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Committee on the Environment, Public Health and Food Safety

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*****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.

CONTENTS

	Page
DRAFT EUROPEAN PARLIAMENT LEGISLATIVE RESOLUTION	5
EXPLANATORY STATEMENT	31

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)¹,
 - 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 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

(5) This Regulation is a lex specialis, which introduces additional provisions to those laid down in Directive 2001/83/EC. The scope of this Regulation should be to regulate advanced therapy medicinal products which are intended to be placed on the market in Member States and either prepared industrially or manufactured by a method involving an industrial process, ***in accordance with the general scope of the Community pharmaceutical legislation laid***

¹ OJ C ... / Not yet published in OJ.

patient, should thus be excluded from the scope of the present Regulation.

down in Title II 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 the present Regulation.

(2nd part = AM 2 of PR FdR 617323EN, diff. just.)

Justification

It should be clarified that this Regulation is a lex specialis in relation to Dir. 2001/83/EC, as it introduces additional requirements that are specific to ATMP. The scope of this Regulation is the general scope of the pharmaceutical legislation, as laid down in Dir. 2001/83/EC. Where hospitals or other institutions prepare products using an established process to create treatments for patients on a routine basis, they should have to comply with the provisions of this Regulation. However, when hospitals produce ATMP for research purposes or on an exceptional, one-off basis, they should not have to comply with the centralised authorisation procedure.

Amendment 2 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.

(AM 7 of PR FdR 617323EN)

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 3
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.

(AM 8 of PR FdR 617323EN)

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 4
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 **physicians** with scientific experience of advanced therapy medicinal products should also be represented.

(AM 9 of PR FdR 617323EN, relevant words mod.)

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 5
RECITAL 15

(15) Clinical trials on advanced therapy medicinal products should be conducted in accordance with the overarching principles and the ethical requirements laid down in Directive 2001/20/EC of the European Parliament and of the Council of 4 April 2001 on the approximation of the laws, regulations and administrative provisions of the Member States relating to the implementation of good clinical practice in the conduct of clinical trials on medicinal products for human use. However, tailored rules should be laid down, adapting Directive 2005/28/EC of 8 April 2005 laying down principles and detailed guidelines for good clinical practice as regards investigational medicinal products for human use, as well as the requirements for authorisation of the manufacturing or importation of such products, in order to fully take into account the specific technical characteristics of advanced therapy medicinal products.

(15) Clinical trials on advanced therapy medicinal products should be conducted in accordance with the overarching principles and the ethical requirements laid down in Directive 2001/20/EC of the European Parliament and of the Council of 4 April 2001 on the approximation of the laws, regulations and administrative provisions of the Member States relating to the implementation of good clinical practice in the conduct of clinical trials on medicinal products for human use. However, tailored rules should be laid down, adapting Directive 2005/28/EC of 8 April 2005 laying down principles and detailed guidelines for good clinical practice as regards investigational medicinal products for human use, as well as the requirements for authorisation of the manufacturing or importation of such products, in order to fully take into account the specific technical characteristics of advanced therapy medicinal products. ***Those rules should ensure an adequate time interval between single clinical trials (including multi-centre clinical trials) and a coordinated surveillance and information exchange.***

(AM 59 of AM FdR 620607EN)

Justification

This amendment shall ensure that clinical trials are conducted in the safest possible manner.

Amendment 6
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.

(AM 11 of PR FdR 617323EN)

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 7
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. **Where available, the**

results of the assessment of the medical device or the active implantable medical device by a notified body in accordance with those Directives should be taken into account by the Agency in the evaluation of a combined product carried out under this Regulation.

(AM 12 of PR FdR 617323EN modified)

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 may assess the medical device or the active implantable medical device part of the combined advanced therapy medicinal product. In that case, the Agency should take into account the results of these assessments in its final evaluation of the combined product.

Amendment 8

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, although donor anonymity must be respected.*** 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.

(AM 13 of PR FdR 617323EN modified)

Amendment 9

RECITAL 19A (new)

(19a) The operation of this Regulation requires the establishment of guidelines, to be drawn up either by the Agency or by the Commission. In both cases, open consultation with all interested parties, in particular the industry, should be enacted in order to allow a pooling of the limited

expertise in this area and ensure proportionality.

Justification

When drawing up guidelines for the implementation of this Regulation, principles of open consultation with all interested parties, in particular the industry should be enacted in order to allow a pooling of the limited expertise in this area and ensure proportionality.

Amendment 10
RECITAL 27

(27) The measures necessary for the implementation of this Regulation should be adopted in accordance with the Council Decision 1999/468/EC of 28 June 1999 laying down the procedures of the exercise of implementing powers conferred to the Commission.

(27) The measures necessary for the implementation of this Regulation should be adopted in accordance with the Council Decision 1999/468/EC of 28 June 1999 laying down the procedures of the exercise of implementing powers conferred to the Commission. ***The regulatory procedure with scrutiny provided for in Article 5a of that Decision should apply to the adoption of amendments to Annexes II to IV to this Regulation and to Annex I to Directive 2001/83/EC.***

Amendment 11
ARTICLE 2, PARAGRAPH 1, POINT (B), INTRODUCTORY PART

(b) tissue engineered product means a product that:

(b) tissue engineered product means a ***medicinal*** product that:

Justification

Adding the term "medicinal" clarifies that products which do not meet the definition of a medicinal product cannot be covered by this regulation.

Amendment 12
ARTICLE 2, PARAGRAPH 1, POINT (B), SUBPARAGRAPH 2 A (new)

Tissue engineered products containing or made exclusively of non-viable human or animal tissues and/or cells, which do not act principally by pharmacological, immunological or metabolic action, are

excluded from this definition.

(AM 62 of AM FdR 620607EN)

Justification

The Medical Devices Directives (MDD) provide a regulatory framework which is readily adapted to the control of devices containing or made of tissue engineered products. If a tissue engineered product falls within the definition of “medical device” in Article 1 of the MDD (and therefore does not have a mode of action which is primarily pharmacological, immunological or metabolic), it should be regulated under the MDD although additional specific requirements may be necessary.

Amendment 13

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

- its cellular or tissue part must be liable to act upon the human body with action that **can** be considered as **primary** to that of the devices referred to.

(AM 17 of PR FdR 617323EN modified)

Justification

A combined product should always be considered as advanced therapy medicinal product when it contains 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 14

ARTICLE 2, PARAGRAPH 1, SUBPARAGRAPH 1 A (new)

Where a product contains viable cells or tissues, the pharmacological, immunological or metabolic action of these cells or tissues shall be considered as the primary mode of action of the product.

Justification

This new provision clarifies the rule concerning products which contain viable cells or tissues, whilst maintaining in principle the criterion of “primary mode of action” for borderline classification. For the patient's safety and the high standards of the evaluation of a

combined product, the most important criterion should be the viability of the cellular or tissue part of such a product.

Amendment 15
ARTICLE 4, PARAGRAPHS 2 AND 3

2. The Commission shall, in accordance with the procedure referred to in Article 26(2), amend Directive 2005/28/EC in order to take account of the specific characteristics of advanced therapy medicinal products.

3. The Commission shall draw up detailed guidelines on good clinical practice specific to advanced therapy medicinal products.

2. The Commission shall, ***after consultation of the Agency and*** in accordance with the procedure referred to in Article 26(2), amend Directive 2005/28/EC in order to take account of the specific characteristics of advanced therapy medicinal products.

3. The Commission shall, ***after consultation of the Agency,*** draw up detailed guidelines on good clinical practice specific to advanced therapy medicinal products.

Justification

The Regulation should set out very clearly that the Commission must involve the EMEA, through the Committee for Advanced Therapies, whenever good clinical practice requirements need to be amended or guidelines related to advanced therapy medicinal products need to be drawn up.

Amendment 16
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.

(AM 23 of PR FdR 617323EN)

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 17
ARTICLE 5

Detailed guidelines in line with the principles of good manufacturing practice and specific to advanced therapy medicinal products **shall be published by the Commission**.

The Commission shall draw up detailed guidelines in line with the principles of good manufacturing practice and specific to advanced therapy medicinal products.

Justification

For the sake of consistency, the wording should be put in line with the equivalent provision in Article 4(3).

Amendment 18
ARTICLE 7

Specific requirements for **tissue engineered products**

Specific requirements for **advanced therapy medicinal products containing devices**

In addition to the requirements laid down in Article 6(1) of Regulation (EC) No 726/2004, applications for the authorisation of **a tissue engineered product** shall include a description of the physical characteristics and performance of the product and a description of the product design methods, in accordance with Annex I to Directive 2001/83/EC.

In addition to the requirements laid down in Article 6(1) of Regulation (EC) No 726/2004, applications for the authorisation of **an advanced therapy medicinal product containing medical devices, bio-materials, scaffolds or matrices** shall include a description of the physical characteristics and performance of the product and a description of the product design methods, in accordance with Annex I to Directive 2001/83/EC.

Justification

The scope of this article should be clarified and amended to encompass all those products in need of these specific requirements. Restricting the requirements to tissue engineered products would exclude those advanced therapy medicinal products that also have special physical characteristics possibly affecting the performance of the product. However, extending these requirements to all advanced therapy products would create unnecessary work for enterprises; all advanced therapy products do not have special physical characteristics that could affect their performance.

Amendment 19
ARTICLE 8

The Commission shall, in accordance with the procedure referred to in **Article 26(2)** of this Regulation, amend Annex I to Directive 2001/83/EC in order to lay down technical requirements that are specific to tissue engineered products, in particular those referred to in Article 7, with a view to taking account of scientific and technical evolution.

The Commission shall, ***after consultation of the Agency and*** in accordance with the procedure referred to in **Article 26(2a)** of this Regulation, amend Annex I to Directive 2001/83/EC in order to lay down technical requirements that are specific to tissue engineered products, in particular those referred to in Article 7, with a view to taking account of scientific and technical evolution.

Justification

The Regulation should set out very clearly that the Commission must involve the EMEA, through the Committee for Advanced Therapies, whenever the technical requirements laid down in Annex I to Directive 2001/83/EC need to be amended.

Amendment 20 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.

(AM 24 of PR FdR 617323EN)

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 21 ARTICLE 9, PARAGRAPH 2 A (new)

2a. 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.

(AM 38 of PR FdR 617323EN)

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 22

ARTICLE 9, PARAGRAPH 2B (new)

2b. The rapporteur or co-rapporteur shall be entitled to question the applicant directly. The applicant may also offer to be questioned. The rapporteur or co-rapporteur shall inform the Committees involved in writing without delay of the details of contacts with the applicant.

(AM 69 of AM FdR 620607EN - par.2B instead 2A)

Justification

The amendment aims at enhancing a more transparent procedure.

Amendment 23

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.

(AM 25 of PR FdR 617323EN)

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 24

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.

(AM 26 of PR FdR 617323EN)

Justification

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

Amendment 25

ARTICLE 10, PARAGRAPH 1

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.

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 **finally** evaluated by the Agency.

(AM 27 of PR FdR 617323EN, just. last phrase modified)

Justification

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

Amendment 26

ARTICLE 10, PARAGRAPH 2, SUBPARAGRAPH 1

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 may include the results of the assessment by a notified body in accordance with Directive 93/42/EEC or Directive 90/385/EEC **of the medical device or active implantable medical device part**. The Agency shall take account of the results of that assessment in its evaluation of the medicinal product concerned.

(AM 28 of PR FdR 617323EN, first part, diff. just.)

Justification

It should be clarified that the applicant has the choice to get the device part of a combined ATMP assessed and certified by a notified body, in accordance with the medical device legislation. In such a case, the Agency should take account of this assessment in its evaluation of the whole combined product.

Amendment 27

ARTICLE 15, PARAGRAPH 1

1. In addition to the requirements for pharmacovigilance laid down in Articles 21 to 29 of Regulation (EC) No 726/2004, the applicant shall detail, in the marketing authorisation application, the measures envisaged to ensure the follow-up of efficacy of advanced therapy medicinal

1. In addition to the requirements for pharmacovigilance laid down in Articles 21 to 29 of Regulation (EC) No 726/2004, the applicant shall detail, in the marketing authorisation application, the measures envisaged to ensure the follow-up of efficacy of advanced therapy medicinal

products.

products *and of adverse reactions thereto.*

(AM 76 of AM FdR 620607EN)

Justification

This amendment would ensure a better coherence with existing pharmaceutical legislation and a high standard of pharmacovigilance.

Amendment 28
ARTICLE 15, PARAGRAPH 2

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.

2. Where there is particular cause for 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, *characterise*, 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.

(Partly AM 29 of PR FdR 617323EN)

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 29
ARTICLE 16, PARAGRAPH 1

1. The holder of a marketing authorisation for an advanced therapy medicinal product shall establish and maintain a system ensuring that the individual product and its starting and raw materials, including all substances coming into contact with the tissues or cells it may contain, can be traced through the sourcing,

1. The holder of a marketing authorisation for an advanced therapy medicinal product shall establish and maintain a system ensuring that the individual product and its starting and raw materials, including all substances coming into contact with the tissues or cells it may contain, can be traced through the sourcing,

manufacturing, packaging, transport and delivery to the hospital, institution or private practice where the product is used.

manufacturing, packaging, **storing**, transport and delivery to the hospital, institution or private practice where the product is used.

Justification

Traceability during storing steps should also be ensured. Adding 'storing' establishes a coherent system of product traceability, and is in line with Directive 2004/23/EC.

Amendment 30
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 *paragraph 1* for a minimum of 30 years after **the expiry date of the product**, or longer if required by the Commission as a term of the marketing authorisation.

Justification

The proposed wording is unambiguous, whereas "placing on the market" might create difficulties in interpretation. The proposed wording provides a pragmatic solution for the marketing authorisation holder to know exactly from when traceability data must be kept.

Amendment 31
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 90% reduction **for SMEs and 65% 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.

(AM 32 of PR FdR 617323EN modified)

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 10% 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 65% should be applied to all companies irrespective of their size.

Amendment 32
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 **genes**, 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 **and within 60 days after receipt of the request.**

Justification

It should be clarified that the procedure foreseen in this Article may apply to all types of advanced therapy medicinal products, including products based on genes. The proposed amendment also 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 33
ARTICLE 21, PARAGRAPH 1, POINT (C)

(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 **physicians**;

(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.

(AM 34 of PR FdR 617323EN modified)

Justification

In order to cover all medical fields which the advanced therapies may relate to, more general medical expertise, i.e. physicians with clinical expertise, 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 34
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, pharmacovigilance, risk management and ethics.

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.

At least one member and one alternate of the Committee for Advanced Therapies shall have scientific expertise in medical devices.

(first part, AM 35 of PR FdR 617323EN)

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. In order to ensure an appropriate level of expertise, it would be important to include experts as members that have a background in the evaluation of medical devices, as many of the products concerned share many characteristics of medical devices.

Amendment 35
ARTICLE 22

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.

In addition to the requirements laid down in Article 63 of Regulation (EC) No 726/2004, members and alternates of the Committee for Advanced Therapies shall have no financial or other interests in the biotechnology sector and medical device sector. All indirect interests that could relate to these sectors shall be entered in the register referred to in Article 63(2) of Regulation (EC) No 726/2004.

2. All indirect interests that could relate to the pharmaceutical sector, medical device sector or biotechnology sector shall be entered in the register referred to in Article 63(2) of Regulation (EC) No 726/2004.

Justification

It should be clarified that an identical level of transparency as for existing Committees within the EMEA (pursuant to Article 63 of Regulation (EC) No 726/2004) applies for the new Committee for Advanced Therapies. It should also be clarified that interests in the biotechnology or medical device sector are forbidden.

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;

(AM 36 of PR FdR 617323EN)

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 qualification 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, on whether a product falls within the definition of an advanced therapy medicinal product;

(AM 37 of PR FdR 617323EN modified)

Justification

Having specific expertise in advanced therapy medicinal products, the Committee for Advanced Therapies should have a prominent role in the classification task of whether a product is or is not an advanced therapy medicinal product.

Amendment 38
ARTICLE 23, POINT (E A) (new)

(ea) to contribute to the scientific advice procedures referred to in Article 17 of this Regulation and in Article 57(1)(n) of Regulation (EC) No 726/2004;

Justification

The Committee on Advanced Therapies should consist of the best possible experts from Member States. Their expertise should therefore be drawn upon for any advice issued regarding an advanced therapy medicinal product.

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, **after consultation of the Agency and** in accordance with procedure referred to in **Article 26(2a)**, amend **Annexes II to IV** in order to adapt them to scientific and technical evolution.

(AM 39 of PR FdR 617323EN modified)

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 co-decision, fully involving the European Parliament. The regulation should set out very clearly that the Commission must involve the EMEA, through the Committee for Advanced Therapies, whenever adaptation of the Annexes to technical progress is required. The adaptation of Annexes II to IV should fall under the new regulatory procedure with scrutiny.

Amendment 40
ARTICLE 25, TITLE

Reporting

Report and review

(AM 97 of AM FdR 620607EN)

Justification

Scientific advances may make additional novel therapies possible which are neither gene therapy, nor cell therapy nor tissue engineering. It would be in the interests of patients for these to be included at some future date in order to allow European authorisation of the resulting products.

Amendment 41
ARTICLE 25, PARAGRAPH 1 A (new)

In this report, the Commission shall assess the impact of technical progress on the application of this Regulation. It shall also, if necessary, make a legislative proposal to review its scope and to include novel therapies which involve neither gene therapy, cell therapy or tissue engineering.

(AM 98 of AM FdR 620607EN)

Justification

Scientific advances may make additional novel therapies possible which are neither gene therapy, cell therapy or tissue engineering. It would be in the interests of patients for these to be included at some future date, in order to allow European authorisation of the resulting products.

Amendment 42
ARTICLE 26, PARAGRAPH 2 A (new)

2a. Where reference is made to this paragraph, Articles 5a(1) to (4) and 7 of Decision 1999/468/EC shall apply, having regard to the provisions of Article 8 thereof.

Justification

This amendment is in line with the new comitology provisions (regulatory procedure with scrutiny).

Amendment 43
ARTICLE 27, POINT -1 (new)
Article 13, paragraph 1 (Regulation (EC) No 726/2004)

(-1) In Article 13, the first sentence of paragraph 1 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."

(AM 40 of PR FdR 617323EN)

Justification

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

Amendment 44
ARTICLE 27, POINT 2 A (new)
Annex, point 3, subparagraph 2 (Regulation (EC) No 726/2004)

(2a) In the Annex, the second subparagraph of point 3 is replaced by the following:

"After 20 May 2008, the Commission, having consulted the Agency, may present any appropriate proposal modifying this point and the European Parliament and the Council shall take a decision thereon in accordance with the Treaty."

(AM 103 of AM FdR 620607EN)

Justification

This part of Regulation 726/2004 determines when a Community authorisation must be obtained. Under the present proposal, it may be that certain AT products will not require Community authorisation either because they do not involve one of the processes referred to in point 1 of the Annex to Reg. 726/2004, or because they are not used for the treatment of any of the diseases referred to in point 3 of that Annex. Currently, the list of diseases in point 3 can be extended by the Council on a Commission proposal, without recourse to the EP. Decisions determining the scope of legislative acts must be dealt with by co-decision.

Amendment 45

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 product as defined in Article 2 of Regulation (EC) No **/** on advanced therapy medicinal products."

(AM 41 of PR FdR 617323EN)

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 46

ARTICLE 28, POINT 1

Article 3, point 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 **under the exclusive professional responsibility of a medical practitioner or for clinical research.**

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

(AM 42 of PR FdR 617323EN, end of 1st part mod.)

Justification

For the justification concerning hospitals, see amendment to Recital 5. Exceptions given in Directive 2001/83/EC (Article 3, points 1 and 2) allow pharmacies to prepare medicinal products in accordance with a medical prescription without complying with medicinal product legislation. This exception would also give the in-house pharmacies of hospitals the possibility of producing TEP using standardized methods and on a routine basis. Therefore this amendment is crucial to ensure that only one-off basis products are excluded from the scope of this Regulation.

Amendment 47
ARTICLE 28 A (new)

Article 28 a

Production for clinical trials

The Commission shall identify, in accordance with the procedure referred to in Article 5 of Decision 1999/468/EC, specific manufacturing requirements for investigational medicinal products, to be applied to the production of advanced therapy medicinal products for clinical trials performed in the same hospital where the production took place.

(AM 111 of AM FdR 620607EN)

Justification

No specific provision is foreseen in the Regulation as far as the production of advanced medicinal products to be used in clinical trials is concerned.

Amendment 48
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.

(AM 44 of PR FdR 617323EN)

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 products that have been safely treating patients up to now being removed from those patients during the transitional period, we suggest a period of 4 years.

Amendment 49

ARTICLE 29, PARAGRAPH 1 A (new)

1a. Tissue engineered products which were legally on the Community market in accordance with national or Community legislation at the date of application specified in the second paragraph of Article 30 must comply with this Regulation no later than 4 years after that date.

(AM 116 of AM FdR 620607EN modified)

Justification

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

Amendment 50

ARTICLE 29, PARAGRAPH 2

2. By way of derogation from Article 3(1) of Regulation (EC) No 297/95, no fee shall

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*.

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*.

(AM 46 of PR FdR 617323EN)

Justification

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

Amendment 51

ARTICLE 30, PARAGRAPHS 2 A AND 2 B (new)

For tissue engineered products this Regulation shall apply as of the entry into force of all the requirements referred to in Articles 4, 5 and 8.

The implementing measures envisaged in Articles 4, 5 and 8 shall be adopted as soon as possible and, in any event, no later than 9 months after the entry into force of this Regulation.

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 9 months time limit for the Commission to adopt the necessary measures.

EXPLANATORY STATEMENT

Rapid development in the fields of biology, biotechnology and medicine and attempts to achieve sustainable growth of health protection within the European Union lead to the development of new treatments and highly innovative medicinal products.

In this context, products which involve intervention in gene therapy, cell therapy and tissue engineering are of great importance, having a high potential in the treatment of diseases such as cancer, cartilage or bone diseases or injuries, repair of genetic disorders, repair of post heart attack damage as well as skin replacement in burn victims.

Nowadays, the legal framework at the Community level related to these advanced therapies remains fragmented, as only gene therapy and somatic cell therapy medicinal products benefit from a legal definition. Tissue engineered products remain unregulated, which leads to the fragmentation of the market and which does not allow patients to have easy access to the necessary treatments.

The current proposal introduces a single harmonising regulatory framework for the evaluation, authorisation and supervision of advanced therapy medicinal products: marketing authorisation requirements and procedure, post-authorisation vigilance and traceability. The proposed Regulation should be seen within the wider perspective of the existing legislation in this field, such as Directive 2001/83/EC on medicinal products, Regulation (EC) No 726/2004 on the European Medicines Agency (EMA) or Directive 2004/23/EC laying down quality and safety standards of human tissues and cells.

The proposal introduces a European centralised marketing authorisation procedure and creates a new Committee for Advanced Therapies within EMA, composed of highly qualified and experienced experts in all fields related to these products. In addition, the proposed Regulation sets up a strengthened requirement for the post-authorisation monitoring system and for traceability of the patient and foresees specific technical requirements for tissue engineered products. Moreover, additional specific incentives for the applicants and especially for SMEs are introduced, in order to promote competitiveness within the EU.

The rapporteur welcomes this proposal for a Regulation and the introduction of a new coherent legal framework for these innovative, specific and complex medicinal products. He agrees on the necessity of a centralised authorisation procedure in order to facilitate the market access and to ensure the free movement of advanced therapy medicinal products within the Community. Priority should be given to the demonstration of quality, safety and efficacy of these products in order to ensure a high level of health protection within the EU. The highest possible level of legal certainty should be guaranteed while allowing sufficient flexibility at the technical level.

Nevertheless, the rapporteur would like to underline the importance of clear definitions in order to avoid a legal uncertainty or grey zones, particularly as regards the definition of combined advanced therapy medicinal products and their evaluation. It should also be made crystal clear that products prepared in a hospital, on a one-off basis for an individual patient, should not comply with the centralised authorisation procedure. Moreover, products applied in the production of advanced therapy medicinal products for clinical trials and products for clinical research should not be forgotten.

In addition, the rapporteur would like to stress the important role of the Committee for Advanced Therapies within EMEA. This highly qualified body should play a vital role in the process of scientific evaluation of advanced therapy medicinal products and its internal decision procedure should be clearly defined.

Moreover, advanced therapy medicinal products could raise serious ethical concerns, as they are likely to contain human cells or tissues. The Commission's proposal should not have an impact on the national legislation prohibiting or restricting the use of certain type of human or animal cells (such as embryonic stem cells) or the sale, supply or use of medicinal products derived from these cells. According to Parliament's legal service, the current drafting of this provision raises serious concerns in the light of the legal basis of the proposal. The rapporteur has asked for a written legal opinion concerning this provision and is still considering the most appropriate formulation for the subsidiarity principle in the Article 28(2). In the meantime, he does not propose any amendment to this article in the draft report.

The development in biotechnology and biomedicine should be carried out while fully respecting fundamental rights. Rights such as the right to human dignity or to the integrity of the person laid down in the Oviedo Convention as well as in the Charter of fundamental rights should be entirely respected. Therefore, in his first draft report the rapporteur underlined that authorisation procedure should be carried out in accordance with the principle of non commercialisation of the human body or its parts as such. Moreover, the rapporteur proposed amendments in order to exclude the European marketing authorization under this regulation for products modifying the germ line genetic identity of human beings and for products derived from human-animal hybrids or chimeras (but allowing the transplantation of somatic animal cells or tissues to the human body for therapeutic purposes, i.e. Xenotransplantation).

These amendments were adopted by the Committee on Legal Affairs. Even though these amendments were adopted by the majority in ENVI committee, the draft report as amended was rejected in the final vote. The rapporteur is still convinced that the approach chosen by the JURI Committee is the most appropriate. Nevertheless, his intention is to find the broadest possible consensus in this area. Therefore, he does not propose any of these amendments in his new draft report and is ready to work on compromises with his colleagues.