also take place at the premises of marketing authorisation holders and of brokers of medicinal products.

1e. 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.

1f. The competent authority of the Member State concerned may carry out inspections of starting material manufacturers at the specific request of the manufacturer.

▼M11

1g. Inspections shall be carried out by officials representing the competent authority who shall be empowered to:

(a) inspect the manufacturing or commercial establishments of manufacturers of medicinal products, 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;

(b) take samples including with a view to independent tests being carried out by an Official Medicines Control Laboratory or a laboratory designated for that purpose by a Member State;

(c) examine any documents relating to the object of the inspection, subject to the provisions in force in the Member States on 21 May 1975 placing restrictions on these powers with regard to the description of the manufacturing method;

(d) inspect the premises, records, 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.

1h. Inspections shall be carried out in accordance with the guidelines referred to in Article 111a.

▼B

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.

▼M11

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.

▼**M11**

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.

▼**M10**

7. If the outcome of the inspection as referred to in points (a), (b) and (c) of ►**M11** paragraph 1g ◄ or the outcome of an inspection of a distributor of medicinal products or active substances or a manufacturer of excipients ►**M11** ———— ◄ 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 ►**M11** 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.

▼**M11**

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

▼M11

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.

▼M16

Article 111c

1. The Commission shall continuously monitor developments in the United Kingdom that could affect the level of protection regarding the regulatory functions referred to in Article 8(2a) and (2b), Article 20, second paragraph, Article 40(1a) and (3a), Article 48(3), Article 104(3) and Article 126c that are carried out in parts of the United Kingdom other than Northern Ireland taking into account, in particular, the following elements:

(a) the rules governing the granting of marketing authorisations, the obligations of the marketing authorisation holder, the granting of manufacturing authorisations, the obligations of the manufacturing authorisation holder, the qualified persons and their obligations, quality control testing, batch release and pharmacovigilance as laid down in United Kingdom law;

(b) whether the competent authorities of the United Kingdom ensure the effective enforcement within their territory of the rules referred to in point (a), by means of, inter alia, inspections and audits of marketing authorisation holders, manufacturing authorisation holders and wholesale distributors located in their territories, and on-the-spot checks at their premises regarding the exercise of the regulatory functions referred to in point (a).

▼M16

2. Where the Commission finds that the level of protection of public health ensured by the United Kingdom through rules governing the production, distribution and use of medicinal products as well as the effective enforcement of those rules is no longer essentially equivalent to that guaranteed within the Union, or where sufficient information is not available to the Commission to enable it to establish whether an essentially equivalent level of protection of public health is ensured by the United Kingdom, the Commission shall inform the United Kingdom through a written notification of that finding and of the detailed reasons therefor.

For a period of six months following the written notification made pursuant to the first subparagraph, the Commission shall enter into consultations with the United Kingdom with a view to remedying the situation giving rise to that written notification. In justified cases, the Commission may extend that period by three months.

3. If the situation giving rise to the written notification made pursuant to paragraph 2, first subparagraph, is not remedied within the time-limit referred to in paragraph 2, second subparagraph, the Commission shall be empowered to adopt a delegated act specifying the provisions among those referred to in paragraph 1 whose application shall be suspended.

4. Where a delegated act pursuant to paragraph 3 has been adopted, the provisions referred to in the introductory sentence of paragraph 1 as specified in the delegated act shall cease to apply on the first day of the month following the entry into force of the delegated act.

5. Where the situation giving rise to the adoption of the delegated act pursuant to paragraph 3 has been remedied, the Commission shall adopt a delegated act specifying those suspended provisions that shall apply again. In that case, the provisions specified in the delegated act adopted pursuant to this paragraph shall apply again on the first day of the month following the entry into force of the delegated act referred to in this paragraph.

▼B

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,

▼B

— 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 ►M4 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 ►M4 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.

▼M10

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.

▼M10

►C2 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.

▼M11

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).

▼B

Article 117

▼M4

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:

▼M10

(a) the medicinal product is harmful; or

▼M4

(b) it lacks therapeutic efficacy; or

▼M10

(c) the risk-benefit balance is not favourable; or

▼M4

(d) its qualitative and quantitative composition is not as declared; or

(e) the controls on the medicinal product and/or on the ingredients and the controls at an intermediate stage of the manufacturing process have not been carried out or if some other requirement or obligation relating to the grant of the manufacturing authorisation has not been fulfilled.

▼B

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.

▼M10

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.

▼M11

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.

▼M11

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.

▼B

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.

▼M11

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.

2. 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;

▼M11

(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.

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.

▼M4

Article 119

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

▼B

TITLE XII

STANDING COMMITTEE

▼M15

Article 120

The Commission is empowered to adopt delegated acts in accordance with Article 121a amending Annex I to take account of scientific and technical progress.

▼M4

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.

▼M4

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.

▼M15

———————

▼M4

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.

▼M7

4. The rules of procedure of the Standing Committee shall be made public.

▼M15

Article 121a

1. The power to adopt delegated acts is conferred on the Commission subject to the conditions laid down in this Article.

2. The power to adopt delegated acts referred to in Article 14(1), Article 22b, Article 23b, Article 46a, Article 47, Article 52b, Article 54a and Article 120 shall be conferred on the Commission for a period of five years from 26 July 2019. The Commission shall draw up a report in respect of the delegation of power not later than nine months before the end of the five-year period. The delegation of power shall be tacitly extended for periods of an identical duration, unless the European Parliament or the Council opposes such extension not later than three months before the end of each period.

▼M16

The power to adopt delegated acts referred to in Article 111c(3) and (5) shall be conferred on the Commission for an indeterminate period of time from 20 April 2022.

3. The delegation of power referred to in Article 14(1), Articles 22b, 23b, 46a, 47, 52b, 54a, Article 111c(3) and (5), and Article 120 may be revoked at any time by the European Parliament or by the Council. A decision to revoke shall put an end to the delegation of the power specified in that decision. It shall take effect the day following the publication of the decision in the *Official Journal of the European Union* or at a later date specified therein. It shall not affect the validity of any delegated acts already in force.

▼M15

4. Before adopting a delegated act, the Commission shall consult experts designated by each Member State in accordance with the principles laid down in the Interinstitutional Agreement of 13 April 2016 on Better Law-Making ([1]).

5. As soon as it adopts a delegated act, the Commission shall notify it simultaneously to the European Parliament and to the Council.

([1]) OJ L 123, 12.5.2016, p. 1.

▼M16

6. A delegated act adopted pursuant to Article 14(1), Articles 22b, 23b, 46a, 47, 52b, 54a, Article 111c(3) or (5), or Article 120 shall enter into force only if no objection has been expressed either by the European Parliament or by the Council within a period of two months of notification of that act to the European Parliament and the Council or if, before the expiry of that period, the European Parliament and the Council have both informed the Commission that they will not object. That period shall be extended by two months at the initiative of the European Parliament or of the Council.

▼B

TITLE XIII

GENERAL PROVISIONS

▼M4

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.

▼M10

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.

▼M4

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.

▼B

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.

▼M12

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).

2a. 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).

2b. 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).

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

▼B

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.

▼M12

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.

▼B

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.

▼M4

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

▼B

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.

▼M4

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.

▼M10

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.

▼M4

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.

▼**M4**

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

Article 126b

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

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

▼**M16**

Article 126c

1. By way of derogation from Article 126a, until 31 December 2024, in the absence of a marketing authorisation or of a pending application for a marketing authorisation the competent authorities of Cyprus and Malta may authorise for justified public health reasons the placing on their national market of a medicinal product authorised in parts of the United Kingdom other than Northern Ireland.

The competent authorities of Cyprus and Malta may also maintain in force or, until 31 December 2024, extend marketing authorisations that were granted pursuant to Article 126a before 20 April 2022 which authorise the placing on their national market of a medicinal product authorised in parts of the United Kingdom other than Northern Ireland.

Authorisations that are granted, extended or maintained in force pursuant to the first or second subparagraph shall not be valid after 31 December 2026.

2. By way of derogation from Article 8(2), the competent authorities of Malta and Cyprus may grant marketing authorisations as referred to in paragraph 1 of this Article to marketing authorisation holders established in parts of the United Kingdom other than Northern Ireland.

3. Where the competent authorities of Cyprus or Malta grant or extend a marketing authorisation as referred to in paragraph 1, they shall ensure compliance with the requirements of this Directive.

4. Before granting a marketing authorisation pursuant to paragraph 1, the competent authorities of Cyprus or Malta:

(a) shall notify the marketing authorisation holder in parts of the United Kingdom other than Northern Ireland of the proposal to grant a marketing authorisation or to extend a marketing authorisation under this Article in respect of the medicinal product concerned;

(b) may request the competent authority in the United Kingdom to submit the relevant information regarding the marketing authorisation of the medicinal product concerned.

▼B

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.

▼M10

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.

▼M4

Article 127b

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

▼M16

Article 127c

The derogations set out in Article 8(2a) and(2b), Article 18a, Article 20, second paragraph, Article 40(1a) and (3a), Article 48(3), Article 104(3a) and Article 126c shall not affect the obligations of the marketing authorisation holder to ensure the quality, safety and efficacy of the medicinal product placed on the markets of Cyprus, Ireland, Malta or Northern Ireland laid down in this Directive.

Article 127d

1. By 20 May 2022, the competent authorities of Cyprus, Ireland, Malta and the United Kingdom in respect of Northern Ireland shall establish, notify to the Commission and publish on their website a list of medicinal products to which they have applied or intend to apply the derogations as set out in this Directive.

2. The competent authorities of Cyprus, Ireland, Malta and the United Kingdom in respect of Northern Ireland shall ensure that the list referred to in paragraph 1 is updated and managed in an independent manner, at least on a six-monthly basis.

▼B

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.

▼M2

ANNEX I

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

TABLE OF CONTENTS

Introduction and general principles

Part I: Standardised marketing authorisation dossier requirements

1. Module 1: Administrative information
1.1. Table of contents
1.2. Application form
1.3. Summary of product characteristics, labelling and package leaflet
1.3.1. Summary of product characteristics
1.3.2. Labelling and package leaflet
1.3.3. Mock-ups and specimens
1.3.4. Summaries of product characteristics already approved in the Member States
1.4. Information about the experts
1.5. Specific requirements for different types of applications
1.6. Environmental risk assessment
2. Module 2: Summaries
2.1. Overall table of contents
2.2. Introduction
2.3. Quality overall summary
2.4. Non-clinical overview
2.5. Clinical overview
2.6. Non-clinical summary
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

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.

▼**M2**

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

3.3.2.3. Characterisation and control strategy

3.3.2.4. Excipients

3.3.2.5. Developmental studies

3.3.2.6. Reference materials

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

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

4. Specific requirements regarding module 4

4.1. Specific requirements for all advanced therapy medicinal products

4.2. Specific requirements for gene therapy medicinal products

4.2.1. Pharmacology

4.2.2. Pharmacokinetics

4.2.3. Toxicology

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

4.3.1. Pharmacology

4.3.2. Pharmacokinetics

4.3.3. Toxicology

5. Specific requirements regarding module 5

5.1. Specific requirements for all advanced therapy medicinal products

5.2. Specific requirements for gene therapy medicinal products

5.2.1. Human pharmacokinetic studies

5.2.2. Human pharmacodynamic studies

5.2.3. Safety studies

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)

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

5.3.3. Safety studies

5.4. Specific requirements for tissue engineered products

5.4.1. Pharmacokinetic studies

5.4.2. Pharmacodynamic studies

5.4.3. Safety studies

▼M2

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 [1] 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 [2] 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) All 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.

[1] International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use.

[2] OJ L 193, 17.7.1991, p. 30.

▼**M2**

(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 ([1]). 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 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 ([2]) and 88/320/EEC on the inspection and verification of good laboratory practice (GLP) ([3]).

(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 ([4]) and (EC) No 1085/2003 ([5]) 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.

([1]) OJ L 121, 1.5.2001, p. 34.
([2]) OJ L 15, 17.1.1987, p. 29.
([3]) OJ L 145, 11.6.1988, p. 35.
([4]) See p. 1 of this Official Journal.
([5]) See p. 24 of this Official Journal.

▼M2

— 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

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.

▼M2

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. **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 ([1]) 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;

([1]) OJ L 106, 17.4.2001, p. 1.

▼M2

— 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;

— 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.

▼M2

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

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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

▼**M2**

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

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— 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).

▼M2

(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

(i) detailed description of the manufacturing process,

(ii) quality control during manufacture, and

(iii) 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.

▼M13

(12) Where, in accordance with the second subparagraph of Article 1(8) or the second subparagraph of Article 1(9) of Regulation (EU) 2017/745 of the European Parliament and of the Council [1], a product is governed by this Directive, the marketing authorisation dossier shall include, where available, the results of the assessment of the conformity of the device part with the relevant general safety and performance requirements set out in Annex I to that Regulation contained in the manufacturer's EU declaration of conformity or the relevant certificate issued by a notified body allowing the manufacturer to affix a CE marking to the medical device.

If the dossier does not include the results of the conformity assessment referred to in the first subparagraph and where for the conformity assessment of the device, if used separately, the involvement of a notified body is required in accordance with Regulation (EU) 2017/745, the authority shall require the applicant to provide an opinion on the conformity of the device part with the relevant general safety and performance requirements set out in Annex I to that Regulation issued by a notified body designated in accordance with that Regulation for the type of device in question.

▼M2

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.

[1] Regulation (EU) 2017/745 of the European Parliament and of the Council of 5 April 2017 on medical devices, amending Directive 2001/83/EC, Regulation (EC) No 178/2002 and Regulation (EC) No 1223/2009 and repealing Council Directives 90/385/EEC and 93/42/EEC (OJ L 117, 5.5.2017, p. 1).

▼M2

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.

▼M2

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 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

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.,

▼M2

— 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) (c):

— 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 [1] and/or European Parliament and Council Directive 94/36/EC of 30 June 1994 on colours for use in foodstuffs [2].

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.

[1] OJ L 11, 14.1.1978, p. 18.
[2] OJ L 237, 10.9.1994, p. 13.

▼M2

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.

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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.

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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.

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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

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— 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.

▼M2

(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).

▼M2

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.

▼M2

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.

▼M2

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

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— 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.

▼M2

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.

▼M2

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).

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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.

▼M2

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.

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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.

▼M2

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.

▼M2

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,

▼M2

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 ([1]).

([1]) OJ L 313, 13.12.2000, p. 22.

▼M2

— 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.

(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.

▼M2

(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 ([1]) 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 ([2]). 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 certification, re-certification or variation of the Plasma Master File on the concerned medicinal product(s).

([1]) OJ L 55, 11.3.1995, p. 15.
([2]) OJ L 214, 24.8.1993, p. 1.

▼M2

— 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.

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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.

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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.

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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.

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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.

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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.

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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 physico-chemical 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.

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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;

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(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 [1], 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.

[1] OJ L 102, 7.4.2004, p. 48.

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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 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.

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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.

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(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.

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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/EEC ([1]), or of conformity of the active implantable device part with the essential requirements laid down in Annex 1 to Council Directive 90/385/EEC ([2]);

(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/EC ([3]);

(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.

([1]) OJ L 169, 12.7.1993, p. 1.
([2]) OJ L 189, 20.7.1990, p. 17.
([3]) OJ L 105, 26.4.2003, p. 18.

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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 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.

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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.

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(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.

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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.

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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.

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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)

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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 ([1])
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 ([2]) 1 January 1995 ([3])
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 ([4]) 1 January 1998 ([5])
Directive 1999/82/EC	1 January 2000
Directive 1999/83/EC	1 March 2000
Directive 2000/38/EC	5 December 2001

([1]) Deadline for transposition applicable to Greece, Spain and Portugal.
([2]) Except Section A, point 3.3 in Part II of the Annex.
([3]) Deadline for transposition applicable to Section A, point 3.3 in Part II of the Annex.
([4]) Except with regard to Article 1(6).
([5]) Deadline for transposition applicable to Article 1(7).

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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)								

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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. 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						

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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. 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							

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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. 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								

▼B

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. 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								

▼B

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. 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

▼B

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. 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)		

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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. 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				

▼B

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. 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)	

▼B

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. 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)					

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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. 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								

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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. 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	—	—	—	—	—	—	—	—	—	—	—