

[^{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**

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.
- 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.

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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 \(Text with EEA relevance\).](#)