What are ATMP’s: Why do they Require Special Scientific and Regulatory Attention?

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What is an ATMP?
DIRECTIVES

COMMISSION DIRECTIVE 2009/120/EC
of 14 September 2009
(Text with EEA relevance)

THE COMMISSION OF THE EUROPEAN COMMUNITIES,

Having regard to the Treaty establishing the European Community,

Having regard to Directive 2001/83/EC of the European Parliament and of the Council of 6 November 2001 on the Community code relating to medicinal products for human...

(4) The measures provided for in this Directive are in accordance with the opinion of the Standing Committee for Medicinal Products for Human Use,

HAS ADOPTED THIS DIRECTIVE.

Article 1
Part IV of Annex I to Directive 2001/83/EC is replaced by the text set out in the Annex to this Directive.
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.
(b) ‘Tissue engineered product’ means a product that:
— contains or consists of engineered cells or tissues, and
— is presented as having properties for, or is used in or administered to human beings with a view to regenerating, repairing or replacing a human tissue.

A tissue engineered product may contain cells or tissues of human or animal origin, or both. The cells or tissues may be viable or non-viable. It may also contain additional substances, such as cellular products, bio-molecules, biomaterials, chemical substances, scaffolds or matrices.

Products containing or consisting exclusively of non-viable human or animal cells and/or tissues, which do not contain any viable cells or tissues and which do not act principally by pharmacological, immunological or metabolic action, shall be excluded from this definition.
(c) Cells or tissues shall be considered "engineered" if they fulfil at least one of the following conditions:

— the cells or tissues have been subject to substantial manipulation, so that biological characteristics, physiological functions or structural properties relevant for the intended regeneration, repair or replacement are achieved. The manipulations listed in Annex I, in particular, shall not be considered as substantial manipulations,

— the cells or tissues are not intended to be used for the same essential function or functions in the recipient as in the donor.
(d) Combined advanced therapy medicinal product means an advanced therapy medicinal product that fulfils the following conditions:
— it must incorporate, as an integral part of the product, one or more medical devices within the meaning of Article 1(2)(a) of Directive 93/42/EEC or one or more active implantable medical devices within the meaning of Article 1(2)(c) of Directive 90/385/EEC, and
— its cellular or tissue part must contain viable cells or tissues, or
— its cellular or tissue part containing non-viable cells or tissues must be liable to act upon the human body with action that can be considered as primary to that of the devices referred to.
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.

**Manipulations referred to in the first indent of Article 2(1)(c)**

- cutting,  
- grinding,  
- shaping,  
- centrifugation,  
- soaking in antibiotic or antimicrobial solutions,  
- sterilization,  
- irradiation,  
- cell separation, concentration or purification,  
- filtering,  
- lyophilization,  
- freezing,  
- cryopreservation,  
- vitrification.
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.
DEFINITION
For the purposes of this general chapter, gene transfer medicinal product (GTMP) 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 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.
3. An advanced therapy medicinal product containing both autologous (emanating from the patient himself) and allogeneic (coming from another human being) cells or tissues shall be considered to be for allogeneic use.

4. A product which may fall within the definition of a tissue engineered product and within the definition of a somatic cell therapy medicinal product shall be considered as a tissue engineered product.

5. A product which may fall within the definition of:
   — a somatic cell therapy medicinal product or a tissue engineered product, and
   — a gene therapy medicinal product,
   shall be considered as a gene therapy medicinal product.

**Regulation (EC) No 1394/2007**
QUALITY
Starting Materials
Definitions

**raw material**
starting materials, reagents and solvents intended for use in the production of intermediates or a drug substance (API).

**starting material**
a raw material, intermediate, or an API that is used in the production of an API and that is incorporated as a significant structural fragment into the structure of the API.

**excipient**
ingredient added intentionally to a drug substance, which does not have pharmacological properties in the quantity used.

From PAS 84: 2008 (published by the BSI)
Regulation of Human and Animal Tissues and Cells for Therapeutic Purposes

- HUMAN Tissues And Cells intended for human use
- Products manufactured from HUMAN Tissues and Cells and intended for human use
- Products manufactured from ANIMAL Tissues and Cells and intended for human use
- Tissues and Cells NOT intended for human use

- Directive 2004/23/EC**
- Dir 2004/23/EC**
- Dir 2001/83/EC*
- Dir 2001/83/EC*
- Other Legislation

Donated Tissues and Cells used to manufacture medicinal products are *starting materials*.

Starting materials need to be of a suitable quality.

EUTCD requirements for non-medicinal applications takes into account the intended use.

*But*

EUTCD requirements for medicinal product manufacture does not take into account the intended use but only applies to donation procurement and testing.

**Directive 2004/23/EC**
European Tissues and Cells Directive

Interface with Medicines Legislation

• EUTCD is therefore not necessarily sufficient to assure the starting material is of a suitable quality for the manufacture of an ATMP.

• But EUTCD does assure ethical donation and donor safety.
3.3.1. Introduction: finished product, active substance and starting materials (continued)

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.
3.2.1.3. 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.
3.3.2.1. Starting materials:

(a) If allogeneic cell populations are being pooled, the pooling strategies and measures to ensure traceability shall be described.

(b) Summary information shall be provided on the 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.
(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.

Directive 2009/120/EC (Annex I, Part IV)
(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.

Note: this means requirements for Gene Therapy Medicinal Products.
(g) The testing regimen of any additional substance (scaffolds, matrices, devices, bio-materials, bio-molecules 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.

Manufacturing
Simplified Manufacturing Flow Diagramme
Typical Early-stage Manufacturing Process for a Stem Cell Therapy

Cells from a biopsy or cell bank are cultured

Cells are expanded

Cells are treated with factors to mature/differentiate

Cells are harvested

Cells are packaged and shipped to patients

Cell Therapy

Factor X

WCB
SCALE-UP?
or
SCALE-OUT?

WHICH SHOULD YOU DO?
Scale-up: Non-Adherent Cells

Cell Expansion

Seeding from Working Cell bank

Harvest

Downstream Processing

Fermentor

Product
Adherent cells present a problem for scale-up
Scale-up: Adherent Cells

Microcarriers can provide a scalable solution for some adherent cell types.

Some cell types such as hES do not grow well on them.
Scale-out

Seeding from Primary or banked cells

Cell Expansion

Seeding from Primary or banked cells

Cell Expansion

Seeding from Primary or banked cells

Cell Expansion

Seeding from Primary or banked cells

Cell Expansion

Seeding from Primary or banked cells

Cell Expansion

Final Formulation

Further Processing

Product
Scale-out
Scale-out
AUTOMATION

Many thanks to TAP for this slide www.automationpartnership.com
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.
(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.

Directive 2009/120/EC (Annex I, Part IV)
(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 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. Where needed, non-clinical investigations shall complement the physicochemical characterisation.
GUIDELINES

- The requirement for characterisation and quality control of xenogeneic cells is identical to human cells (EMEA/CHMP/410869/2006).
- Guidance for characterisation of genetically modified cells can be obtained from the Guideline on the Quality, Preclinical and Clinical aspects of Medicinal Products containing Genetically modified Cells (EMEA/CHMP/GTWP/28311/2007).
- The transgenes and vectors should comply with the Note for Guidance on the Quality, Preclinical and Clinical aspects of Gene Transfer Medicinal Products (CPMP/BWP/3088/99).
3.3.2.4. Excipients

For excipient(s) used in cell or tissue-based medicinal products (e.g. the components of the transport medium, matrices, scaffolds, devices, biomaterials or biomolecules which are not an integral part of the active substance, ), the requirements for novel excipients, as laid down in Part I of this Annex, shall apply, unless data exist on the interactions between the cells or tissues and the excipients.
3.3.2.6. Reference materials

A reference standard, relevant and specific for the active substance and/or the finished product, shall be documented and characterised.
Potency is the quantitative measure of biological activity based on the attribute of the product, which is linked to the relevant biological properties (ICH guideline 6QB29).

The “Human cell-based medicinal products” guideline (CHMP/410869/06) also refers to the Guideline on Potency testing of cell based immunotherapy medicinal products for the treatment of cancer (CHMP/BWP/271475/06).
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).

Directive 2009/120/EC (Annex I, Part IV)
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.
3.2.2. Specific requirements

(a) Information shall be provided on all the starting materials used for the manufacture of the active substance, including the products necessary for the genetic modification of human or animal cells and, as applicable, subsequent culture and preservation of the genetically modified cells, taking into consideration the possible absence of purification steps.
(b) For products containing a microorganism or a virus, data on the genetic modification, sequence analysis, attenuation of virulence, tropism for specific tissues and cell types, cell cycle dependence of the microorganism or virus, pathogenicity and characteristics of the parental strain shall be provided.

(c) Process-related impurities and product-related impurities shall be described in the relevant sections of the dossier, and in particular replication competent virus contaminants if the vector is designed to be replication incompetent.
(d) For plasmids, quantification of the different plasmid forms shall be undertaken throughout the shelf life of the product.

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

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

NON-CLINICAL
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.
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 germ line 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.

Directive 2009/120/EC (Annex I, Part IV)
4.2.3. Toxicology

(a) Toxicity of the finished gene therapy medicinal product shall be assessed. In addition, depending on the type of product, individual testing of active substance and excipients shall be taken into consideration, the \textit{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, \textit{e.g.} to investigate persistence.

\textit{Directive 2009/120/EC (Annex I, Part IV)}
(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 tumorogogenic 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 germ line transmission.

Immunogenicity and immunotoxicity: potential immunogenic and immunotoxic effects shall be studied.
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.

Directive 2009/120/EC (Annex I, Part IV)
5.1.3. Given that, due to the nature of advanced therapy medicinal products, their manufacturing process may change during clinical development, additional studies to demonstrate comparability may be required.

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

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

5.1.7. A strategy for the long term follow-up of safety and efficacy shall be included in the Risk Management Plan.

5.1.8. For combined advanced therapy medicinal products, the safety and efficacy studies shall be designed for and performed on the combined product as a whole.
5.2. 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.
5.3.1. 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.

Directive 2009/120/EC (Annex I, Part IV)
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