

[^{F1}ANNEX IANALYTICAL, 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**

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.

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- 3.2.1.3. In the case of products consisting of viruses or viral vectors, the starting materials shall be the components from which the viral vector is obtained, i.e. the master virus vector seed or the plasmids used to transfect the packaging cells and the master cell bank of the packaging cell line.
- 3.2.1.4. In the case of products consisting of plasmids, non-viral vectors and genetically modified microorganism(s) other than viruses or viral vectors, the starting materials shall be the components used to generate the producing cell, i.e. the plasmid, the host bacteria and the master cell bank of recombinant microbial cells.
- 3.2.1.5. In the case of genetically modified cells, the starting materials shall be the components used to obtain the genetically modified cells, i.e. the starting materials to produce the vector, the vector and the human or animal cells. The principles of good manufacturing practice shall apply from the bank system used to produce the vector onwards.

3.2.2. *Specific requirements*

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

- (a) information shall be provided on all the starting materials used for the manufacture of the active substance, including the products necessary for the genetic modification of human or animal cells and, as applicable, subsequent culture and preservation of the genetically modified cells, taking into consideration the possible absence of purification steps;
- (b) for products containing a microorganism or a virus, data on the genetic modification, sequence analysis, attenuation of virulence, tropism for specific tissues and cell types, cell cycle dependence of the microorganism or virus, pathogenicity and characteristics of the parental strain shall be provided;
- (c) process-related impurities and product-related impurities shall be described in the relevant sections of the dossier, and in particular replication competent virus contaminants if the vector is designed to be replication incompetent;
- (d) for plasmids, quantification of the different plasmid forms shall be undertaken throughout the shelf life of the product;
- (e) for genetically modified cells, the characteristics of the cells before and after the genetic modification, as well as before and after any subsequent freezing/storage procedures, shall be tested.

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

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.

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- (b) If cells are grown directly inside or on a matrix, scaffold or device, information shall be provided on the validation of the cell culture process with respect to cell-growth, function and integrity of the combination.

3.3.2.3. Characterisation and control strategy

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

3.3.2.4. Excipients

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

3.3.2.5. Developmental studies

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

3.3.2.6. Reference materials

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

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 I 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.]]

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.]]

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