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ENTERPRISE AND INDUSTRY DIRECTORATE-GENERAL

Consumer goods
Pharmaceuticals

IMPLEMENTATION OF THE 'ADVANCED THERAPIES' REGULATION

Regulation (EC) No 1394/2007

PUBLIC CONSULTATION PAPER

PROPOSALS TO AMEND ANNEX I TO DIRECTIVE 2001/83/EC AS REGARDS ADVANCED THERAPY MEDICINAL PRODUCTS

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This document does not represent an official position of the European Commission. It is a tool to explore the views of interested parties on a preliminary proposal. The suggestions contained in this document do not prejudge the form and content of any future proposal by the European Commission.

Contact:
Nicolas Rossignol
European Commission, DG Enterprise & Industry, Unit F2 'Pharmaceuticals'
B-1049 Brussels - Belgium. 45 Avenue d'Auderghem, Office 10/128.
Telephone: direct line (32-2) 2987354. Fax: (32-2) 2998046.
E-mail: nicolas.rossignol@ec.europa.eu
http://ec.europa.eu/enterprise/pharmaceuticals/advtherapies/index.htm

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1. ABOUT THE CONSULTATION

1.1. What is the purpose of this consultation?

Regulation (EC) No 1394/2007 on advanced therapy medicinal products[1] ("the Regulation") lays down specific rules concerning the authorisation, supervision and pharmacovigilance of advanced therapy medicinal products (gene therapy, somatic cell therapy and tissue engineering). This Regulation will apply from 30 December 2008.

The European Commission has published on 13 December 2007 an implementation plan, outlining its priorities for the implementation of the Regulation[2]. The implementation plan has been developed and agreed with the European Medicines Agency (EMEA).

As part of this plan, the Commission intends to revise Part IV, Annex I to Directive 2001/83/EC[3] in order to adapt it to the specificities of advanced therapy medicinal products. This public consultation document presents preliminary proposals to replace the existing Part IV of this Annex I.

1.2. Who is consulted?

Comments on this document are invited from all stakeholders dealing with advanced therapy medicinal products. Stakeholders who are not established within the European Union are equally invited to comment. Comments from Small and Medium-sized Enterprises (SMEs) involved in the sector are especially welcomed.

1.3. How can I contribute?

Contributions should be sent by e-mail to nicolas.rossignol@ec.europa.eu, **before 10 June 2008**. An acknowledgement of receipt will be issued for each contribution received, within five working days. Contributions will be made publicly available on the 'Pharmaceuticals' website of the Commission once the consultation period is over, unless a specific request for confidentiality is made, in which case only an indication of the contributor will be disclosed. If you do not wish your contribution to be made public, please clearly indicate so.

1.4. What will happen next?

All contributions will be carefully analysed. A summary of the outcome of the consultation will be published on the 'Pharmaceuticals' website of the European Commission and also sent directly to all contributors. Any future proposal on the revision of Annex I to Directive 2001/83/EC as regards advanced therapy medicinal products will build on this consultation and will outline how its outcome was taken into account.

1.5. Any questions?

Please contact at the European Commission:
Nicolas Rossignol: Nicolas.rossignol@ec.europa.eu (tel.: +32 2 298 73 54)

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[1] OJ L324, 10.12.2007, p. 121.
[2] http://ec.europa.eu/enterprise/pharmaceuticals/advtherapies/index.htm
[3] See Commission Directive 2003/63/EC, OJ L 159, 27.6.2003, p. 46.

2. PROPOSALS TO REVIEW PART IV OF ANNEX I TO DIRECTIVE 2001/83/EC

Note: the sections below outline preliminary proposals to replace the current Part IV of Annex I to Directive 2001/83/EC. The purpose is not to outline detailed legal amendments, but to provide a basis for discussion on key elements for revision of this Annex.

In the following sections, the term "the Annex" refers to Annex I to Directive 2001/83/EC.

2.1. Introduction

As for any other medicinal product, marketing authorisation applications regarding advanced therapy medicinal products must follow the format requirements (Modules 1, 2, 3, 4 and 5) described in Part I of the Annex.

Advanced therapy medicinal products may share features of several types of medicinal products; therefore, requirements from several types may apply.

In principle, all relevant guidelines developed by the European Medicines Agency (EMEA) or the International Conference on Harmonisation (ICH) should be followed. Any exception and/or deviation shall be appropriately justified in Module 2.

Due to the specific nature of advanced therapy medicinal products, a risk-based approach can be applied to determine the extent of characterisation in terms of Quality, Nonclinical and Clinical data to be included in the marketing authorisation application. Such a risk analysis, when applied, shall be included and described in section 2.2 of Module 2. The implications for the development and evaluation program shall be discussed.

The risk analysis may cover the entire development. Risk factors include but are not limited to: the origin of the cells, the ability to proliferate, to 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 integration of nucleic acids sequences or genes into the genome, their long time functionality or oncogenicity and the mode of use.

Relevant available clinical data or experience with other, related advanced therapy medicinal products may also be considered.

2.2. Definitions

2.2.1. Gene therapy medicinal product

means a medicinal product:

- that contains or consists of a nucleic acid sequence used in or administered to human beings, *in vivo* or *ex vivo*, with a view to regulating, repairing or replacing a targeted genetic sequence; and
- whose therapeutic, prophylactic or diagnostic effect relates directly to the nucleic acid sequence it contains, or to the product of genetic expression of this sequence.

2.2.2. Somatic cell therapy medicinal product

means a medicinal product that:

- contains or consists of engineered cells or tissues within the meaning of Article 2(1)(c) of Regulation 1394/2007/EC, and
- 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.

2.2.3. Tissue engineered product

means a product as defined in Article 2(1)(b) of Regulation 1394/2007/EC.

2.3. Technical Requirements regarding Module 3 (Quality data)

2.3.1. General requirements for advanced therapy medicinal products

In principle, the requirements for Module 3 as described in Part I of the Annex should apply. Deviations from Module 3 and from applicable existing guidelines shall be scientifically justified in Module 2.

2.3.2. Specific requirements for gene therapy medicinal products

1. In case where a gene therapy medicinal product contains ready-prepared nucleic acid sequence(s) or genetically modified microorganism(s) or virus(es):

The finished medicinal product consists of nucleic acid sequence(s) or genetically modified microorganism(s) or virus(es) formulated in their final immediate container for the intended medical use. In special cases, the finished medicinal product may be combined with a medical device. The active substance consists of bulk of nucleic acid sequence(s) or genetically modified microorganism(s) or virus(es). The starting materials are:

- in the case of viruses and viral vectors: the master virus/viral vector seed or the plasmids used to transfect the packaging cells, and the master cell bank of the cell line;
- in the case of plasmids, non-viral vectors and of genetically modified microorganism(s) other than viruses or viral vectors: the plasmids and/or the master cell bank of recombinant microbial cells.

2. In the case of a gene therapy medicinal product containing genetically modified cells:

The finished medicinal product consists of genetically modified cells formulated in the final immediate container for the intended medical use. In some cases, the finished medicinal product may be grown on or within a medical device. The active substance consists of cells genetically modified by one of the products described under paragraph 1 above. The starting materials are:

- the cells as sourced from human subject or animal;
- the starting material described under paragraph 1 pertaining to the product used to genetically modify the cells.

3. For gene therapy medicinal products, the general requirements for medicinal products apply.

4. For genetically modified cells, relevant quality requirement for somatic cell therapy medicinal products (see section 2.3.3) shall apply.

5. Special attention shall be paid to the following requirements which shall be documented in the relevant sections of the dossier:

(a) Starting materials:

(i) In the case of products consisting of viral vectors, the starting materials are the components from which the viral vector is obtained, *i.e.* virus seed and packaging cell line.

(ii) In the case of products consisting of plasmids, the starting materials are the components used to generate the producing cell, *i.e.* the plasmid and the host bacteria.

(iii) In the case of genetically modified cells, the starting materials are the components used to obtain the genetically modified cells, *i.e.* 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.

(b) For products containing a microorganism or a virus, data on the genetic modification, 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) Information shall be provided on all the materials used for the manufacture of the drug substance, including the products necessary for the genetic modification of human/animal cells and, as applicable, subsequent culture and preservation of the genetically modified cells, taking into consideration the possible absence of purification steps.

(d) Product-related impurities shall be described in the relevant sections of the dossier, in particular replication competent virus contaminants if the vector is designed to be replication incompetent.

(e) For plasmids quantification of the different plasmid forms shall be undertaken throughout the shelf life of the product.

(f) For genetically modified cells the phenotypic characteristics of the cells pre- and post-transduction shall be tested, before and after any subsequent freezing/storage procedures.

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

1. The finished medicinal product consists 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.

2. The active substance is composed of the manipulated or engineered cells and/or tissues. Additional substances (*e.g.* scaffolds, matrices, devices, biomaterials, biomolecules and/or other components) when combined as an integral part with the manipulated cells are considered part of the active substance and are therefore considered as starting materials, even if not of biological origin.

3. Information shall be provided for all starting and raw materials which are part of the manufacturing process, the active substance or the final product.

4. For certain somatic cell therapy medicinal products and tissue engineered products, the active substance and the finished product can be closely related or nearly identical. In those cases, only relevant sections and items need to be completed, if justified.

5. For somatic cell therapy medicinal products and tissue engineered medicinal products, the general requirements for biological medicinal products apply.

6. Special attention shall be paid to the following requirements which shall be documented in the different relevant sections of the dossier:

(a) Starting materials:

(i) Information on donation, procurement and testing shall be provided. Where animal cells or tissues are used, specific acceptance criteria shall be provided. If non-healthy cells or tissues are used as starting materials, their use shall be justified.

(ii) A description of a system allowing complete traceability from the starting materials to the delivery of finished product to the hospital, institution or private practice shall be included. If allogeneic cell populations are being pooled, the pooling strategies and measures to ensure traceability shall be described.

(iii) The potential variability introduced through the starting material (*e.g.* variability of donor population such as age, characteristics of cells) shall be addressed insofar as manufacturing process, validation, characterisation, control, stability are concerned, both for the active substance and the finished product.

(iv) For xenogeneic cell-based products, information on the source of animals (such as geographical origin, animal husbandry, age), measures to prevent and monitor infections in the source/donor animals, testing of the animals for infectious agents and suitability of the animal facilities shall be provided.

(v) 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 transgenic animal shall be provided.

(vi) For genetically modified cells used as starting material of cell-based MPs, technical requirements as specified in section 2.3.2 shall apply.

(b) Manufacturing process:

(i) All steps of the manufacturing process starting from the receipt of the organs/tissue/cells up to the formulation and filling of the finished product shall be described.

(ii) A definition of a production batch shall be provided.

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

(c) Characterisation and control strategy

(i) Relevant information on the characterisation of the cell population or cell mixture in terms of identity, purity (*i.e.* adventitious microbial agents and cellular contaminants), viability, potency, karyology, tumorigenicity and suitability for the intended medicinal use should be provided, unless justified. Genetic stability of the cells shall be described.

(ii) Qualitative and quantitative information on product- and process-related impurities as well as on any material capable of introducing degradation products during production shall be provided.

(iii) 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 needs to be justified.

(iv) If biologically active molecules are present as components of the cell-based product, their impact and interaction with other components of the active substance shall be characterised, unless justified.

(v) Where a 3-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.

(d) Excipients

(i) For excipient(s) used for the first time in combination with cells and/or tissues, the requirements for novel excipients, as laid down in part I of the Annex, shall apply. Conventional excipients shall also be characterised with respect to their combination with cells.

(ii) Matrices, scaffolds, devices, biomaterials or biomolecules which are not an integral part of the active substance, shall be considered excipients of the finished product.

(e) Developmental studies

The description of the development program shall address the choice of materials and processes. Particularly, the integrity of the cell population regarding its biological characteristics, differentiation state and therapeutic function in the presence of the final formulation shall be discussed.

(f) Reference materials

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

2.3.4. Specific requirements for advanced therapy medicinal products containing devices

1. For advanced therapy medicinal product containing medical devices, bio-materials, scaffolds or matrices, 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.

2. For combined advanced therapy medicinal products as defined in Article 2(1)(d) of Regulation 1394/2007/EC:

(a) Information on the choice and intended function of the medical device / implantable medical device shall be provided. Compatibility of the device with other components of the product shall be demonstrated.

(b) Evidence of conformity of the device part with the essential requirements laid down in Annex I to Directive 93/42/EEC, or of conformity of the active implantable device part with the essential requirements laid down in Annex 1 to Directive 90/385/EEC, shall be provided.

(c) Where available, the results of the assessment by a notified body in accordance with Directive 93/42/EEC or Directive 90/385/EEC of the medical device part or active implantable medical device part shall be provided.

2.4. Technical requirements regarding Module 4 (Non-clinical data)

2.4.1. General requirements for advanced therapy medicinal products

1. Conventional requirements as detailed in Part I, Module 4 for pharmacological and toxicological testing of medicinal products may not always be appropriate due to unique and diverse structural and biological properties of the products. Any deviation from these requirements shall be scientifically justified in Module 2.

2. The rationale for the non-clinical development should be based on the above mentioned risk analysis and discussed/justified in the Nonclinical overview. The criteria used to choose the relevant species and models (*in vitro* and *in vivo*) shall be justified in the Non-clinical Overview. The chosen animal model(s) may include immuno-compromised, knockout or transgenic animals. Homologous models (*e.g.* mouse cells analysed in mice) or disease mimicking models may be advantageous.

3. The safety, suitability and biocompatibility of any additional substances such as cellular products, bio-molecules, biomaterials, and chemical substances shall be provided. Their physical, mechanical, chemical and biological properties should be taken into account.

2.4.2. Specific requirements for gene therapy medicinal products

The appropriate level of non-clinical safety evaluation should be provided: the extent and type of non-clinical studies should take into account the design and type of the gene therapy medicinal product.

1. Pharmacology

(a) *In vitro* and *in vivo* pharmacodynamic "proof of concept"studies should be provided using appropriate models and relevant animal species designed to show that the nucleic acid sequence provides its intended function (appropriate target organ, or cells, 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.

2. Pharmacokinetics

(a) Biodistribution studies, shall include investigations on persistence, clearance and mobilisation. Biodistribution studies should especially address the risk of germ line transmission.

(b) Investigations of shedding of transmissible vector, micro-organism or virus and risk of transmission to third parties shall be provided with the environmental risk assessment where appropriate.

3. Toxicology

(a) Toxicity of the finished gene therapy medicinal product shall be assessed. Individual testing of active substance and excipients shall be taken into consideration, where appropriate. 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 administration is mainly needed to evaluate the duration of the nucleic acid sequence functionality (*e.g.* persistence).

(c) Repeated dose toxicity studies shall be provided when multiple dosing of human subjects is intended. The mode and scheme of administration should 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.

(d) Genotoxicity: Standard genotoxicity studies are not required except for testing a specific impurity or a component of the delivery system.

(e) Carcinogenicity studies: Standard lifetime rodent carcinogenicity studies are not generally required. However, the oncogenic potential shall be evaluated in relevant *in vivo/in vitro* models where appropriate.

(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, where appropriate according to relevant guidelines.

(g) Other 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 germ line transmission.

Immunogenicity and immunotoxicity: the use of homologous models mimicking the clinical approach is recommended to address immunogenicity and immunotoxicity.

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

1. Pharmacology

(a) The primary pharmacological studies should be adequate to demonstrate the proof of principle. The desired interaction of the applied cells with the non-cellular structural component(s) of the product and the interaction of the cell-based products with the surrounding tissue should be studied.

(b) The amount of product needed to achieve the desired effect/the effective dose, and where appropriate, the frequency of dosing should be determined.

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

2. Pharmacokinetics

(a) Conventional pharmacokinetic studies to investigate absorption, distribution, metabolism and excretion are usually not relevant. However, parameters such as viability, longevity, distribution, growth, differentiation and migration should be investigated over time, as appropriate.

(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.

3. Toxicology

(a) It is essential that 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, where appropriate.

(b) The duration of observations may be longer than in standard toxicity studies, depending on the lifespan of the medicinal product.

(c) Conventional carcinogenicity and genotoxicity studies are normally not required. However, the tumourigenic potential of the product shall be studied unless otherwise justified.

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

(e) In case of cell-based products containing animal cells, the associated specific safety concerns such as virus reactivation shall be addressed.

2.5. Technical requirements regarding Module 5 (Clinical data)

2.5.1. General requirements for advanced therapy medicinal products

1. In general, the requirements for Module 5, as described in Part I of the Annex shall apply. Deviations from Module 5 and from applicable existing guidelines shall be justified in Module 2.

2. The clinical application of advanced therapy medicinal products may require specific concomitant therapy and may involve surgical procedures. The therapeutic procedure as a whole shall be investigated and described. Information on the standardisation and optimisation of these procedures during clinical development 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.

3. Due to the nature of advanced therapy medicinal products, their manufacturing process might change during clinical development. Additional studies to demonstrate comparability might be needed.

4. Dose selection and schedule of use should be defined by dose-finding studies, unless otherwise justified.

5. 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.

6. Proposed indications should 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 should be provided.

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

8. A strategy for long term safety and efficacy follow-up should be included in the Risk Management Plan.

2.5.2. Specific requirements for gene therapy medicinal products

1. Human Pharmacokinetic (PK) Studies shall include the following aspects:

- shedding studies to address the excretion of the gene therapy medicinal products;
- biodistribution studies, including distribution to gonads;
- pharmacokinetic studies of the medicinal product and the gene expression moieties (*e.g.* expressed proteins or genomic signatures).

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

3. Safety studies shall address aspects such as:

- emergence of replication competent vector;
- emergence of new strains;
- reassortment of existing genomic sequences;
- neoplastic proliferation due to insertional mutagenicity.

2.5.3. Specific requirements for somatic cell therapy medicinal products

1. 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 these molecules shall be addressed.

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

3. Safety studies shall address aspects, such as:

- distribution and engrafting following administration;
- ectopic engraftment;
- oncogenic transformation and cell/tissue lineage fidelity.

2.5.4. Specific requirements for tissue engineered products

1. Conventional pharmacokinetic studies might not be relevant for tissue engineered products. However, the biodistribution, persistence and degradation of the tissue engineered product components should be addressed during the clinical development, as appropriate.

2. Pharmacodynamic studies should be designed and tailored to the specificities of tissue engineered products. The evidence for the proof of principle and the kinetic of the product to obtain the intended regeneration, repairing or replacement should be provided, unless justified. Suitable pharmacodynamic markers, related to the intended function(s) and structure should be considered.

3. Safety studies shall address aspects, such as:

- distribution and engrafting following administration;
- ectopic engraftment;
- oncogenic transformation and cell/tissue lineage fidelity.