

# EUROPEAN PARLIAMENT

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*Committee on the Environment, Public Health and Food Safety*

PROVISIONAL  
**2005/0227(COD)**

12.5.2006

**\*\*\*I**

## **DRAFT REPORT**

on the proposal for a regulation of the European Parliament and of the Council on advanced therapy medicinal products and amending Directive 2001/83/EC and Regulation (EC) No 726/2004 (COM(2005)0567 – C6-0401/2005 – 2005/0227(COD))

Committee on the Environment, Public Health and Food Safety

Rapporteur: Miroslav Mikolášik

Draftswoman (\*) : Hiltrud Breyer, Committee on Legal Affairs

(\*) Enhanced cooperation between committees - Rule 47 of the Rules of Procedure

### ***Symbols for procedures***

- \* Consultation procedure  
*majority of the votes cast*
- \*\*I Cooperation procedure (first reading)  
*majority of the votes cast*
- \*\*II Cooperation procedure (second reading)  
*majority of the votes cast, to approve the common position  
majority of Parliament's component Members, to reject or amend  
the common position*
- \*\*\* Assent procedure  
*majority of Parliament's component Members except in cases  
covered by Articles 105, 107, 161 and 300 of the EC Treaty and  
Article 7 of the EU Treaty*
- \*\*\*I Codecision procedure (first reading)  
*majority of the votes cast*
- \*\*\*II Codecision procedure (second reading)  
*majority of the votes cast, to approve the common position  
majority of Parliament's component Members, to reject or amend  
the common position*
- \*\*\*III Codecision procedure (third reading)  
*majority of the votes cast, to approve the joint text*

(The type of procedure depends on the legal basis proposed by the Commission.)

### ***Amendments to a legislative text***

In amendments by Parliament, amended text is highlighted in ***bold italics***. Highlighting in *normal italics* is an indication for the relevant departments showing parts of the legislative text for which a correction is proposed, to assist preparation of the final text (for instance, obvious errors or omissions in a given language version). These suggested corrections are subject to the agreement of the departments concerned.

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## DRAFT EUROPEAN PARLIAMENT LEGISLATIVE RESOLUTION

**on the proposal for a regulation of the European Parliament and of the Council on advanced therapy medicinal products and amending Directive 2001/83/EC and Regulation (EC) No 726/2004  
(COM(2005)0567 – C6-0401/2005 – 2005/0227(COD))**

**(Codecision procedure: first reading)**

*The European Parliament,*

- having regard to the Commission proposal to the European Parliament and the Council (COM(2005)0567)<sup>1</sup>,
  - having regard to Article 251(2) and Article 95 of the EC Treaty, pursuant to which the Commission submitted the proposal to Parliament (C6-0401/2005),
  - having regard to Rule 51 of its Rules of Procedure,
  - having regard to the report of the Committee on the Environment, Public Health and Food Safety and the opinions of the Committee on Legal Affairs and the Committee on Industry, Research and Energy (A6-0000/2006),
1. Approves the Commission proposal as amended;
  2. Calls on the Commission to refer the matter to Parliament again if it intends to amend its proposal substantially or replace it with another text;
  3. Instructs its President to forward its position to the Council and Commission.

Text proposed by the Commission

Amendments by Parliament

### Amendment 1 TITLE

Proposal for a Regulation of the European Parliament and of the Council on advanced therapy medicinal products and amending Directive 2001/83/EC **and** Regulation (EC) No 726/2004

Proposal for a Regulation of the European Parliament and of the Council on advanced therapy medicinal products and amending Directive 2001/83/EC, Regulation (EC) No 726/2004 **and Directive 2004/23/EC**

### *Justification*

*The title of the proposal need to be changed, as Directive 2004/23/EC is also amended (see amendment 43).*

<sup>1</sup> OJ C ... / Not yet published in OJ.

Amendment 2  
RECITAL 5

(5) Advanced therapy medicinal products should be regulated in so far as they are intended to be placed on the market in Member States and either prepared industrially or manufactured by a method involving an industrial process, within the meaning of Article 2(1) of Directive 2001/83/EC. Advanced therapy medicinal products which are both prepared in full and used in a hospital, *in accordance with a* medical prescription for an individual patient, should thus be excluded from the scope of *the present* Regulation.

(5) Advanced therapy medicinal products should be regulated in so far as they are intended to be placed on the market in Member States and either prepared industrially or manufactured by a method involving an industrial process, within the meaning of Article 2(1) of Directive 2001/83/EC. Advanced therapy medicinal products which are prepared in full *in a hospital on a one-off basis according to a specific, non-standardised and non-patented process*, and used in a hospital, *in order to comply with an individual* medical prescription for an individual patient, should thus be excluded from the scope of *this* Regulation.

*Justification*

*Where hospitals or other institutions prepare products using an established process to create treatments for patients on a serial and routine basis, they should have to comply with the provisions of this Regulation. However, when hospitals produce advanced therapy products for research purposes or on an exceptional, one-off basis, they should not have to comply with the centralised authorisation procedure. The mentioned requirements for an exemption are imperative to ensure that this regulation only applies to industrially produced AT medicinal products and not to products produced via non-standardised and non-patented process.*

Amendment 3  
RECITAL 7

(7) This Regulation respects the fundamental rights and *observes* the principles reflected in the Charter of Fundamental Rights of the European Union *and takes also into account* the Convention for the protection of human rights and dignity of the human being with regard to the application of biology and medicine: Convention on human rights and biomedicine.

(7) This Regulation *fully* respects the fundamental rights and the principles reflected in the Charter of Fundamental Rights of the European Union, the Convention for the protection of human rights and dignity of the human being with regard to the application of biology and medicine: Convention on human rights and biomedicine (*the "Oviedo Convention"*), *additional protocols to that Convention on the prohibition of cloning human beings (CETS No. 168), transplantation of organs and tissues of human origin (CETS No. 186) and biomedical research (CETS No.*

**195), as well as the UN Declaration on human cloning.**

Or. en

*Justification*

*This Regulation should fully respect the Oviedo Convention because of the significance of principles settled down in this document. Moreover, fundamental rights and principles related to biology and medicine are also set out in the additional protocols and in the UN Declaration on human cloning. Therefore, these texts should be mentioned.*

Amendment 4  
RECITAL 7 A (new)

***(7a) This Regulation fully respects the prohibition on making the human body and its parts as such a source of financial gain, as set out as an inalienable minimum protection in the Charter of Fundamental Rights of the European Union and further underlined by the European Parliament in its Resolution of 10 March 2005 on the trade in human egg cells. To achieve this objective it is necessary to ensure that the donation of tissues and cells is voluntary and unpaid and that their procurement is carried out on a non-profit basis.***

*Justification*

*Rapid developments in biotechnology and biomedicine must not be allowed to compromise the protection of fundamental rights. These rights of which one of the most important one is the right to the integrity of the person are laid down in the Oviedo Convention as well as in the Charter of Fundamental Rights. These standards should be met especially for tissue- and cell-based advanced therapy medicinal products as highly innovative new products. In this context, voluntary and unpaid donation as well as procurement on a non-profit basis are the key principles that should be imperatively respected all around the Community.*

Amendment 5  
RECITAL 7 B (new)

***(7b) Directive 2001/20/EC on clinical trials prohibits gene therapy trials that result in modifications to a subject's germ***

***line genetic identity. Directive 98/44/EC on the legal protection of biotechnological innovations considers processes for modifying the human germ line genetic identity non-patentable. To ensure legal coherence, this Regulation should prohibit any authorisation of products that modify the germ line genetic identity of human beings.***

*Justification*

*As Articles 1 and 13 of the Oviedo Convention make it clear, human dignity is compromised when the inheritance of genetic identity is altered. Products which are neither properly subject to clinical trials under Directive 2001/20/EC nor legally patentable under Directive 98/44/EC should not be eligible for authorisation under this regulation.*

Amendment 6  
RECITAL 7 C (new)

***(7c) This Regulation should prohibit any authorisation of products derived from human-animal hybrids or chimeras or containing tissues or cells originating or derived from human-animal hybrids or chimeras. This provision should not exclude the transplantation of somatic animal cells or tissues to the human body for therapeutic purposes, in so far as it does not interfere with the germ line.***

*Justification*

*The physical and mental integrity of the person and human dignity must be respected, as underlined in Articles 1 and 3 of the Charter of fundamental rights of the European Union. The creation of human-animal hybrids or chimeras is a threat to the right to integrity of a person and a violation of human dignity. Therefore, no authorisation for products containing or originating from human-animal hybrids or chimeras should be granted under this regulation. However, the Xenotransplantation for therapeutic purposes should not be excluded, as far as it does not interfere with the germ line.*

Amendment 7  
RECITAL 9

(9) The evaluation of advanced therapy medicinal products often requires very specific expertise, which goes beyond the traditional pharmaceutical field and covers areas on the borderline to other sectors such as biotechnology and medical devices. For this reason, it is appropriate to create, within the Agency, a Committee for Advanced Therapies, which the Committee for Medicinal Products for Human Use of the Agency **should consult on the assessment of data related to advanced therapy medicinal products, before issuing its final scientific opinion.** In addition, the Committee for Advanced Therapies **may** be consulted for the evaluation of any other medicinal product which requires specific expertise falling within its area of competence.

(9) The evaluation of advanced therapy medicinal products often requires very specific expertise, which goes beyond the traditional pharmaceutical field and covers areas on the borderline to other sectors such as biotechnology and medical devices. For this reason, it is appropriate to create, within the Agency, a Committee for Advanced Therapies, which **should be responsible for preparing a draft opinion on the quality, safety and efficacy of each advanced therapy medicinal product for final approval by** the Committee for Medicinal Products for Human Use of the Agency. In addition, the Committee for Advanced Therapies **should** be consulted for the evaluation of any other medicinal product which requires specific expertise falling within its area of competence.

#### *Justification*

*Due to a highly specific and unique character of the advanced therapy medicinal products, a new Committee for Advanced Therapies is established within EMEA and composed of experts having specific qualifications or experience in this highly innovative and quickly developing field. Therefore, the new structure should be responsible for drafting an opinion on the quality, safety, and efficacy of products for the final approval by the CHMP. Furthermore, the committee should be consulted for the evaluation of other products under its competence.*

#### Amendment 8 RECITAL 9 A (new)

***(9a) The Committee for Advanced Therapies should provide advice to the Committee for Medicinal Products for Human Use on whether a product falls within the definition of an advanced therapy medicinal product.***

#### *Justification*

*Due to its specific expertise in advanced therapy medicinal products, the Committee for Advanced Therapies should assist the CHMP in its classification task of whether a product is or is not an advanced therapy medicinal product.*

Amendment 9  
RECITAL 10

(10) The Committee for Advanced Therapies should gather the best available Community expertise on advanced therapy medicinal products. The composition of the Committee for Advanced Therapies should ensure appropriate coverage of the scientific areas relevant to advanced therapies, including gene therapy, cell therapy, tissue-engineering, medical devices, pharmacovigilance and ethics. Patient associations and *surgeons* with scientific experience of advanced therapy medicinal products should also be represented.

(10) The Committee for Advanced Therapies should gather the best available Community expertise on advanced therapy medicinal products. The composition of the Committee for Advanced Therapies should ensure appropriate coverage of the scientific areas relevant to advanced therapies, including gene therapy, cell therapy, tissue-engineering, medical devices, pharmacovigilance and ethics. Patient associations and *medical doctors* with scientific experience of advanced therapy medicinal products should also be represented.

*Justification*

*In order to cover all other medical fields which the advanced therapies may relate to, the Committee for Advanced Therapies should be represented by a more general medical expertise.*

Amendment 10  
RECITAL 14

***(14) As a matter of principle, human cells or tissues contained in advanced therapy medicinal products should be procured from voluntary and unpaid donation. Voluntary and unpaid tissue and cell donations are a factor which may contribute to high safety standards for tissues and cells and therefore to the protection of human health.*** *deleted*

*Justification*

*We propose to delete this recital as a consequence to the introduction of a new recital 7a and new articles 3a and 28a.*

Amendment 11  
RECITAL 16

(16) The manufacture of advanced therapy medicinal products should be in compliance with the principles of good manufacturing practice, as set out in Commission Directive 2003/94/EC of 8 October 2003 laying down the principles and guidelines of good manufacturing practice in respect of medicinal products for human use and investigational medicinal products for human use\*. Furthermore, guidelines specific to advanced therapy medicinal products should be drawn up, so as to properly reflect the particular nature of their manufacturing process.

(16) The manufacture of advanced therapy medicinal products should be in compliance with the principles of good manufacturing practice, as set out in Commission Directive 2003/94/EC of 8 October 2003 laying down the principles and guidelines of good manufacturing practice in respect of medicinal products for human use and investigational medicinal products for human use, **and adapted, where necessary, to reflect the specific nature of the products.** Furthermore, guidelines specific to advanced therapy medicinal products should be drawn up, so as to properly reflect the particular nature of their manufacturing process.

#### *Justification*

*Advanced Therapy medicinal products have specific characteristics that differ greatly from traditional medicinal products. That leads to important differences in their manufacturing process (e.g. in Article 11.4. the GMP Directive requires that sample batches of finished products should be kept for 1 year after expiry date. It is, however, difficult to consider expiry dates for certain classes of ATMPs).*

#### Amendment 12 RECITAL 17

(17) Advanced therapy medicinal products may incorporate medical devices or active implantable medical devices. Those devices should meet the essential requirements laid down in Council Directive 93/42/EEC of 14 June 1993 concerning medical devices and Council Directive 90/385/EEC of 20 June 1990 on the approximation of the laws of the Member States relating to active implantable medical devices, respectively, in order to ensure an appropriate level of quality and safety.

(17) Advanced therapy medicinal products may incorporate medical devices or active implantable medical devices. Those devices should meet the essential requirements laid down in Council Directive 93/42/EEC of 14 June 1993 concerning medical devices and Council Directive 90/385/EEC of 20 June 1990 on the approximation of the laws of the Member States relating to active implantable medical devices, respectively, in order to ensure an appropriate level of quality and safety. ***An assessment of the medical device or the active implantable medical device by a notified body in accordance with these Directives should be incorporated in the evaluation of a combined product carried out under this***

***Regulation by the Agency.***

*Justification*

*In order to ensure the continuous utilisation of the vast experience and expertise of the notified bodies on the evaluation of medical devices or active implantable medical devices, the notified bodies should assess the medical device or the active implantable medical device part of the combined advanced therapy medicinal product. The Agency should incorporate these assessments in its final evaluation of the combined product.*

Amendment 13

RECITAL 18

(18) Specific rules should be laid down, adapting the requirements in Directive 2001/83/EC as regards the summary of product characteristics, labelling and package leaflet to the technical specificities of advanced therapy medicinal products.

(18) ***Patients have a right to know the origin of any tissues and cells used in the preparation of advanced therapy medicinal products.*** Specific rules should be laid down, adapting the requirements in Directive 2001/83/EC as regards the summary of product characteristics, labelling and package leaflet to the technical specificities of advanced therapy medicinal products.

Amendment 14

RECITAL 28

(28) Directive 2001/83/EC ***and*** Regulation (EC) No 726/2004 of the European Parliament and of the Council of 31 March 2004 laying down Community procedures for the authorisation and supervision of medicinal products for human and veterinary use and establishing European Medicines Agency should therefore be amended accordingly,

(28) Directive 2001/83/EC, Regulation (EC) No 726/2004 of the European Parliament and of the Council of 31 March 2004 laying down Community procedures for the authorisation and supervision of medicinal products for human and veterinary use and establishing European Medicines Agency ***and Directive 2004/23/EC*** should therefore be amended accordingly,

*Justification*

*This is a consequential amendment to the amendment of the Article 28a (new) modifying Directive 2004/23/EC on tissues and cells.*

Amendment 15  
ARTICLE 1 A (new)

*Article 1a*

*Exclusion from the scope*

***This Regulation shall not apply to any advanced therapy medicinal product which is prepared in full in a hospital on a one-off basis according to a specific, non-standardised and non-patented process, and used in a hospital, in order to comply with an individual medical prescription for an individual patient.***

*Justification*

*Where hospitals or other institutions prepare products by using an established process to create treatments for patients on a serial and routine basis, they should have to comply with the provisions of this Regulation, ensuring quality, safety and efficacy of products. However, when hospitals produce ATPs for research purposes or on an exceptional, one-off basis, they should not have to comply with the centralised authorisation process. To ensure the coherence with the Article 28, paragraph 1 we introduce the exclusion from the scope in the present Regulation.*

Amendment 16  
ARTICLE 2, PARAGRAPH 1, POINT (D), INDENT 1 A (new)

***- its cellular or tissue part contains viable cells or tissues; or***

*Justification*

*For the purposes of this Regulation, the most important criterion when defining a combined advanced therapy medicinal product should be the viability of its cellular or tissue part. For the patient's safety and the high standards of the evaluation of a product, a combined product should be always classified as an advanced therapy medicinal product when it contains viable tissues or cells.*

Amendment 17  
ARTICLE 2, PARAGRAPH 1, POINT (D), INDENT 2

- its cellular or tissue part must be liable to act upon the human body with action that

- its cellular or tissue part ***containing non-viable cells or tissues*** must be liable to act

*cannot* be considered as *ancillary* to that of the devices referred to.

upon the human body with action that *can* be considered as *primary* to that of the devices referred to.

*Justification*

*A combined product should always be considered as advanced therapy medicinal product when it contains non-viable cells or tissues which act upon human body in a manner that is considered as primary to the action of the device part of the product concerned.*

Amendment 18

ARTICLE 2, PARAGRAPH 1, POINT (D A) (new)

*(da) chimera means :*

- an embryo into which a cell of any non-human life form has been introduced; or*
- an embryo that consists of cells of more than one embryo, foetus or human being.*

*Justification*

*We introduce this definition for the purpose of Article 3c of the present Regulation.*

*Source: Canadian assisted human reproduction act 2004*

Amendment 19

ARTICLE 2, PARAGRAPH 1, POINT (D B) (new)

*(db) hybrid means :*

- a human ovum that has been fertilised by a sperm of a non-human life form;*
- an ovum of a non-human life form that has been fertilised by a human sperm;*
- a human ovum into which the nucleus of a cell of a non-human life form has been introduced;*
- an ovum of a non-human life form into which the nucleus of a human cell has been introduced; or*

**- a human ovum or an ovum of a non-human life form that otherwise contains haploid sets of chromosomes from both a human being and a non-human life form.**

*Justification*

*We introduce this definition for the purpose of Article 3c of the present Regulation.  
Source: Canadian assisted human reproduction act 2004*

Amendment 20  
ARTICLE 3 A (new)

*Article 3a*

***Ban of commercialisation of the human body***

***Where an advanced therapy medicinal product contains human tissues or cells, every stage of the authorisation procedure shall be carried out in accordance with the principle of non-commercialisation of the human body or its parts as such. To this end, and for the purposes of this Regulation, Member States shall ensure that:***

- the donation of human cells and tissues is voluntary and unpaid and is made of the donor's free will without payment except compensation; and***
- the procurement of tissues and cells is carried out on a non-profit basis.***

*Justification*

*Rapid developments in biotechnology and biomedicine must not be allowed to compromise the protection of fundamental rights. These rights of which one of the most important one is the right to the integrity of the person are laid down in the Oviedo Convention as well as in the Charter of Fundamental Rights. These standards can only be upheld if they are carefully observed at every stage of the authorisation process. Therefore, EMEA should be subject to this specific obligation. Moreover, to this end, Member States shall have an obligation to ensure voluntary and unpaid donation and to guarantee the procurement of tissues or cells on a non-profit basis.*

Amendment 21  
ARTICLE 3 B (new)

**Article 3b**

***Ban of products modifying the human germ line***

***No authorisation shall be granted to products modifying the germ line genetic identity of human beings.***

*Justification*

*As Articles 1 and 13 of the Oviedo Convention make it clear, human dignity is compromised when the inheritance of genetic identity is altered. Products which are neither properly subject to clinical trials under Directive 2001/20/EC nor legally patentable under Directive 98/44/EC should not be eligible for authorisation under this Regulation.*

Amendment 22  
ARTICLE 3 C (new)

**Article 3c**

***Ban of products derived from human-animal hybrids or chimeras***

***No authorisation shall be granted to products derived from human-animal hybrids or chimeras or containing tissues or cells originating or derived from human-animal hybrids or chimeras.***

***This provision does not preclude the transplantation of somatic animal cells or tissues to the human body for therapeutic purposes, in so far as it does not interfere with the germ line.***

*Justification*

*The physical and mental integrity of the person and human dignity must be respected, as underlined by the Charter of fundamental rights of the EU. The creation of human-animal hybrids or chimeras is a breach of the right to integrity of a person and a violation of human dignity. In addition, the Directive 98/44/EC on the legal protection of biotechnological inventions stresses that the production of chimeras from germ cells is excluded from patentability. Therefore, no authorisation under this regulation should be granted to products containing or derived from such tissues and cells.*

Amendment 23  
ARTICLE 5, PARAGRAPH -1 (new)

***The Commission shall, in accordance with the procedure referred to in Article 26(2), amend Directive 2003/94/EC to take into account the specific characteristics of advanced therapy medicinal product and especially tissue engineered products.***

*Justification*

*Advanced therapy medicinal products have specific characteristics that differ greatly from traditional medicinal products. That leads to important differences in their manufacturing process (e.g. Article 11.4. of the GMP Directive requires that sample batches of finished products should be kept for 1 year after the expiry date. It is, however, difficult to consider expiry dates for certain classes of ATMPs).*

Amendment 24  
ARTICLE 9, PARAGRAPH 2

2. The rapporteur or co-rapporteur appointed by the Committee for Medicinal Products for Human Use pursuant to Article 62 of Regulation (EC) No 726/2004 shall be a member of the Committee for Advanced Therapies. This member shall also act as rapporteur or co-rapporteur for the Committee for Advanced Therapies.

2. The rapporteur or co-rapporteur appointed by the Committee for Medicinal Products for Human Use pursuant to Article 62 of Regulation (EC) No 726/2004 shall be a member of the Committee for Advanced Therapies, ***proposed by the Committee for Advanced Therapies and having specific expertise for the product.*** This member shall also act as rapporteur or co-rapporteur for the Committee for Advanced Therapies.

*Justification*

*In order to ensure the highest level of expertise, the rapporteur and co-rapporteur appointed by the CHMP should be proposed by the Committee for Advanced Therapies and should have specific expertise for the relevant product.*

Amendment 25  
ARTICLE 9, PARAGRAPH 3

3. The **advice** given by the Committee for Advanced Therapies under paragraph 1 shall be sent to the chairman of the Committee for Medicinal Products for Human Use in a timely manner so as to ensure that the deadline laid down in Article 6(3) of Regulation (EC) No 726/2004 can be met.

3. The **draft opinion** given by the Committee for Advanced Therapies under paragraph 1 shall be sent to the chairman of the Committee for Medicinal Products for Human Use in a timely manner so as to ensure that the deadline laid down in Article 6(3) **or 9(2)** of Regulation (EC) No 726/2004 can be met.

#### *Justification*

*Due to the highly specific and unique character of the advanced therapy medicinal products, a new Committee for Advanced Therapies is established within EMEA, composed of experts having specific qualifications or experience in this highly innovative and quickly developing field. Therefore, this new structure should be responsible for drafting an opinion on the quality, safety, and efficacy of products for the final approval by the CHMP. The draft opinion should be given in a timely manner so the deadline laid down in Article 9(2) of Regulation (EC) No 726/2004 can also be met.*

#### Amendment 26 ARTICLE 9, PARAGRAPH 4

4. Where the scientific opinion on an advanced therapy medicinal product drawn up by the Committee for Medicinal Products for Human Use under *Article 5, paragraphs 2 and 3* of Regulation (EC) No 726/2004 is not in accordance with the **advice** 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.

4. Where the scientific opinion on an advanced therapy medicinal product drawn up by the Committee for Medicinal Products for Human Use under *Article 5(2) and (3)* of Regulation (EC) No 726/2004 is not in accordance with the **draft 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.

#### *Justification*

*See the justification for the amendment of the Article 9, paragraph 3.*

#### Amendment 27 ARTICLE 10, PARAGRAPH 1

1. Where a combined advanced therapy

1. Where a combined advanced therapy

medicinal product is concerned, the whole product, including any medical device or any active implantable medical device incorporated in the medicinal product, shall be evaluated by the Agency.

medicinal product is concerned, the whole product, including any medical device or any active implantable medical device incorporated in the medicinal product, shall be **finally** evaluated by the Agency.

#### *Justification*

*According to paragraph 2, a medical device or the active implantable medical device part of a combined advanced therapy medicinal product have to be assessed by a notified body in order to benefit from its extensive specific experience. The final evaluation should be carried out by the Agency who should incorporate the assessment of a notified body in its final opinion.*

#### Amendment 28 ARTICLE 10, PARAGRAPH 2

**2. Where the medical device or active implantable medical device which is part of a combined advanced therapy medicinal product has already been assessed** by a notified body in accordance with Directive 93/42/EEC or Directive 90/385/EEC, the Agency shall **take account of** the results of that assessment in its evaluation of the medicinal product concerned.

**2. The application for a marketing authorisation for a combined advanced therapy medicinal product shall include an assessment** by a notified body identified in conjunction with the applicant in accordance with Directive 93/42/EEC or Directive 90/385/EEC **of the medical device or active implantable medical device which forms part of the combined advanced therapy medicinal product.** The Agency shall **incorporate** the results of that assessment in its evaluation of the medicinal product concerned.

#### *Justification*

*In order to ensure the continuous utilisation of the vast experience and expert knowledge of the notified bodies concerning the evaluation of medical devices or active implantable medical devices, the notified bodies should assess the medical device or the active implantable medical device part of the combined advanced therapy medicinal product. The Agency should incorporate these assessments in its final evaluation of the combined product in accordance with paragraph 1.*

#### Amendment 29 ARTICLE 15, PARAGRAPH 2

2. Where there is particular cause for

2. Where there is particular cause for

concern, the Commission **may**, on the advice of the Agency, require as part of the marketing authorisation that a risk management system designed to identify, prevent or minimise risks related to advanced therapy medicinal products, including an evaluation of the effectiveness of that system, be set up, or that specific post-marketing studies be carried out by the holder of the marketing authorisation and submitted for review to the Agency.

concern, the Commission **shall**, on the advice of the Agency, require as part of the marketing authorisation that a risk management system designed to identify, prevent or minimise risks related to advanced therapy medicinal products, including an evaluation of the effectiveness of that system, be set up, or that specific post-marketing studies be carried out by the holder of the marketing authorisation and submitted for review to the Agency.

#### *Justification*

*In order to ensure the effectiveness of the risk management system, the Commission should have an obligation to require necessary measures to be carried out when there is a cause for concern.*

#### Amendment 30 ARTICLE 15, PARAGRAPH 4

4. The Agency shall draw up detailed guidelines relating to the application of paragraphs 1, 2 and 3.

4. The Agency shall draw up detailed guidelines relating to the application of paragraphs 1, 2 and 3. ***They shall be based on the principles of regulatory cooperation and dialogue with the marketing authorisation holder.***

#### *Justification*

*When drawing up post-authorisation risk management guidelines, principles of regulatory cooperation and dialogue with the marketing authorization holder should be enacted in order to allow a pooling of the limited expertise in this area.*

#### Amendment 31 ARTICLE 16, PARAGRAPH 4

4. The marketing authorisation holder shall keep the data referred to in the first paragraph for a minimum of 30 years after placing the product on the market, ***or longer if required by the Commission as a term of the marketing authorisation.***

4. The marketing authorisation holder shall keep the data referred to in the first paragraph for a minimum of 30 years after placing the product on the market, ***and for the entire lifetime of the patient.***

### *Justification*

*It is of primordial importance to secure the patients traceability for a lifetime in order to ensure the quality and safety of the received treatment.*

### Amendment 32 ARTICLE 17, PARAGRAPH 2

2. By way of derogation from Article 8(1) of Regulation (EC) No 297/95, a **90%** reduction shall apply to the fee payable to the Agency for any advice referred to in paragraph 1 and in Article 57(1)(n) of Regulation (EC) No 726/2004 in respect of advanced therapy medicinal products.

2. By way of derogation from Article 8(1) of Regulation (EC) No 297/95, a **95% reduction for SMEs and 70% for other applicants** shall apply to the fee payable to the Agency for any advice referred to in paragraph 1 and in Article 57(1)(n) of Regulation (EC) No 726/2004 in respect of advanced therapy medicinal products.

### *Justification*

*This Regulation seeks to encourage and support SME's in the development of ATMPs. Therefore, it is necessary to introduce special fee-waivers applicable to SME's on scientific advice. The 5% of the basic fee which the SME's should cover themselves is a symbolic amount, in order to prevent any abuse of the totally gratis system. Moreover, to support the applicants which do not fall under the SME criteria and to ensure the competitiveness of the whole sector, a reduction of 70% should be applied to all companies irrespective of their size.*

### Amendment 33 ARTICLE 18, PARAGRAPH 1

1. Any applicant developing a product based on cells or tissues may request a scientific recommendation of the Agency with a view to determining whether the referred product falls, on scientific grounds, within the definition of an advanced therapy medicinal product. The Agency shall deliver this recommendation after consultation with the Commission.

1. Any applicant developing a product based on cells or tissues may request a scientific recommendation of the Agency with a view to determining whether the referred product falls, on scientific grounds, within the definition of an advanced therapy medicinal product. The Agency shall deliver this recommendation, after consultation with **the Committee for Advanced Therapies and** the Commission, **within 60 days after receipt of the request.**

### *Justification*

*The proposed amendment foresees that an applicant will get clarity on the classification of*

*the concerned product in a timely manner, thus facilitating business planning and further development of the product.*

#### Amendment 34

#### ARTICLE 21, PARAGRAPH 1, POINT (C) AND (C A) (new)

(c) **four** members appointed by the Commission, on the basis of a public call for expressions of interest, **two of them** to represent **surgeons and two of them** to represent patients associations.

(c) **two** members **and two alternates** appointed by the Commission, on the basis of a public call for expressions of interest **and after consultation of the European Parliament**, to represent **medical doctors**;

**(ca) two members and two alternates appointed by the Commission, on the basis of a public call for expressions of interest and after consultation of the European Parliament**, to represent patients associations.

#### *Justification*

*In order to cover all medical fields which the advanced therapies may relate to, more general medical expertise, i.e. medical doctors, should be represented in the Committee for Advanced Therapies . In addition, by introducing alternate members, we would like to ensure a permanent representation of the groups involved. The appointment of these members and their alternates should take place in consultation with the European Parliament.*

#### Amendment 35

#### ARTICLE 21, PARAGRAPH 2

2. All members of the Committee for Advanced Therapies shall be chosen for their scientific qualification or experience in respect of advanced therapy medicinal products. For the purposes of point (b) of paragraph 1, 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 appropriately and in a balanced way covers the scientific areas relevant to advanced therapies, including medical devices, tissue-engineering, gene therapy, cell therapy, biotechnology,

2. All members **and alternates** of the Committee for Advanced Therapies shall be chosen for their scientific qualification or experience in respect of advanced therapy medicinal products. For the purposes of point (b) of paragraph 1, 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, appropriately and in a balanced way covers the scientific areas relevant to advanced therapies, including medical devices, tissue-engineering, gene therapy, cell therapy, biotechnology,

pharmacovigilance, risk management and ethics.

pharmacovigilance, risk management and ethics.

*Justification*

*The alternate members of the Committee for Advanced therapies introduced in paragraph 1 shall comply with the same criteria of scientific qualification or experience in the field of advanced therapy medicinal products as its members.*

Amendment 36  
ARTICLE 23, POINT (A)

(a) **to advise** the Committee for Medicinal Products for Human Use on any data generated in the development of **an advanced therapy medicinal product, for the formulation of an opinion on its quality, safety and efficacy;**

(a) **to formulate a draft opinion on the quality, safety and efficacy of an advanced therapy medicinal product for final approval by** the Committee for Medicinal Products for Human Use **and to advise it** on any data generated in the development of **such a** product;

*Justification*

*Due to the highly specific and unique character of the advanced therapy medicinal products, a new Committee for Advanced Therapies is established within EMEA, composed of experts having specific qualifications or experience in this highly innovative and quickly developing field. Therefore, the new structure should be responsible for drafting an opinion on the quality, safety, and efficacy of products for the final approval by the CHMP. Furthermore, the committee should be consulted for the evaluation of other products under its competence.*

Amendment 37  
ARTICLE 23, POINT (A A) (new)

**(aa) to provide advice, pursuant to Article 18, to the Committee for Medicinal Products for Human Use on whether a product falls within the definition of an advanced therapy medicinal product;**

*Justification*

*Having specific expertise in advanced therapy medicinal products, the Committee for Advanced Therapies should assist the CHMP in its classification task of whether a product is or is not an advanced therapy medicinal product.*

Amendment 38  
ARTICLE 23, PARAGRAPH 1 A (new)

***When preparing a draft opinion for final approval by the Committee for Medicinal Products for Human Use, the Committee for Advanced Therapies shall endeavour to reach a scientific consensus. If such consensus cannot be reached, the Committee for Advanced Therapies shall adopt the position of the majority of its members. The draft opinion shall mention the divergent positions and the grounds on which they are based.***

*Justification*

*In order to guarantee transparency in the process of preparation of a draft opinion, a clear decision procedure should be defined within Committee for Advanced Therapies. Consequently, we suggest that a scientific consensus should be reached by its members.*

Amendment 39  
ARTICLE 24

The Commission shall, in accordance with procedure referred to in Article 26(2), amend ***Annexes I to IV*** in order to adapt them to scientific and technical evolution.

The Commission shall, in accordance with procedure referred to in Article 26(2), amend ***Annexes II to IV*** in order to adapt them to scientific and technical evolution.

*Justification*

*Annex I contains a fundamental and substantial definition. We therefore consider that it should not be subject to any changes through comitology. Should any changes be necessary due to scientific progress, they should be adopted in codecision, fully involving the European Parliament.*

Amendment 40  
ARTICLE 27, POINT -1 (new)  
Article 13, paragraph 1 (Regulation (EC) No 726/2004)

***(-1) In Article 13, the first sentence is replaced by the following:***

***"Without prejudice to Article 4(4) and (5) of Directive 2001/83/EC, a marketing authorisation which has been granted in accordance with this Regulation shall be valid throughout the Community."***

*Justification*

*This is a consequential amendment to Article 28(2) to ensure legal coherence.*

Amendment 41  
ARTICLE 28, POINT -1 (new)  
Article 1, point 4 a (new) (Directive 2001/83/EC)

***(-1) In Article 1, the following point 4a is added:***

***"4a. Tissue engineered product:***

***A tissue engineered product means a product as defined in Article 2 of Regulation (EC) No \*\*/\*\* on advanced therapy medicinal products."***

*Justification*

*For the sake of legal coherence and clarity, it is necessary to include a cross reference to the definition of a tissue engineered product in Directive 2001/83/EC on medicinal products, which already contains the definitions of a gene therapy medicinal product and a somatic cell therapy medicinal product.*

Amendment 42  
ARTICLE 28, POINT 1  
Article 3, paragraph 7 (Directive 2001/83/EC)

7. Any advanced therapy medicinal product, as defined in Regulation (EC) No [.../of the European Parliament and of the Council (Regulation on Advanced Therapy Medicinal Products)\*], which is **both** prepared in full and used in a hospital, **in accordance with a** medical prescription for an individual patient.

7. Any advanced therapy medicinal product, as defined in Regulation (EC) No [.../of the European Parliament and of the Council (Regulation on Advanced Therapy Medicinal Products)\*], which is prepared in full in a hospital **on a one-off basis according to a specific, non-standardised and non-patented process, and used in a hospital, in order to comply with an individual** medical prescription for an individual patient.

**Paragraphs 1 and 2 do not apply to advanced therapy medicinal products.**

*Justification*

*For the justification concerning hospitals, see amendment 14. Exceptions given in Directive 2001/83/EC (Article 3, paragraphs 1 and 2) allow pharmacies to prepare medicinal products in accordance with a medical prescription without complying with medicinal product legislation. This exception would as well give the in-house pharmacies of hospitals the possibility producing TEP using standardized methods and on routinely basis. Therefore this amendment is crucial to ensure that only one-off basis products are excluded from the scope of this Regulation.*

Amendment 43

ARTICLE 28 A (new)

Article 2, paragraph 1, subparagraph 2 (Directive 2004/23/EC)

**Article 28a**

**Amendment to Directive 2004/23/EC**

***In Article 2(1) of Directive 2004/23/EC, the second subparagraph is replaced by the following:***

***"Where such manufactured products are covered by other Community legislation, this Directive shall apply only to donation, procurement and testing. However, the donation, procurement and testing provisions of this Directive shall be without prejudice to more specific provisions contained in other Community legislation."***

*Justification*

*According to the existing legislation, the donation, procurement and testing of human tissues and cells should comply with high standards of quality and safety in order to ensure a high level of health protection in the Community. Moreover, it also has to be ensured that the human body or its parts as such are not commercialised. Therefore, for the purposes of this Regulation, Member States shall have an imperative obligation to ensure voluntary and unpaid donation and to guarantee that the procurement of tissues or cells is carried out on a non-profit basis.*

Amendment 44

## ARTICLE 29, PARAGRAPH 1

1. Advanced therapy medicinal products which were legally on the Community market in accordance with national or Community legislation at the time of entry into force of this Regulation shall comply with this Regulation no later than **2 years** after its entry into force.

1. Advanced therapy medicinal products, ***other than tissue engineered products***, which were legally on the Community market in accordance with national or Community legislation at the time of entry into force of this Regulation shall comply with this Regulation no later than **4 years** after its entry into force.

### *Justification*

*Today companies are already producing and marketing TEP at national level through national authorisation systems. In order for a company to obtain a centralised marketing authorisation (e.g. design the new trials together with the EMEA, to conduct the trials, to develop the dossier and to submit it to the EMEA for evaluation) the proposed timeframe of 2 years is too short. Taking into account the time required for the above-mentioned steps and in order to avoid that products that have been safely treating patients up to now are not removed from those patients during the transitional period, we suggest a period of 4 years.*

### Amendment 45

#### ARTICLE 29, PARAGRAPH 1 A (new)

***1a. Tissue engineered products which are legally on the Community market in accordance with national or Community legislation at the time of entry into force of the technical requirements referred to in Article 8 must comply with this Regulation no later than 4 years after the entry into force of those technical requirements.***

### *Justification*

*Manufacturers will not be in a position to design development protocols until the technical requirements specific to tissue engineering products are published. The transitional period for these products must therefore take into account the time to publish these technical requirements.*

### Amendment 46

#### ARTICLE 29, PARAGRAPH 2

2. By way of derogation from Article 3(1) of Regulation (EC) No 297/95, no fee shall be payable to the Agency in respect of applications submitted for the authorisation of the advanced therapy medicinal products mentioned in **paragraph 1**.

2. By way of derogation from Article 3(1) of Regulation (EC) No 297/95, no fee shall be payable to the Agency in respect of applications submitted for the authorisation of the advanced therapy medicinal products mentioned in **paragraphs 1 and 1a**.

*Justification*

*See the amendment for the Article 29, paragraph 1a (new).*

Amendment 47  
ARTICLE 30

This Regulation shall enter into force on the 20th day following that of its publication in the *Official Journal of the European Union*.

*It shall apply from [3 months after entry into force]*

This Regulation shall enter into force on the 20th day following that of its publication in the *Official Journal of the European Union*.

***The measures envisaged in Articles 4, 5 and 8 shall be adopted not later than [6 months after the publication of this Regulation in the Official Journal of the European Union].***

***This Regulation shall apply from [3 months after its entry into force]. For tissue engineered products this Regulation shall apply as of the entry into force of the technical requirements referred to in Article 8.***

*Justification*

*Manufacturers will not be in a position to design development protocols until the technical requirements are published and the adaptations of the Good Clinical Practice Directive and the Good Manufacturing Practice Directive are finalised. Therefore, we propose 6 months time limit for the Commission to adopt the necessary measures.*

## EXPLANATORY STATEMENT