3. Characterisation of the active substance

4. Quality control of the active substance

5. Reference standard and materials

6. Container and closure system of the active substance

7. Stability of the active substance.

c) Evaluation and Certification

— For novel vaccines, which contain a novel vaccine antigen, the applicant shall submit to a competent authority a full marketing-authorisation application dossier including all the Vaccine Antigen Master Files corresponding to each single vaccine antigen that is part of the novel vaccine where no master file already exists for the single vaccine antigen. A scientific and technical evaluation of each Vaccine Antigen Master File shall be carried out by the Agency. A positive evaluation shall result in a certificate of compliance to the European legislation for each Vaccine Antigen Master File, which shall be accompanied by the evaluation report. The certificate shall apply throughout the Community.

— The provisions of the first indent shall also apply to every vaccine, which consists of a novel combination of vaccine antigens, irrespective of whether or not one or more of these vaccine antigens are part of vaccines already authorised in the Community.

— Changes to the content of a Vaccine Antigen Master File for a vaccine authorised in the Community shall be subject to a scientific and technical evaluation carried out by the Agency in accordance with the procedure laid down in Commission Regulation (EC) No 1085/2003. In the case of a positive evaluation the Agency shall issue a certificate of compliance with Community legislation for the Vaccine Antigen Master File. The certificate issued shall apply throughout the Community.

— By derogation from the provisions of the first, second and third indents of the present point (evaluation and certification), where a Vaccine Antigen Master File corresponds only to a vaccine which is the subject of a marketing authorisation which has not been/will not be granted according to a Community procedure, and, provided the authorised vaccine includes vaccine antigens which have not been evaluated through a Community procedure, the scientific and technical evaluation of the said Vaccine Antigen Master File and its subsequent changes, shall be carried out by the national competent authority that has granted the marketing authorisation.

— As a second step to the provisions in the first, second, third and fourth indents, the competent authority that will grant or has granted the marketing authorisation shall take into account the certification, re-certification or variation of the Vaccine Antigen Master File on the concerned medicinal product(s).

2. RADIO-PHARMACEUTICALS AND PRECURSORS

2.1. **Radio-pharmaceuticals**

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

Module 3

a) In the context of a radio-pharmaceutical kit, which is to be radio-labelled after supply by the manufacturer, the active substance is considered to be that part of the formulation which is intended to carry or bind the radio-nuclide. The description of the manufacturing method of radio-pharmaceutical kits shall include details of the manufacture of the kit and details of its recommended final processing to produce the radioactive medicinal product. The necessary specifications of the radio-nuclide shall be described in accordance, where relevant, with the general monograph or specific monographs of the European Pharmacopoeia . In addition, any compounds essential for the radio-labelling shall be described. The structure of the radio-labelled compound shall also be described.

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

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

b) Details of the nature of the radio-nuclide, the identity of the isotope, likely impurities, the carrier, the use and the specific activity shall be provided.

c) Starting materials include irradiation target materials.

d) Considerations on chemical/radiochemical purity and its relationship to bio-distribution shall be provided.

e) Radio-nuclide purity, radiochemical purity and specific activity shall be described.

f) For generators, details on the testing for mother and daughter radio-nuclides are required. For generator-eluates, tests for mother radio-nuclides and for other constituents of the generator system shall be provided.

g) The requirement to express the content of active substances in terms of the mass of active entities shall onlyapply to radio-pharmaceutical kits. For radio-nuclides, radioactivity shall be expressed in Becquerels at a given date and, if necessary, time with reference to time zone. The type of radiation shall be indicated.

h) For kits, the specifications of the finished product shall include tests on performance of products after radio-labelling. Appropriate controls on radiochemical and radio-nuclidic purity of the radio-labelled compound shall be included. Any material essential for radio-labelling shall be identified and assayed.

i) Information on stability shall be given for radio-nuclide generators, radio-nuclide kits and radio-labelled products. The stability during use of radio-pharmaceuticals in multi-dose vials shall be documented.

Module 4

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

Module 5

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

2.2. **Radio-pharmaceutical precursors for radio-labelling purposes**

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

In particular, the following information where applicable shall be provided:

Module 3

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

Module 4

Concerning single dose and repeat dose toxicity, the results of studies carried out in conformity with the provisions related to good laboratory practice laid down in Council Directives 87/18/EEC and 88/320/EEC shall be provided, unless otherwise justified.

Mutagenicity studies on the radio-nuclide are not considered to be useful in this particular case.

Information relating to the chemical toxicity and disposition of the relevant 'cold' nuclide shall be presented.

Module 5

Clinical information generated from clinical studies using on the precursor itself is not considered to be relevant in the specific case of a radio-pharmaceutical precursor intended solely for radio-labelling purposes.

However, information demonstrating the clinical utility of the radio-pharmaceutical precursor when attached to relevant carrier molecules shall be presented.

3. HOMEOPATHIC MEDICINAL PRODUCTS

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

Module 3

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

a) Terminology

The Latin name of the homeopathic stock described in the marketing authorisation application dossier must be in accordance with the Latin title of the European Pharmacopoeia or, in absence thereof, by an official pharmacopoeia of a Member State. Where relevant the traditional name(s) used in each Member State shall be provided.

b) Control of starting materials

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

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

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

c) Control tests on the finished medicinal product

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

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

d) Stability tests

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

Module 4

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

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

4. HERBAL MEDICINAL PRODUCTS

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

Module 3

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

The following aspects specific to herbal medicinal products shall be considered:

(1) Herbal substances and herbal preparations

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

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

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

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

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

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

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

With respect to the description of manufacturing process and process controls for the herbal preparation, information shall be provided to adequately describe the manufacturing process of the herbal preparation, including description of the processing, solvents and reagents, purification stages and standardisation.

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

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

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

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

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

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

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

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

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

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

(2) Herbal Medicinal Products

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

5. ORPHAN MEDICINAL PRODUCTS

— In the case of an orphan medicinal product in the meaning of Regulation (EC) No 141/2000, general provisions of Part II-6 (exceptional circumstances) can be applied. The applicant shall then justify in the non-clinical and clinical summaries the reasons for which it is not possible to provide the complete information and shall provide a justification of the benefit/risk balance for the orphan medicinal product concerned.

— When an applicant for an marketing authorisation for an orphan medicinal product invokes the provisions of Article 10 (1)(a)(ii) and Part II-1 of this Annex (well-established medicinal use), the systematic and documented use of the concerned substance can refer — as way of derogation — to the use of that substance in accordance with the provisions of Article 5 of this Directive.

PART IV

ADVANCED THERAPY MEDICINAL PRODUCTS

Advanced therapy medicinal products are based on manufacturing processes focussed on various gene transfer-produced bio-molecules, and/or biologically advanced therapeutic modified cells as active substances or part of active substances.

For those medicinal products the presentation of the Marketing Authorisation application dossier shall fulfil the format requirements as described in Part I of this Annex.

Modules 1 to 5 shall apply. For Genetically Modified Organisms deliberate release in the environment, attention shall be paid to the persistence of the Genetically Modified Organisms in the recipient and to the possible replication and/or modification of the Genetically Modified Organisms when released in the environment. The information concerning the environmental risk should appear in the Annex to Module 1.

1. GENE THERAPY MEDICINAL PRODUCTS (HUMAN AND XENOGENEIC)

For the purposes of this Annex, gene therapy medicinal product shall mean a product obtained through a set of manufacturing processes aimed at the transfer, to be performed either in vivo or ex vivo, of a prophylactic, diagnostic or therapeutic gene (i.e. a piece of nucleic acid), to human/animal cells and its subsequent expression in vivo. The gene transfer involves an expression system contained in a delivery system known as a vector, which can be of viral, as well as non-viral origin. The vector can also be included in a human or animal cell.

1.1. Diversity of gene therapy medicinal products

a) Gene therapy medicinal products based on allogeneic or xenogeneic cells

The vector is ready-prepared and stored before its transfer into the host cells.

The cells have been obtained previously and may be processed as a cell bank (bank collection or bank established from procurement of primary cells) with a limited viability.

The cells genetically modified by the vector represent an active substance.

Additional steps may be carried out in order to obtain the finished product. By essence, such a medicinal product is intended to be administered to a certain number of patients.

b) Gene therapy medicinal products using autologous human cells

The active substance is a batch of ready-prepared vector stored before its transfer into the autologous cells.

Additional steps may be carried out in order to obtain the finished medicinal product.

Those products are prepared from cells obtained from an individual patient. The cells are then genetically modified using a ready-prepared vector containing the appropriate gene that has been prepared in advance and that constitutes the active substance. The preparation is re-injected into the patient and is by definition intended to a single patient. The whole manufacturing process from the collection of the cells from the patient up to the re-injection to the patient shall be considered as one intervention.

c) Administration of ready-prepared vectors with inserted (prophylactic, diagnostic or therapeutic) genetic material

The active substance is a batch of ready-prepared vector.

Additional steps may be carried out in order to obtain the finished medicinal product. This type of medicinal product is intended to be administered to several patients.

Transfer of genetic material may be carried out by direct injection of the ready-prepared vector to the recipients.

1.2. **Specific requirements regarding Module 3**

Gene therapy medicinal products include:

— naked nucleic acid

— complex nucleic acid or non viral vectors

— viral vectors

— genetically modified cells

As for other medicinal products, one can identify the three main elements of the manufacturing process, i.e.:

— starting materials: materials from which the active substance is manufactured such as, gene of interest, expression plasmids, cell banks and virus stocks or non viral vector;

— active substance: recombinant vector, virus, naked or complex plasmids, virus producing cells, in vitro genetically modified cells;

— finished medicinal product: active substance formulated in its final immediate container for the intended medical use. Depending on the type of gene therapy medicinal product, the route of administration and conditions of use may necessitate an ex vivo treatment of the cells of the patient (see 1.1.b).

A special attention shall be paid to the following items:

a) Information shall be provided on the relevant characteristics of the gene therapy medicinal product including its expression in the target cell population. Information concerning the source, construction, characterisation and verification of the encoding gene sequence including its integrity and stability shall be provided. Apart from therapeutic gene, the complete sequence of other genes, regulatory elements and the vector backbone shall be provided.

b) Information concerning the characterisation of the vector used to transfer and deliver the gene shall be provided. This must include its physico-chemical characterisation and/or biological/ immunological characterisation.

For medicinal products that utilise a micro-organism such as bacteria or viruses to facilitate gene transfer (biological gene transfer), data on the pathogenesis of the parental strain and on its tropism for specific tissues and cell types as well as the cell cycle-dependence of the interaction shall be provided.

For medicinal products that utilise non-biological means to facilitate gene transfer, the physico-chemical properties of the constituents individually and in combination shall be provided.

c) The principles for cell banking or seed lot establishment and characterisation shall apply to gene transfer medicinal products as appropriate.

d) The source of the cells hosting the recombinant vector shall be provided.

The characteristics of the human source such as age, sex, results of microbiological and viral testing, exclusion criteria and country of origin shall be documented.

For cells of animal origin, detailed information related to the following items shall be provided:

— Sourcing of the animals

— Animal husbandry and care

— Transgenic animals (methods of creation, characterisation of transgenic cells, nature of the inserted gene)

— Measures to prevent and monitor infections in the source/donor animals

— Testing for infectious agents

— Facilities

— Control of starting and raw materials.

Description of cell collection methodology including location, type of tissue, operating process, transportation, storage and traceability as well as controls carried out during the collection process shall be documented.

e) The evaluation of the viral safety as well as the traceability of the products from the donor to the finished medicinal product, are an essential part of the documentation to be supplied. E.g., the presence of replication competent virus in stocks of non-replication competent viral vectors must be excluded.

2. SOMATIC CELL THERAPY MEDICINAL PRODUCTS (HUMAN AND XENOGENEIC)

For the purposes of this Annex, somatic cell therapy medicinal products shall mean the use in humans of autologous (emanating from the patient himself), allogeneic (coming from another human being) or xenogeneic (coming from animals) somatic living cells, the biological characteristics of which have been substantially altered as a result of their manipulation to obtain a therapeutic, diagnostic or preventive effect through metabolic, pharmacological and immunological means. This manipulation includes the expansion or activation of autologous cell populations ex vivo (e.g., adoptive immuno-therapy), the use of allogeneic and xenogeneic cells associated with medical devices used ex vivo or in vivo (e.g., micro-capsules, intrinsic matrix scaffolds, bio-degradable or not).

Specific requirements for cell therapy medicinal products regarding Module 3

Somatic cell therapy medicinal products include:

— Cells manipulated to modify their immunological, metabolic or other functional properties in qualitative or quantitative aspects;

— Cells sorted, selected and manipulated and subsequently undergoing a manufacturing process in order to obtain the finished medicinal product;

— Cells manipulated and combined with non-cellular components (e.g. biological or inert matrixes or medical devices) and exerting the principle intended action in the finished product;

— Autologous cell derivatives expressed in vitro under specific culture conditions;

— Cells genetically modified or otherwise manipulated to express previously unexpressed homologous or non-homologous functional properties.

The whole manufacturing process from the collection of the cells from the patient (autologous situation) up to the re-injection to the patient shall be considered as one single intervention.

As for other medicinal products, the three elements of the manufacturing process are identified:

— starting materials: materials from which the active substance is manufactured, i.e., organs, tissues, body fluids or cells;

— active substance: manipulated cells, cell lysates, proliferating cells and cells used in conjunction with inert matrixes and medical devices;

— finished medicinal products: active substance formulated in its final immediate container for the intended medical use.

a) General information on active substance(s)

The active substances of cell therapy medicinal products consist of cells which as a consequence of in vitro processing display prophylactic, diagnostic or therapeutic properties different from the original physiological and biological one.

This section shall describe the type of cells and culture concerned. Tissues, organs or biological fluids from which cells are derived as well as the autologous, allogeneic, or xenogeneic nature of the donation and its geographical origin shall be documented. Collection of the cells, sampling and storage prior further processing shall be detailed. For allogeneic cells, special attention shall be paid to the very first step of the process, which covers selection of donors. The type of manipulation carried out and the physiological function of the cells that are used as active substance shall be provided.

b) Information related to the starting materials of active substance(s)

1. Human somatic cells

Human somatic cell therapy medicinal products are made of a defined number (pool) of viable cells, which are derived from a manufacturing process starting either at the level of organs or tissues retrieved from a human being, or, at the level of a well defined cell bank system where the pool of cells relies on continuous cell lines. For the purposes of this chapter, active substance shall mean the seed pool of human cells and finished medicinal product shall mean seed pool of human cells formulated for the intended medical use.

Starting materials and each step of the manufacturing process shall be fully documented including viral safety aspects.

(1) Organs, tissues, body fluids and cells of human origin

The characteristics of the human source such as age, sex, microbiological status, exclusion criteria and country of origin shall be documented.

Description of sampling including site, type, operating process, pooling, transportation, storage and traceability as well as controls carried out on sampling shall be documented.

(2) Cell banking systems

Relevant requirements depicted in part I shall apply for the preparation and quality control of cell banking systems. This may essentially be the case for allogeneic or xenogeneic cells.

(3) Ancillary materials or ancillary medical devices

Information shall be provided on the use of any raw materials (e.g., cytokines, growth factors, culture media) or of possible ancillary products and medical devices e.g., cell sorting devices, biocompatible polymers, matrix, fibres, beads in terms of bio-compatibility, functionality as well as the risk of infectious agents.

2. Animal somatic cells (xenogeneic)

Detailed information related to the following items shall be provided:

— Sourcing of the animals

— Animal husbandry and care

— Genetically modified animals (methods of creation, characterisation of transgenic cells, nature of the inserted or excised (knock out) gene)

— Measures to prevent and monitor infections in the source/donor animals

— Testing for infectious agents including vertically transmitted micro-organisms (also endogenous retro viruses)

— Facilities

— Cell banking systems

— Control of starting and raw materials.

a) Information on the manufacturing process of the active substance(s) and the finished product

The different steps of the manufacturing process such as organ/tissue dissociation, selection of the cell population of interest, in vitro cell culture, cell transformation either by physico-chemical agents or gene transfer shall be documented.

b) Characterisation of active substance(s)

All of the relevant information on the characterisation of the cell population of interest in terms of identity (species of origin, banding cytogenetics, morphological analysis), purity (adventitious microbial agents and cellular contaminants), potency (defined biological activity), and suitability (karyology and tumorigenicity tests) for the intended medicinal use shall be provided.

c) Pharmaceutical development of finished medicinal product

Apart from the specific method of administration used (intravenous infusion, site-injection, transplantation surgery), information shall also be provided on the use of possible ancillary medical devices (bio-compatible polymers, matrix, fibres, beads) in terms of bio-compatibility and durability.

d) Traceability

A detailed flow chart shall be provided insuring the traceability of the products from the donor to the finished medicinal product.

3. SPECIFIC REQUIREMENTS FOR GENE THERAPY AND SOMATIC CELL THERAPY (HUMAN AND XENOGENEIC) MEDICINAL PRODUCTS REGARDING MODULES 4 AND 5

3.1. **Module 4**

For gene and somatic cell therapy medicinal products, it is recognised that conventional requirements as laid down in Module 4 for non-clinical testing of medicinal products may not always be appropriate due to unique and diverse structural and biological properties of the products in question, including high degree of species specificity, subject specificity, immunological barriers and differences in pleiotropic responses.

The rationale underpinning the non-clinical development and the criteria used to choose relevant species and models shall be properly captioned in Module 2.

It may be necessary to identify or develop new animal models in order to assist in the extrapolation of specific findings on functional endpoints and toxicity to in vivo activity of the products in human beings. The scientific justification for the use of these animal models of disease to support safety and proof of concept for efficacy shall be provided.

3.2. **Module 5**

The efficacy of advanced therapy medicinal products must be demonstrated as described in Module 5. For some products and for some therapeutic indications, however, it may not be possible to perform conventional clinical trials. Any deviation from the existing guidelines shall be justified in Module 2.

The clinical development of advanced therapy medicinal products will have some special features owing to the complex and labile nature of the active substances. It requires additional considerations because of issues related to viability, proliferation, migration and differentiation of cells (somatic cell therapy), because of the special clinical circumstances where the products are used or because of the special mode of action through gene expression (somatic gene therapy).

Special risks associated with such products arising from potential contamination with infectious agents must be addressed in the application for marketing authorisation for advanced therapy medicinal products. Special emphasis should be put on both the early stages of development in one hand, including the choice of donors in the case of cell therapy medicinal products, and on the therapeutic intervention as a whole, including the proper handling and administration of the product on the other hand.

Furthermore, Module 5 of the application should contain, as relevant, data on the measures to surveying and control of the functions and development of living cells in the recipient, to prevent transmission of infectious agents to the recipient and to minimise any potential risks to public health.

3.2.1. *Human pharmacology and efficacy studies*

Human pharmacology studies should provide information on the expected mode of action, expected efficacy based on justified end-points, bio-distribution, adequate dose, schedule, and methods of administration or modality of use desirable for efficacy studies.

Conventional pharmaco-kinetic studies may not be relevant for some advanced therapy products. Sometimes studies in healthy volunteers are not feasible and the establishment of dose and kinetics will be difficult to determine in clinical trials. It is necessary, however, to study the distribution and in vivo behaviour of the product including cell proliferation and long-term function as well as the extent, distribution of the gene product and duration of the desired gene expression. Appropriate tests shall be used and, if necessary, developed for the tracing of the cell product or cell expressing the desired gene in the human body and for the monitoring of the function of the cells that were administered or transfected.

The assessment of the efficacy and safety of an advanced therapy medicinal product must include the careful description and evaluation of the therapeutic procedure as a whole, including special ways of administration, (such as transfection of cells ex vivo, in vitro manipulation, or use of interventional techniques), and testing of the possible associated regimens (including immuno-suppressive, antiviral, cytotoxic treatment).

The whole procedure must be tested in clinical trials and described in the product information.

3.2.2. *Safety*

Safety issues arising from immune response to the medicinal products or to the expressed proteins, immune rejection, immuno-suppression, and breakdown of immuno-isolation devices shall be considered.

Certain advanced gene therapy and somatic cell therapy medicinal products (e.g. xenogeneic cell therapy and certain gene transfer products) may contain replication-competent particles and/or infectious agents. The patient may have to be monitored for the development of possible infections and/or their pathological sequelae during pre- and/or post-authorisation phases; this surveillance may have to be extended to close contacts of the patient including health-care workers.

The risk of contamination with potentially transmissible agents cannot be totally eliminated in the use of certain somatic cell therapy medicinal products and certain gene transfer medicinal products. The risk can be minimised, however, by appropriate measures as described in Module 3.

The measures included in the production process must be complemented with accompanied testing methods, quality control processes and by appropriate surveillance methods that must be described in Module 5.

The use of certain advanced somatic cell therapy medicinal products may have to be limited, temporarily or permanently, to establishments that have documented expertise and facilities for assuring a specific follow up of the safety of the patients. A similar approach may be relevant for certain gene therapy medicinal products that are associated with a potential risk of replication-competent infectious agents.

The long term monitoring aspects for the development of late complications shall also be considered and addressed in the submission, where relevant.

Where appropriate, the applicant has to submit a detailed risk management plan covering clinical and laboratory data of the patient, emerging epidemiological data, and, if relevant, data from archives of tissue samples from the donor and the recipient. Such a system is needed to ensure the traceability of the medicinal product and the rapid response to suspicious patterns of adverse events.

4. SPECIFIC STATEMENT ON XENO-TRANSPLANTATION MEDICINAL PRODUCTS

For the purposes of this Annex, xeno-transplantation shall mean any procedure that involves the transplantation, implantation, or infusion into a human recipient of either live tissues or organs retrieved from animals, or, human body fluids, cells, tissues or organs that have undergone ex vivo contact with live non-human animal cells, tissues or organs.

Specific emphasis shall be paid to the starting materials.

In this respect, detailed information related to the following items shall be provided according to specific guidelines:

— Sourcing of the animals

— Animal husbandry and care

— Genetically modified animals (methods of creation, characterisation of transgenic cells, nature of the inserted or excised (knock out) gene)

— Measures to prevent and monitor infections in the source/donor animals

— Testing for infectious agents

— Facilities

— Control of starting and raw materials

— Traceability.

►B

COUNCIL DIRECTIVE 93/42/EEC

of 14 June 1993

concerning medical devices

(OJ L 169, 12.7.1993, p. 1)

Amended by:

		Official Journal		
		No	page	date
►M1	Directive 98/79/EC of the European Parliament and of the Council of 27 October 1998	L 331	1	7.12.1998
►M2	Directive 2000/70/EC of the European Parliament and of the Council of 16 November 2000	L 313	22	13.12.2000
►M3	Directive 2001/104/EC of the European Parliament and of the Council of 7 December 2001	L 6	50	10.1.2002
►M4	Regulation (EC) No 1882/2003 of the European Parliament and of the Council of 29 September 2003	L 284	1	31.10.2003

▼B

COUNCIL DIRECTIVE 93/42/EEC

of 14 June 1993

concerning medical devices

THE COUNCIL OF THE EUROPEAN COMMUNITIES,

Having regard to the Treaty establishing the European Economic Community, and in particular Article 100a thereof,

Having regard to the proposal from the Commission (1),

In cooperation with the European Parliament (2),

Having regard to the opinion of the Economic and Social Committee (3),

Whereas measures should be adopted in the context of the internal market; whereas the internal market is an area without internal frontiers in which the free movement of goods, persons, services and capital is ensured;

Whereas the content and scope of the laws, regulations and administrative provisions in force in the Member States with regard to the safety, health protection and performance characteristics of medical devices are different; whereas the certification and inspection procedures for such devices differ from one Member State to another; whereas such disparities constitute barriers to trade within the Community;

Whereas the national provisions for the safety and health protection of patients, users and, where appropriate, other persons, with regard to the use of medical devices should be harmonized in order to guarantee the free movement of such devices within the internal market;

Whereas the harmonized provisions must be distinguished from the measures adopted by the Member States to manage the funding of public health and sickness insurance schemes relating directly or indirectly to such devices; whereas, therefore, the provisions do not affect the ability of the Member States to implement the abovementioned measures provided Community law is complied with;

Whereas medical devices should provide patients, users and third parties with a high level of protection and attain the performance levels attributed to them by the manufacturer; whereas, therefore, the maintenance or improvement of the level of protection attained in the Member States is one of the essential objectives of this Directive;

Whereas certain medical devices are intended to administer medicinal products within the meaning of Council Directive 65/65/EEC of 26 January 1965 on the approximation of provisions laid down by law, regulation or administrative action relating to proprietary medicinal products (4); whereas, in such cases, the placing on the market of the medical device as a general rule is governed by the present Directive and the placing on the market of the medicinal product is governed by Directive 65/65/EEC; whereas if, however, such a device is placed on the market in such a way that the device and the medicinal product form a single integral unit which is intended exclusively for use in the given combination and which is not reusable, that single-unit product shall be governed by Directive 65/65/EEC; whereas a distinction must be drawn between the abovementioned devices and medical devices incorporating, *inter alia*, substances which, if used separately, may be considered to be a medicinal substance within the meaning of Directive 65/65/EEC; whereas in such cases, if the substances incorporated in the medical devices are liable to act upon the body with action ancillary to that of the device, the placing of the devices on the market is governed by this Directive; whereas, in this context, the safety, quality and

(1) OJ No C 237, 12. 9. 1991 and OJ No C 251, 28. 9. 1992, p. 40.
(2) OJ No C 150, 31. 5. 1993 and OJ No C 176, 28. 6. 1993.
(3) OJ No C 79, 30. 3. 1992, p. 1.
(4) OJ No 22, 9. 6. 1965, p. 369/65. Directive as last amended by Directive 92/27/EEC (OJ No L 113, 30. 4. 1992, p. 8).

▼B

usefulness of the substances must be verified by analogy with the appropriate methods specified in Council Directive 75/318/EEC of 20 May 1975 on the approximation of the laws of the Member States relating to analytical, pharmaco-toxicological and clinical standards and protocols in respect of the testing of proprietary medicinal products [1];

Whereas the essential requirements and other requirements set out in the Annexes to this Directive, including any reference to 'minimizing' or 'reducing' risk must be interpreted and applied in such a way as to take account of technology and practice existing at the time of design and of technical and economical considerations compatible with a high level of protection of health and safety;

Whereas, in accordance with the principles set out in the Council resolution of 7 May 1985 concerning a new approach to technical harmonization and standardization [2], rules regarding the design and manufacture of medical devices must be confined to the provisions required to meet the essential requirements; whereas, because they are essential, such requirements should replace the corresponding national provisions; whereas the essential requirements should be applied with discretion to take account of the technological level existing at the time of design and of technical and economic considerations compatible with a high level of protection of health and safety;

Whereas Council Directive 90/385/EEC of 20 June 1990 on the approximation of the laws of the Member States relating to active implantable medical devices [3] is the first case of application of the new approach to the field of medical devices; whereas in the interest of uniform Community rules applicable to all medical devices, this Directive is based largely on the provisions of Directive 90/385/EEC; whereas for the same reasons Directive 90/385/EEC must be amended to insert the general provisions laid down in this Directive;

Whereas the electromagnetic compatibility aspects form an integral part of the safety of medical devices; whereas this Directive should contain specific rules on this subject with regard to Council Directive 89/336/EEC of 3 May 1989 on the approximation of the laws of the Member States relating to electromagnetic compatibility [4];

Whereas this Directive should include requirements regarding the design and manufacture of devices emitting ionizing radiation; whereas this Directive does not affect the authorization required by Council Directive 80/836/Euratom of 15 July 1980 amending the Directives laying down the basic safety standards for the health protection of the general public and workers against the dangers of ionizing radiation [5], nor application of Council Directive 84/466/Euratom of 3 September 1984 laying down basic measures for the radiation protection of persons undergoing medical examination or treatment [6]; whereas Council Directive 89/391/EEC of 12 June 1989 on the introduction of measures to encourage improvements in the safety and health of workers at work [7] and the specific directives on the same subject should continue to apply;

Whereas, in order to demonstrate conformity with the essential requirements and to enable conformity to be verified, it is desirable to have harmonized European standards to protect against the risks associated with the design, manufacture and packaging of medical devices; whereas such harmonized European standards are drawn up by private-law bodies and should retain their status as non-mandatory

[1] OJ No L 147, 9. 6. 1975, p. 1. Directive as last amended by Directive 91/507/EEC (OJ No L 270, 26. 9. 1991, p. 32).
[2] OJ No C 136, 4. 6. 1985, p. 1.
[3] OJ No L 189, 20. 7. 1990, p. 17.
[4] OJ No L 139, 23. 5. 1989, p. 19. Directive as last amended by Directive 92/31/EEC (OJ No L 126, 12. 5. 1992, p. 11).
[5] OJ No L 246, 17. 9. 1980, p. 1. Directive as last amended by Directive 84/467/Euratom (OJ No L 265, 5. 10. 1984, p. 4).
[6] OJ No L 265, 5. 10. 1984, p. 1.
[7] OJ No L 183, 29. 6. 1989, p. 1.

▼B

texts; whereas, to this end, the European Committee for Standardization (CEN) and the European Committee for Electrotechnical Standardization (Cenelec) are recognized as the competent bodies for the adoption of harmonized standards in accordance with the general guidelines on cooperation between the Commission and these two bodies signed on 13 November 1984;

Whereas, for the purpose of this Directive, a harmonized standard is a technical specification (European standard or harmonization document) adopted, on a mandate from the Commission, by either or both of these bodies in accordance with Council Directive 83/189/EEC of 28 March 1983 laying down a procedure for the provision of information in the field of technical standards and regulations [1], and pursuant to the abovementioned general guidelines; whereas with regard to possible amendment of the harmonized standards, the Commission should be assisted by the Committee set up pursuant to Directive 83/189/EEC; whereas the measures to be taken must be defined in line with procedure I, as laid down in Council Decision 87/373/EEC [2]; whereas, for specific fields, what already exists in the form of European *Pharmacopoeia* monographs should be incorporated within the framework of this Directive; whereas, therefore, several European *Pharmacopoeia* monographs may be considered equal to the abovementioned harmonized standards;

Whereas, in Decision 90/683/EEC of 13 December 1990 concerning the modules for the various phases of the conformity assessment procedures which are intended to be used in the technical harmonization directives [3], the Council has laid down harmonized conformity assessment procedures; whereas the application of these modules to medical devices enables the responsibility of manufacturers and notified bodies to be determined during conformity assessment procedures on the basis of the type of devices concerned; whereas the details added to these modules are justified by the nature of the verification required for medical devices;

Whereas it is necessary, essentially for the purpose of the conformity assessment procedures, to group the devices into four product classes; whereas the classification rules are based on the vulnerability of the human body taking account of the potential risks associated with the technical design and manufacture of the devices; whereas the conformity assessment procedures for Class I devices can be carried out, as a general rule, under the sole responsibility of the manufacturers in view of the low level of vulnerability associated with these products; whereas, for Class IIa devices, the intervention of a notified body should be compulsory at the production stage; whereas, for devices falling within Classes IIb and III which constitute a high risk potential, inspection by a notified body is required with regard to the design and manufacture of the devices; whereas Class III is set aside for the most critical devices for which explicit prior authorization with regard to conformity is required for them to be placed on the market;

Whereas in cases where the conformity of the devices can be assessed under the responsibility of the manufacturer the competent authorities must be able, particularly in emergencies, to contact a person responsible for placing the device on the market and established in the Community, whether the manufacturer or another person established in the Community and designated by the manufacturer for the purpose;

Whereas medical devices should, as a general rule, bear the CE mark to indicate their conformity with the provisions of this Directive to enable them to move freely within the Community and to be put into service in accordance with their intended purpose;

[1] OJ No L 109, 26. 4. 1983, p. 8. Directive as last amended by Commission Decision 92/400/EEC (OJ No L 221, 6. 8. 1992, p. 55).
[2] OJ No L 197, 18. 7. 1987, p. 33.
[3] OJ No L 147, 9. 6. 1975, p. 1. Directive as last amended by Directive 91/507/EEC (OJ No L 270, 26. 9. 1991, p. 32).

▼B

Whereas, in the fight against AIDS and in the light of the conclusions of the Council adopted on 16 May 1989 regarding future activities on AIDS prevention and control at Community level [1], medical devices used for protection against the HIV virus must afford a high level of protection; whereas the design and manufacture of such products should be verified by a notified body;

Whereas the classification rules generally enable medical devices to be appropriately classified; whereas, in view of the diverse nature of the devices and technological progress in this field, steps must be taken to include amongst the implementing powers conferred on the Commission the decisions to be taken with regard to the proper classification or reclassification of the devices or, where appropriate, the adjustment of the classification rules themselves; whereas since these issues are closely connected with the protection of health, it is appropriate that these decisions should come under procedure IIIa, as provided for in Directive 87/373/EEC;

Whereas the confirmation of complicance with the essential requirements may mean that clinical investigations have to be carried out under the responsibility of the manufacturer; whereas, for the purpose of carrying out the clinical investigations, appropriate means have to be specified for the protection of public health and public order;

Whereas the protection of health and the associated controls may be made more effective by means of medical device vigilance systems which are integrated at Community level;

Whereas this Directive covers the medical devices referred to in Council Directive 76/764/EEC of 27 July 1976 on the approximation of the laws of the Member States on clinical mercury-in-glass, maximum reading thermometers [2]; whereas the abovementioned Directive must therefore be repealed; whereas for the same reasons Council Directive 84/539/EEC on 17 September 1984 on the approximation of the laws of the Member States relating to electro-medical equipment used in human or veterinary medicine [3] must be amended,

HAS ADOPTED THIS DIRECTIVE:

Article 1

Definitions, scope

1. This Directive shall apply to medical devices and their accessories. For the purposes of this Directive, accessories shall be treated as medical devices in their own right. Both medical devices and accessories shall hereinafter be termed devices.

2. For the purposes of this Directive, the following definitions shall apply:

(a) 'medical device' means any instrument, apparatus, appliance, material or other article, whether used alone or in combination, including the software necessary for its proper application intended by the manufacturer to be used for human beings for the purpose of:

— diagnosis, prevention, monitoring, treatment or alleviation of disease,

— diagnosis, monitoring, treatment, alleviation of or compensation for an injury or handicap,

— investigation, replacement or modification of the anatomy or of a physiological process,

— control of conception,

[1] OJ No C 185, 22. 7. 1989, p. 8.
[2] OJ No L 262, 27. 9. 1976, p. 139. Directive as last amended by Directive 84/414/EEC (OJ No L 228, 25. 8. 1984, p. 25).
[3] OJ No L 300, 19. 11. 1984, p. 179. Directive as amended by the Act of Accession of Spain and Portugal.

▼B

and which does not achieve its principal intended action in or on the human body by pharmacological, immunological or metabolic means, but which may be assisted in its function by such means;

(b) 'accessory' means an article which whilst not being a device is intended specifically by its manufacturer to be used together with a device to enable it to be used in accordance with the use of the device intended by the manufacturer of the device;

▼M1

(c) '*in vitro* diagnostic medical device' means any medical device which is a reagent, reagent product, calibrator, control material, kit, instrument, apparatus, equipment or system, whether used alone or in combination, intended by the manufacturer to be used *in vitro* for the examination of specimens, including blood and tissue donations,

derived from the human body, solely or principally for the purpose of providing information:

— concerning a physiological or pathological state, or

— concerning a congenital abnormality, or

— to determine the safety and compatibility with potential recipients, or

— to monitor therapeutic measures.

Specimen receptacles are considered to be *in vitro* diagnostic medical devices. 'Specimen receptacles' are those devices, whether vacuum-type or not, specifically intended by their manufacturers for the primary containment and preservation of specimens derived from the human body for the purpose of *in vitro* diagnostic examination.

Products for general laboratory use are not *in vitro* diagnostic medical devices unless such products, in view of their characteristics, are specifically intended by their manufacturer to be used for *in vitro* diagnostic examination;

▼B

(d) 'custom-made device' means any device specifically made in accordance with a duly qualified medical practitioner's written prescription which gives, under his responsibility, specific design characteristics and is intended for the sole use of a particular patient.

The abovementioned prescription may also be made out by any other person authorized by virtue of his professional qualifications to do so.

Mass-produced devices which need to be adapted to meet the specific requirements of the medical practitioner or any other professional user are not considered to be custom-made devices;

(e) 'device intended for clinical investigation' means any device intended for use by a duly qualified medical practitioner when conducting investigations as referred to in Section 2.1 of Annex X in an adequate human clinical environment.

For the purpose of conducting clinical investigation, any other person who, by virtue of his professional qualifications, is authorized to carry out such investigation shall be accepted as equivalent to a duly qualified medical practitioner;

(f) 'manufacturer' means the natural or legal person with responsibility for the design, manufacture, packaging and labelling of a device before it is placed on the market under his own name, regardless of whether these operations are carried out by that person himself or on his behalf by a third party.

The obligations of this Directive to be met by manufacturers also apply to the natural or legal person who assembles, packages, processes, fully refurbishes and/or labels one or more ready-made products and/or assigns to them their intended purpose as a device with a view to their being placed on the market under his own name. This subparagraph does not apply to the person who, while not a manufacturer within the meaning of the first subparagraph,

▼B

assembles or adapts devices already on the market to their intended purpose for an individual patient;

(g) 'intended purpose' means the use for which the device is intended according to the data supplied by the manufacturer on the labelling, in the instructions and/or in promotional materials;

(h) 'placing on the market' means the first making available in return for payment or free of charge of a device other than a device intended for clinical investigation, with a view to distribution and/or use on the Community market, regardless of whether it is new or fully refurbished;

▼M1

(i) 'putting into service' means the stage at which a device has been made available to the final user as being ready for use on the Community market for the first time for its intended purpose;

(j) 'authorised representative' means any natural or legal person established in the Community who, explicitly designated by the manufacturer, acts and may be addressed by authorities and bodies in the Community instead of the manufacturer with regard to the latter's obligations under this Directive.

▼B

3. Where a device is intended to administer a medicinal product within the meaning of Article 1 of Directive 65/65/EEC, that device shall be governed by the present Directive, without prejudice to the provisions of Directive 65/65/EEC with regard to the medicinal product.

If, however, such a device is placed on the market in such a way that the device and the medicinal product form a single integral product which is intended exclusively for use in the given combination and which is not reusable, that single product shall be governed by Directive 65/65/EEC. The relevant essential requirements of Annex I to the present Directive shall apply as far as safety and performance related device features are concerned.

4. Where a device incorporates, as an integral part, a substance which, if used separately, may be considered to be a medicinal product within the meaning of Article 1 of Directive 65/65/EEC and which is liable to act upon the body with action ancillary to that of the device, that device must be assessed and authorized in accordance with this Directive.

▼M2

4 a. Where a device incorporates, as an integral part, a substance which, if used separately, may be considered to be a medicinal product constituent or a medicinal product derived from human blood or human plasma within the meaning of Article 1 of Directive 89/381/EEC [1] and which is liable to act upon the human body with action ancillary to that of the device, hereinafter referred to as a 'human blood derivative', that device must be assessed and authorised in accordance with this Directive.

▼B

5. This Directive does not apply to:

(a) *in vitro* diagnostic devices;

(b) active implantable devices covered by Directive 90/385/EEC;

▼M3

(c) medicinal products covered by Directive 65/65/EEC, including medicinal products derived from blood as covered by Directive 89/381/EEC;

[1] Council Directive 89/381/EEC of 14 June 1989 extending the scope of Directives 65/65/EEC and 75/319/EEC on the approximation of provisions laid down by law, regulation or administrative action relating to proprietary medicinal products and laying down special provisions for medicinal products derived from human blood or human plasma (OJ L 181, 28.6.1989, p. 44).

▼B

(d) cosmetic products covered by Directive 76/768/EEC [1];

▼M3

(e) human blood, blood products, plasma or blood cells of human origin or to devices which incorporate at the time of placing on the market such blood products, plasma or cells, with the exception of devices referred to in paragraph 4a;

▼B

(f) transplants or tissues or cells of human origin nor to products incorporating or derived from tissues or cells of human origin;

(g) transplants or tissues or cells of animal origin, unless a device is manufactured utilizing animal tissue which is rendered non-viable or non-viable products derived from animal tissue.

6. This Directive does not apply to personal protective equipment covered by Directive 89/686/EEC. In deciding whether a product falls under that Directive or the present Directive, particular account shall be taken of the principal intended purpose of the product.

7. This Directive is a specific Directive within the meaning of Article 2 (2) of Directive 89/336/EEC.

8. This Directive does not affect the application of Directive 80/836/Euratom, nor of Directive 84/466/Euratom.

▼M1

Article 2

Placing on the market and putting into service

Member States shall take all necessary steps to ensure that devices may be placed on the market and/or put into service only if they comply with the requirements laid down in this Directive when duly supplied and properly installed, maintained and used in accordance with their intended purpose.

▼B

Article 3

Essential requirements

The devices must meet the essential requirements set out in Annex I which apply to them, taking account of the intended purpose of the devices concerned.

Article 4

Free movement, devices intended for special purposes

1. Member States shall not create any obstacle to the placing on the market or the putting into service within their territory of devices bearing the CE marking provided for in Article 17 which indicate that they have been the subject of an assessment of their conformity in accordance with the provisions of Article 11.

2. Member States shall not create any obstacle to:

— devices intended for clinical investigation being made available to medical practitioners or authorized persons for that purpose if they meet the conditions laid down in Article 15 and in Annex VIII,

— custom-made devices being placed on the market and put into service if they meet the conditions laid down in Article 11 in combination with Annex VIII; Class IIa, IIb and III devices shall be accompanied by the statement referred to in Annex VIII.

These devices shall not bear the CE marking.

3. At trade fairs, exhibitions, demonstrations, etc. Member States shall not create any obstacle to the showing of devices which do not

[1] OJ No L 262, 27. 9. 1976, p. 169. Directive as last amended by Commission Directive 92/86/EEC (OJ No L 325, 11. 11. 1992, p. 18).