

HUMAN TISSUE ENGINEERING AND BEYOND:
PROPOSAL FOR A COMMUNITY REGULATORY FRAMEWORK
ON ADVANCED THERAPIES

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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 prejudice the form and content of any future proposal by the European Commission.

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<http://pharmacos.eudra.org/F2/advtherapies/index.htm>

Proposal for a

REGULATION OF THE EUROPEAN PARLIAMENT AND OF THE COUNCIL

on Advanced Therapies and amending Regulation (EC) No 726/2004

THE EUROPEAN PARLIAMENT AND THE COUNCIL OF THE EUROPEAN UNION,

Having regard to the Treaty establishing the European Community, and in particular Article 95 thereof,

Having regard to the proposal from the Commission¹,

Having regard to the opinion of the European Economic and Social Committee²,

Having regard to the opinion of the Committee of the Regions³,

Acting in accordance with the procedure laid down in Article 251 of the Treaty⁴,

Whereas:

HAVE ADOPTED THIS REGULATION:

¹ OJ C [...], [...], p. [...].

² OJ C [...], [...], p. [...].

³ OJ C [...], [...], p. [...].

⁴ OJ C [...], [...], p. [...].

TITLE I

Introductory provisions

CHAPTER 1

SUBJECT MATTER, SCOPE AND DEFINITIONS

Article 1

(Subject matter and Scope)

1. The purpose of this Regulation is to lay down specific rules concerning the authorisation, supervision and pharmacovigilance of advanced therapy medicinal products.
2. This Regulation shall not apply to:
 - a) Any advanced therapy medicinal product which is made on a one-off basis, according to a specific and non-industrial manufacturing process, in order to comply with a medical prescription for an individual patient;
 - b) Any human tissue engineered products containing, or derived from, cells or tissues of animal origin, except when such cells and tissues are used in the manufacture without being present in the final product or, if present, only in trace amounts and without being viable.

Article 2

(Definitions)

The definitions laid down in Article 1 of Directive 2001/83/EC and those laid down in Article 3 of Directive 2004/23/EC shall apply for the purposes of this Regulation.

In addition, the following definitions shall apply:

(1) *Advanced therapy medicinal product:*

Any medicinal product for human use which is:

- a gene therapy medicinal product as referred to in Annex I to Directive 2001/83/EC;
- a somatic cell therapy medicinal product as referred to in Annex I to Directive 2001/83/EC;
- a human tissue engineered product as defined in this Regulation.

An advanced therapy medicinal product containing both autologous (emanating from the patient himself) and allogeneic (coming from another human being) cells or tissues is considered to be for allogeneic use, within the meaning of Article 3(p) of Directive 2004/23/EC.

(2) *Human tissue engineered product:*

Any product for autologous or allogeneic use which:

- contains or consists of engineered human 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 human tissue engineered product may also be a combined advanced therapy medicinal product, as defined in this Regulation. It may also contain additional substances, such as cellular products, bio-molecules, bio-materials, chemical substances, scaffolds or matrices.

(3) *Engineered human cells or tissues:*

Cells or tissues removed from a human donor and manipulated *via* a manufacturing process, so that their normal biological characteristics, physiological functions or structural properties are substantially altered.

(4) *Combined advanced therapy medicinal product:*

An advanced therapy medicinal product which incorporates, as an integral part of the product, one or several medical devices within the meaning of Directive 93/42/EEC, and which is liable to act upon the human body with action that cannot be considered as ancillary to that of the referred device(s).

(5) *Risk-management system:*

A set of activities and interventions designed to prevent or minimise risks related to advanced therapy medicinal products, including the evaluation of the effectiveness of those activities and interventions.

CHAPTER 2 COMMITTEE FOR ADVANCED THERAPIES

Article 3

(Committee for Advanced Therapies)

1. A Committee for Advanced Therapies is established within the European Medicines Agency set up under Regulation (EC) No 726/2004, hereinafter “the Agency”.
2. Save where otherwise provided in this Regulation, Regulation (EC) No 726/2004 shall apply to the Committee for Advanced Therapies.
3. The Executive Director of the Agency shall ensure appropriate co-ordination between the Committee for Advanced Therapies and the other Committees of the Agency, in particular the Committee for Medicinal Products for Human Use and the Committee for Orphan Medicinal Products, their working parties and any other scientific advisory groups.

Article 4

(Composition of the Committee for Advanced Therapies)

1. The Committee for Advanced Therapies shall be composed of the following:
 - a) five members and five alternates of the Committee for Medicinal Products for Human Use, appointed by the latter;
 - b) one member and one alternate appointed by each Member State whose national competent authority is not represented through the members and alternates appointed by the Committee for Medicinal Products for Human Use;
 - c) six persons appointed by the Commission, on the basis of a public call for expressions of interest, in order to represent medical practitioners (two persons), surgeons (two persons), basic research in the field of advanced therapies (one person), and the interests of patients associations (one person).

For the purposes of point (b), the Member States shall cooperate, under the coordination of the Executive Director of the Agency, in order to ensure that the final composition of the Committee for Advanced Therapies covers the scientific areas relevant to advanced therapies, and including at least: medical devices, tissue-engineering, gene therapy, cell therapy, biotechnology, pharmacovigilance, risk management and ethics.

2. The members of the Committee for Advanced Therapies shall be appointed for a renewable period of three years. At meetings of the Committee for Advanced Therapies, they may be accompanied by experts.
3. The Committee for Advanced Therapies shall elect its Chairman from among its members for a term of three years renewable once.
4. The names and scientific qualifications of the members shall be published by the Agency.

Article 5

(Conflicts of Interest)

1. Members of the Committee for Advanced Therapies and its experts shall undertake to act in the public interest and in an independent manner. They shall not have financial or other interests in the pharmaceutical sector, medical device sector or biotechnology sector that could affect their impartiality.
2. All indirect interests that could relate to the pharmaceutical sector, medical device sector or biotechnology sector shall be entered in a register held by the Agency which the public may consult. The register shall be updated annually.
3. Members of the Committee for Advanced Therapies and its experts shall declare at each meeting any specific interests which could be considered to be prejudicial to their independence with respect to the points on the agenda.

4. Members of the Committee for Advanced Therapies and its experts shall be required, even after their duties have ceased, not to disclose any information of the kind covered by the obligation of professional secrecy.

Article 6

(Tasks of the Committee for Advanced Therapies)

The Committee for Advanced Therapies shall have the following tasks:

- a) to assess any data generated in the development of an advanced therapy medicinal product, and to formulate an opinion on the quality, safety or efficacy of any advanced therapy medicinal product;
- b) at the request of the Committee for Medicinal Products for Human Use, to formulate an opinion on any medicinal product which may require, for the evaluation of its quality, safety or efficacy, expertise in one of the scientific areas referred to in Article 4(1);
- c) to provide advice on any question related to advanced therapy medicinal products, at the request of the Executive Director of the Agency or the Commission;
- d) to assist scientifically in the elaboration of any documents related to the fulfilment of the objectives of this Regulation;
- e) upon request, to provide scientific expertise and advice for any Community initiative related to the development of innovative medicines and therapies;

TITLE II

Marketing Authorisation Requirements

CHAPTER 1

GENERAL AUTHORISATION REQUIREMENTS

Article 7

(Applicability of Regulation (EC) No 726/2004)

Save where otherwise provided in this Regulation, Regulation (EC) No 726/2004 shall apply for the authorisation, supervision and pharmacovigilance of advanced therapy medicinal products.

Article 8

(Donation, procurement and testing)

The donation, procurement and testing of human cells and tissues used in the manufacture of advanced therapy medicinal products shall be made in accordance with the provisions laid down in Directive 2004/23/EC.

Article 9

(Good Clinical Practice)

5. Clinical trials on advanced therapy medicinal products shall be conducted in accordance with the provisions laid down in Directive 2001/20/EC. The procedures set out in Articles 6(7), 9(4) and 9(6) of Directive 2001/20/EC for non-xenogeneic somatic cell therapy medicinal products shall be applicable to human tissue engineered products.
6. Detailed guidelines in line with the principles laid down in Directive 2001/20/EC and specific to advanced therapy medicinal products shall be published by the Commission and, if necessary, revised to take account of technical and scientific evolution.

Article 10

(Good Manufacturing Practice)

1. Advanced therapy medicinal products shall be manufactured in compliance with the principles and guidelines of good manufacturing practice laid down in Directive 2003/94/EC.
2. Detailed guidelines in line with those principles and specific to advanced therapy medicinal products shall be published by the Commission and, if necessary, revised to take account of technical and scientific evolution.

Article 11

(Medical Device-specific issues)

Without prejudice to Article 6(1) of Regulation (EC) No 726/2004, any medical device which forms part of an advanced therapy medicinal product shall meet the essential requirements laid down in Annex I to Directive 93/42/EEC.

CHAPTER 2

SPECIFIC REQUIREMENTS FOR TISSUE ENGINEERED PRODUCTS

Article 12

(Specific requirements for tissue engineered products)

Without prejudice to Article 6(1) of Regulation (EC) No 726/2004, each application for the authorisation of a human tissue engineered product shall include a description of the physical characteristics and performance of the product and a description of the product design methods.

Article 13

(Technical requirements)

The Commission shall amend Annex I to Directive 2001/83/EC in order to lay down technical requirements that are specific to human tissue engineered products, in particular those referred to in Article 12, with a view to taking account of scientific and technical evolution and of the specific nature of this field. Those amendments shall be adopted in accordance with the procedure referred to in Article 27(2).

TITLE III

Marketing Authorisation Procedure

Article 14

(Centralised procedure)

No advanced therapy medicinal product may be placed on the market within the Community unless a marketing authorisation has been granted by the Community in accordance with the provisions of Regulation (EC) No 726/2004 and of this Regulation.

Article 15

(Evaluation procedure)

Where an advanced therapy medicinal product is concerned, the following procedure shall apply:

1. The rapporteur appointed by the Committee for Medicinal Products for Human Use in accordance with Article 62 of Regulation (EC) No 726/2004 shall also be a member of the Committee for Advanced Therapies. No co-rapporteur shall be appointed.
2. The Committee for Medicinal Products for Human Use shall delegate to the Committee for Advanced Therapies any scientific assessment of advanced therapy

medicinal products necessary to draw up the scientific opinions referred to in Article 5 of Regulation (EC) No 726/2004.

3. For the assessment of an advanced therapy medicinal product, the member of the Committee for Advanced Therapies referred to in the first paragraph shall act as rapporteur for the coordination of the evaluation. The Committee for Advanced Therapies shall also appoint a second member to act as co-rapporteur.
4. The opinion issued by the Committee for Advanced Therapies shall be forwarded to the Chairman of the Committee for Medicinal Products for Human Use in such a way as to ensure that the deadline laid down in Article 6(3) of Regulation (EC) No 726/2004 is met.
5. When drawing up an opinion in accordance with Article 5 of Regulation (EC) No 726/2004, the Committee for Medicinal Products for Human Use shall fully take into account the opinion issued by the Committee for Advanced Therapies. If necessary, the Committee for Medicinal Products for Human Use may invite the Chairman of the Committee for Advanced Therapies to present orally the views of the Committee for Advanced Therapies.
6. Where the opinion of the Committee for Medicinal Products for Human Use is not in accordance with the opinion of the Committee for Advanced Therapies, the Committee for Medicinal Products for Human Use shall annex to its opinion a detailed explanation of the scientific grounds for the differences.
7. The Agency shall draw up specific procedures for the application of this Article.

Article 16

(Consultation procedure for other medicinal products)

Without prejudice to Article 15, where a medicinal product requires, for the evaluation of its quality, safety and efficacy, expertise in one of the scientific areas referred to in Article 4(1), the Committee for Medicinal Products for Human Use may consult the Committee for Advanced Therapies, before issuing a final opinion on the concerned medicinal product.

The Agency shall draw up specific procedures for the application of this Article.

Article 17

(Combined advanced therapy medicinal products)

During the process of evaluating a combined advanced therapy medicinal product, the Committee for Advanced Therapies may carry out consultations of one or several notified bodies as defined in Directive 93/42/EEC, for the purpose of assessing the design and manufacture of the medical device(s) included in the concerned medicinal product. At the request of the Committee for Advanced Therapies, the concerned notified body shall transmit, within a period of one month, all information deemed necessary by the Committee to perform its assessment.

TITLE IV

Summary of Product Characteristics, Labelling and Package Leaflet

CHAPTER 1

SUMMARY OF PRODUCT CHARACTERISTICS

Article 18

(Summary of Product Characteristics)

By derogation from Article 11 of Directive 2001/83/EC, the summary of the product characteristics for advanced therapy medicinal products shall contain the information listed in Annex I, in the same order.

CHAPTER 2

LABELLING

Article 19

(Outer/immediate packaging)

By derogation from Article 54 of Directive 2001/83/EC, the particulars listed in Annex II shall appear on the outer packaging of advanced therapy medicinal products or, where there is no outer packaging, on the immediate packaging.

Article 20

(Special immediate packaging)

Without prejudice to Article 55 of Directive 2001/83/EC, the following particulars shall appear on the immediate packagings referred to in Article 55(2) and 55(3) of Directive 2001/83/EC:

- the unique donation identifier, as referred to in Article 8(2) of Directive 2004/23/EC,
- in the case of advanced therapy medicinal products for autologous use, the unique patient identifier and the statement “For autologous use only”.

CHAPTER 3 PACKAGE LEAFLET

Article 21

(Package leaflet)

1. By derogation from Article 59 of Directive 2001/83/EC, the package leaflet for an advanced therapy medicinal product shall be drawn up in accordance with the summary of product characteristics; it shall include the information listed in Annex III, in the same order.
2. The list set out in point (c) of Annex III shall:
 - (a) take into account the particular condition of certain categories of users (*e.g.* children, pregnant or breastfeeding women, the elderly, persons with specific pathological conditions);
 - (b) mention, if appropriate, possible effects on the ability to drive vehicles or to operate machinery;
 - (c) list those components knowledge of which is important for the safe and effective use of the medicinal product and which are included in the detailed guidance published pursuant to Article 65 of Directive 2001/83/EC;
3. The package leaflet shall reflect the results of consultations with target patient groups to ensure that it is legible, clear and easy to use.

TITLE V Post-authorisation Requirements

Article 22

(Risk Management)

1. In addition to the requirements for post-marketing monitoring laid down in Regulation (EC) No 726/2004, the applicant shall detail, in the marketing authorisation application, the measures to ensure the follow-up of efficacy and of possible adverse reactions to advanced therapy medicinal products.
2. Where there is particular cause for concern, the Commission may require, as a condition for granting marketing authorisation, that a risk management system be set up or that specific post-marketing studies be performed and submitted for review by the Agency. Evaluation of the effectiveness of any risk management system and the results of any studies performed shall be included in the periodic safety update reports referred to in Article 24(3) of Regulation (EC) No 726/2004.

In addition, the Agency may request submission of additional reports evaluating the effectiveness of any risk management system and the results of any such studies performed.

3. The Agency shall forthwith inform the Commission if it is found that the marketing authorisation holder has failed to comply with the conditions referred to in the second paragraph.
4. The Agency shall draw up detailed guidelines relating to the application of this Article.

Article 23

(Traceability)

1. The holder of a marketing authorisation for an advanced therapy medicinal product shall establish and maintain a system ensuring complete individual traceability of its starting materials, as well as their treatment during manufacture, packaging and transport. He shall also establish and maintain a system for patient and product traceability. This system shall contain sufficient detail to allow linking of each batch of product to the patient who received the advanced therapy medicinal product.
2. Where the concerned medicinal product contains human cells or tissues, the marketing authorisation holder shall ensure that the traceability systems established in accordance with the first paragraph are complementary to, and compatible with, those established in accordance with Article 8 of Directive 2004/23/EC as regards the donation, procurement and testing of human cells and tissues.
3. The marketing authorisation holder shall keep the data referred to in the first paragraph for a minimum of 30 years after implantation or administration of the advanced therapy medicinal product, or longer if required by the Commission when granting the marketing authorisation.
4. The hospital, institution or private practice responsible for the implantation or administration of the advanced therapy medicinal product shall provide all necessary information to the marketing authorisation holder in order to fulfil the obligations laid down in the first, second and third paragraph.
6. In case of bankruptcy or liquidation of the marketing authorisation holder, and in the event that the marketing authorisation is not transferred to another legal entity, the data referred to in the first paragraph shall be transferred to the Agency.
7. In the event that the marketing authorisation is suspended, revoked or withdrawn, the holder of the marketing authorisation shall remain subject to the obligations laid down in the first, second and third paragraph.
8. The Agency shall draw up detailed guidelines relating to the application of this Article, in particular the type and amount of data referred to in the first paragraph.

TITLE VI Incentives

Article 24

(Scientific Advice)

1. The sponsor, applicant or holder of a marketing authorisation for an advanced therapy medicinal product may request advice from the Agency on the design and conduct of the various tests and studies necessary to demonstrate the quality, safety and efficacy of the medicinal product, in accordance with Article 57(1)(n) of Regulation (EC) No 726/2004.

In addition, the applicant may request advice on the design and conduct of pharmacovigilance and risk management systems as referred to in Article 22.

2. By derogation from Regulation (EC) No 297/95, a 90% fee reduction shall apply to the fee payable to the Agency for the advice referred to in the first paragraph.

TITLE VII General and Final Provisions

CHAPTER 1 GENERAL

Article 25

(Reporting)

Within 5 years of entry into force of this Regulation, the Commission shall publish a general report on the experience acquired as a result of its application.

Article 26

(Annexes)

Any changes which are necessary in order to adapt Annex I, II and III to this Regulation to scientific and technical evolution shall be adopted in accordance with the procedure referred to in Article 27(2).

Article 27

(Comitology)

1. The Commission shall be assisted by the Standing Committee on Medicinal Products for Human Use set up by Article 121(1) of Directive 2001/83/EC.

2. Where reference is made to this paragraph, Articles 5 and 7 of Decision 1999/468/EC shall apply, having regard to the provisions of Article 8 thereof.

The period laid down in Article 5(6) of Decision 1999/468/EC shall be set at three months.

CHAPTER 2 AMENDMENTS

Article 28

(Amendments)

Regulation (EC) No.726/2004 is amended as follows:

- (1) In Article 56(1), the following point (da) is inserted:

“(da) the Committee for Advanced Therapies;”

- (2) In the Annex, the following point 1a is inserted:

“1a. Advanced therapy medicinal products, as defined in [this Regulation]”

CHAPTER 3 FINAL PROVISIONS

Article 29

(Transitional period)

1. Products falling within the definition of “Advanced therapy medicinal product” which were already on the market in the Community and legally authorised at the time of entry into force of this Regulation shall comply with this Regulation no later than 3 years after its entry into force.

2. By derogation to Regulation (EC) No 297/95, the assessment of an application submitted for the purpose of complying with the first paragraph shall be provided free of charge by the Agency.

Article 30

This Regulation shall enter into force on the [...] day following that of its publication in the *Official Journal of the European Union*.

This Regulation shall be binding in its entirety and directly applicable in all Member States.

Done at Brussels, [...]

For the European Parliament
The President
[...]

For the Council
The President
[...]

ANNEX I: Summary of Product Characteristics

To be drafted

ANNEX II: Labelling

To be drafted

ANNEX III: Package Leaflet

To be drafted