

[^{F1}ANNEX I

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

Textual Amendments

- F1** Substituted by [Commission directive 2003/63/EC of 25 June 2003 amending Directive 2001/83/EC of the European Parliament and of the Council on the Community code relating to medicinal products for human use \(Text with EEA relevance\)](#).

[^{F2}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

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

2.1. **Gene therapy medicinal product**

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

- (a) it contains an active substance which contains or consists of a recombinant nucleic acid used in or administered to human beings with a view to regulating, repairing, replacing, adding or deleting a genetic sequence;
- (b) its therapeutic, prophylactic or diagnostic effect relates directly to the recombinant nucleic acid sequence it contains, or to the product of genetic expression of this sequence.

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

2.2. **Somatic cell therapy medicinal product**

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

- (a) contains or consists of cells or tissues that have been subject to substantial manipulation so that biological characteristics, physiological functions or structural properties relevant for the intended clinical use have been altered, or of cells or tissues that are not intended to be used for the same essential function(s) in the recipient and the donor;
- (b) is presented as having properties for, or is used in or administered to human beings with a view to treating, preventing or diagnosing a disease through the pharmacological, immunological or metabolic action of its cells or tissues.

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

3. **SPECIFIC REQUIREMENTS REGARDING MODULE 3**

3.1. **Specific requirements for all advanced therapy medicinal products**

A description of the traceability system that the marketing authorisation holder intends to establish and maintain to ensure that the individual product and its starting and raw materials, including all substances coming into contact with the cells or tissues it may contain, can be traced through the sourcing, manufacturing, packaging, storage, transport and delivery to the hospital, institution or private practice where the product is used, shall be provided.

The traceability system shall be complementary to, and compatible with, the requirements established in Directive 2004/23/EC of the European Parliament and of the Council⁽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.

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;

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- (e) for genetically modified cells, the characteristics of the cells before and after the genetic modification, as well as before and after any subsequent freezing/storage procedures, shall be tested.

For genetically modified cells, in addition to the specific requirements for gene therapy medicinal products, the quality requirements for somatic cell therapy medicinal products and tissue engineered products (see section 3.3) shall apply.

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

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

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

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

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

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

3.3.2. *Specific requirements*

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

3.3.2.1. Starting materials

- (a) Summary information shall be provided on donation, procurement and testing of the human tissue and cells used as starting materials and made in accordance with Directive 2004/23/EC. If non-healthy cells or tissues (e.g. cancer tissue) are used as starting materials, their use shall be justified.
- (b) If allogeneic cell populations are being pooled, the pooling strategies and measures to ensure traceability shall be described.
- (c) The potential variability introduced through the human or animal tissues and cells shall be addressed as part of the validation of the manufacturing process, characterisation of the active substance and the finished product, development of assays, setting of specifications and stability.
- (d) For xenogeneic cell-based products, information on the source of animals (such as geographical origin, animal husbandry, age), specific acceptance criteria, measures to prevent and monitor infections in the source/donor animals, testing of the animals for infectious agents, including vertically transmitted micro-organisms and viruses, and evidence of the suitability of the animal facilities shall be provided.
- (e) For cell-based products derived from genetically modified animals, the specific characteristics of the cells related to the genetic modification shall be described. A detailed description of the method of creation and the characterisation of the transgenic animal shall be provided.

- (f) For the genetic modification of the cells, the technical requirements specified in section 3.2 shall apply.
- (g) The testing regimen of any additional substance (scaffolds, matrices, devices, biomaterials, biomolecules or other components), which are combined with engineered cells of which they form an integral part, shall be described and justified.
- (h) For scaffolds, matrices and devices that fall under the definition of a medical device or active implantable medical device, the information required under section 3.4 for the evaluation of the combined advanced therapy medicinal product shall be provided.

3.3.2.2. Manufacturing process

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

3.3.2.3. Characterisation and control strategy

- (a) Relevant information shall be provided on the characterisation of the cell population or cell mixture in terms of identity, purity (e.g. adventitious microbial agents and cellular contaminants), viability, potency, karyology, tumourigenicity and suitability for the intended medicinal use. The genetic stability of the cells shall be demonstrated.
- (b) Qualitative and, where possible, quantitative information on product- and process-related impurities, as well as on any material capable of introducing degradation products during production, shall be provided. The extent of the determination of impurities shall be justified.
- (c) If certain release tests cannot be performed on the active substance or finished product, but only on key intermediates and/or as in-process testing, this shall be justified.
- (d) Where biologically active molecules (such as growth factors, cytokines) are present as components of the cell-based product, their impact and interaction with other components of the active substance shall be characterised.
- (e) Where a three-dimensional structure is part of the intended function, the differentiation state, structural and functional organisation of the cells and, where applicable, the extracellular matrix generated shall be part of the characterisation for these cell-based products. Where needed, non-clinical investigations shall complement the physicochemical characterisation.

3.3.2.4. Excipients

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

3.3.2.5. Developmental studies

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

3.3.2.6. Reference materials

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

3.4. Specific requirements for advanced therapy medicinal products containing devices

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

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

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

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

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

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

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

- (a) information on the choice and intended function of the medical device or implantable medical device and demonstration of compatibility of the device with other components of the product;
- (b) evidence of conformity of the medical device part with the essential requirements laid down in Annex I to Council Directive 93/42/EEC⁽²⁾, or of conformity of the active implantable device part with the essential requirements laid down in Annex 1 to Council Directive 90/385/EEC⁽³⁾;
- (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⁽⁴⁾;
- (d) where available, the results of any assessment of the medical device part or the active implantable medical device part by a notified body in accordance with Directive 93/42/EEC or Directive 90/385/EEC.

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

4. SPECIFIC REQUIREMENTS REGARDING MODULE 4

4.1. Specific requirements for all advanced therapy medicinal products

The requirements of Part I, Module 4 of this Annex on the pharmacological and toxicological testing of medicinal products may not always be appropriate due to unique and diverse structural and biological properties of advanced therapy medicinal products. The technical requirements in sections 4.1, 4.2 and 4.3 below explain how the requirements in Part I of this Annex apply to advanced therapy medicinal products. Where appropriate and taking into account the specificities of advanced therapy medicinal products, additional requirements have been set.

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

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

4.2. Specific requirements for gene therapy medicinal products

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

4.2.1. Pharmacology

- (a) *In vitro* and *in vivo* studies of actions relating to the proposed therapeutic use (i.e. pharmacodynamic ‘proof of concept’ studies) shall be provided using models and relevant animal species designed to show that the nucleic acid sequence reaches its intended target (target organ or cells) and provides its intended function (level of expression and functional activity). The duration of the nucleic acid sequence function and the proposed dosing regimen in the clinical studies shall be provided.
- (b) Target selectivity: When the gene therapy medicinal product is intended to have a selective or target-restricted functionality, studies to confirm the specificity and duration of functionality and activity in target cells and tissues shall be provided.

4.2.2. Pharmacokinetics

- (a) Biodistribution studies shall include investigations on persistence, clearance and mobilisation. Biodistribution studies shall additionally address the risk of germline transmission.
- (b) Investigations of shedding and risk of transmission to third parties shall be provided with the environmental risk assessment, unless otherwise duly justified in the application on the basis of the type of product concerned.

4.2.3. Toxicology

- (a) Toxicity of the finished gene therapy medicinal product shall be assessed. In addition, depending on the type of product, individual testing of active substance and excipients

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shall be taken into consideration, the *in vivo* effect of expressed nucleic acid sequence-related products which are not intended for the physiological function shall be evaluated.

- (b) Single-dose toxicity studies may be combined with safety pharmacology and pharmacokinetic studies, e.g. to investigate persistence.
- (c) Repeated dose toxicity studies shall be provided when multiple dosing of human subjects is intended. The mode and scheme of administration shall closely reflect the planned clinical dosing. For those cases where single dosing may result in prolonged functionality of the nucleic acid sequence in humans, repeated toxicity studies shall be considered. The duration of the studies may be longer than in standard toxicity studies depending on the persistence of the gene therapy medicinal product and the anticipated potential risks. A justification for the duration shall be provided.
- (d) Genotoxicity shall be studied. However, standard genotoxicity studies shall only be conducted when they are necessary for testing a specific impurity or a component of the delivery system.
- (e) Carcinogenicity shall be studied. Standard lifetime rodent carcinogenicity studies shall not be required. However, depending on the type of product, the tumourigenic potential shall be evaluated in relevant *in vivo/in vitro* models.
- (f) Reproductive and developmental toxicity: Studies on the effects on fertility and general reproductive function shall be provided. Embryo-foetal and perinatal toxicity studies and germline transmission studies shall be provided, unless otherwise duly justified in the application on the basis of the type of product concerned.
- (g) *Additional toxicity studies*
 - Integration studies: integration studies shall be provided for any gene therapy medicinal product, unless the lack of these studies is scientifically justified, e.g. because nucleic acid sequences will not enter into the cell nucleus. For gene therapy medicinal products not expected to be capable of integration, integration studies shall be performed, if biodistribution data indicate a risk for germline transmission.
 - Immunogenicity and immunotoxicity: potential immunogenic and immunotoxic effects shall be studied.

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

4.3.1. *Pharmacology*

- (a) The primary pharmacological studies shall be adequate to demonstrate the proof of concept. The interaction of the cell-based products with the surrounding tissue shall be studied.
- (b) The amount of product needed to achieve the desired effect/the effective dose, and, depending on the type of product, the frequency of dosing shall be determined.
- (c) Secondary pharmacological studies shall be taken into account to evaluate potential physiological effects that are not related to the desired therapeutic effect of the somatic cell therapy medicinal product, of the tissue engineered product or of additional substances, as biologically active molecules besides the protein(s) of interest might be secreted or the protein(s) of interest could have unwanted target sites.

4.3.2. *Pharmacokinetics*

- (a) Conventional pharmacokinetic studies to investigate absorption, distribution, metabolism and excretion shall not be required. However, parameters such as viability, longevity, distribution, growth, differentiation and migration shall be investigated, unless otherwise duly justified in the application on the basis of the type of product concerned.
- (b) For somatic cell therapy medicinal products and tissue engineered products, producing systemically active biomolecules, the distribution, duration and amount of expression of these molecules shall be studied.

4.3.3. *Toxicology*

- (a) The toxicity of the finished product shall be assessed. Individual testing of active substance(s), excipients, additional substances and any process-related impurities shall be taken into consideration.
- (b) The duration of observations may be longer than in standard toxicity studies and the anticipated lifespan of the medicinal product, together with its pharmacodynamic and pharmacokinetic profile, shall be taken into consideration. A justification of the duration shall be provided.
- (c) Conventional carcinogenicity and genotoxicity studies shall not be required, except with regard to the tumourigenic potential of the product.
- (d) Potential immunogenic and immunotoxic effects shall be studied.
- (e) In the case of cell-based products containing animal cells, the associated specific safety concerns such as transmission to humans of xenogeneic pathogens shall be addressed.

5. SPECIFIC REQUIREMENTS REGARDING MODULE 5

5.1. **Specific requirements for all advanced therapy medicinal products**

- 5.1.1. The specific requirements in this section of Part IV are additional requirements to those set in Module 5 in Part I of this Annex.
- 5.1.2. Where the clinical application of advanced therapy medicinal products requires specific concomitant therapy and involve surgical procedures, the therapeutic procedure as a whole shall be investigated and described. Information on the standardisation and optimisation of those procedures during clinical development shall be provided.

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

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

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

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- 5.1.4. During clinical development, risks arising from potential infectious agents or the use of material derived from animal sources and measures taken to reduce such risk shall be addressed.
- 5.1.5. Dose selection and schedule of use shall be defined by dose-finding studies.
- 5.1.6. The efficacy of the proposed indications shall be supported by relevant results from clinical studies using clinically meaningful endpoints for the intended use. In certain clinical conditions, evidence of long-term efficacy may be required. The strategy to evaluate long-term efficacy shall be provided.
- 5.1.7. A strategy for the long-term follow-up of safety and efficacy shall be included in the risk management plan.
- 5.1.8. For combined advanced therapy medicinal products, the safety and efficacy studies shall be designed for and performed on the combined product as a whole.

5.2. **Specific requirements for gene therapy medicinal products**

5.2.1. *Human pharmacokinetic studies*

Human pharmacokinetic studies shall include the following aspects:

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

5.2.2. *Human pharmacodynamic studies*

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

5.2.3. *Safety studies*

Safety studies shall address the following aspects:

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

5.3. **Specific requirements for somatic cell therapy medicinal products**

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

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

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

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

5.3.3. *Safety studies*

Safety studies shall address the following aspects:

- (a) distribution and engrafting following administration;
- (b) ectopic engraftment;
- (c) oncogenic transformation and cell/tissue lineage fidelity.

5.4. **Specific requirements for tissue engineered products**

5.4.1. *Pharmacokinetic studies*

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

5.4.2. *Pharmacodynamic studies*

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

5.4.3. *Safety studies*

Section 5.3.3 shall apply.]]

Textual Amendments

- F2** Substituted by [Commission Directive 2009/120/EC of 14 September 2009 amending Directive 2001/83/EC of the European Parliament and of the Council on the Community code relating to medicinal products for human use as regards advanced therapy medicinal products \(Text with EEA relevance\).](#)

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- (1) [^{F1}[^{F2}OJ L 102, 7.4.2004, p. 48.]]
- (2) [^{F1}[^{F2}OJ L 169, 12.7.1993, p. 1.]]
- (3) [^{F1}[^{F2}OJ L 189, 20.7.1990, p. 17.]]
- (4) [^{F1}[^{F2}OJ L 105, 26.4.2003, p. 18.]]

Textual Amendments

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