



COMMISSION OF THE EUROPEAN COMMUNITIES

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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**

{SEC(2005) 1444}

(presented by the Commission)

## EXPLANATORY MEMORANDUM

### 1. INTRODUCTION AND BACKGROUND

#### *The current picture*

The advancement of science in the fields of biology, biotechnology and medicine, has fuelled the development of promising gene- and cell-based approaches for the prevention and treatment of diseases or dysfunctions of the human body. A number of gene therapy and somatic cell therapy products are already being tested at clinical level for the treatment of inherited diseases, cancer, diabetes, Parkinson's disease and other neurodegenerative disorders.

In addition, a new biotechnology area has emerged: tissue engineering, which combines various aspects of medicine, cell and molecular biology, materials science and engineering, for the purpose of regenerating, repairing or replacing human tissues. Current applications of this nascent field of “regenerative medicine” include treatment for skin, cartilage and bone diseases or injuries. More complex products are already in development, and could reach the Community market in a near future<sup>1</sup>.

#### *Advanced therapies: a coherent ensemble*

These three kinds of **advanced therapies** (gene therapy, somatic cell therapy, and tissue engineering) are expected to have a major impact on public health, by improving the quality of life of patients and changing medical practice significantly. Moreover, they constitute a coherent ensemble insofar as they share several key scientific, regulatory and economic features:

- They are based on complex, highly innovative manufacturing processes. The specificity of the product precisely lies *in* the process.
- Regulatory and scientific expertise for the evaluation of advanced therapies is scarce: pooling of that expertise at Community level is therefore essential to ensure a high level of public health protection.
- Traceability from the donor to the patient, long-term patient follow-up and a thorough post-authorisation risk management strategy are crucial aspects to be addressed when evaluating advanced therapies.
- Advanced therapy products are usually developed by innovative small and medium-sized enterprises, highly-specialised divisions of larger operators in the Life Science sector (biotechnology, medical devices and pharmaceuticals), hospitals or tissue banks. They are subject to rapid and often radical innovation.

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<sup>1</sup> See Bock, A.K., Ibarreta, D., Rodriguez-Cerezo, E.: *Human tissue-engineered products - Today's markets and future prospects*, Joint Research Centre - Institute for Prospective Technological Studies (European Commission), EUR 21000 EN, October 2003.

## *The current regulatory gap and its implications on public health*

Despite these common elements, the regulatory picture for advanced therapies remains incomplete. In particular, while products intended for gene and somatic cell therapy have been classified as medicinal products and regulated as such in the Community<sup>2</sup>, tissue-engineered products currently lie outside of any Community legislative framework. This leads to divergent, national approaches as to their legal classification and authorisation, thereby impairing the free movement of tissue engineered products in the Community, and hindering patients' access to these innovative therapies.

There is therefore a need to bridge the regulatory gap by addressing all advanced therapies - including in particular tissue engineering- within a single, integrated framework, fully taking into account their scientific and technical characteristics as well as the specificities of the economic operators concerned.

## **2. JUSTIFICATION**

### **2.1. Objectives**

The overall policy objective is to improve patients' safe access to advanced therapies by increasing the research, development and authorisation of gene therapy, somatic cell therapy, and tissue engineered products.

More specifically, the main objectives are:

- To guarantee a **high level of health protection** for European patients treated with advanced therapy products;
- To **harmonise market access** and to improve the functioning of the internal market by establishing a tailored and comprehensive regulatory framework for the authorisation, supervision and post-authorisation vigilance of advanced therapy products;
- To **foster the competitiveness** of European undertakings operating in this field;
- To **provide overall legal certainty**, while allowing for **sufficient flexibility at technical level**, in order to keep the pace with the evolution of science and technology.

### **2.2. Scope, legal basis and procedure**

#### *Scope*

The proposal covers all advanced therapy products (gene therapy medicinal products, somatic cell therapy medicinal products, and tissue engineered products) falling within the global scope of the pharmaceutical legislation (Article 2(1) of Directive 2001/83/EC<sup>3</sup>), i.e. intended

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<sup>2</sup> Part IV of Annex I to Directive 2001/83/EC, as amended by Directive 2003/63/EC, OJ L159, 27.6.2003, p.46. See also 'Commission Communication on the Community marketing authorisation procedures for medicinal products', 98/C 229/03, OJ C 229/4, 22.7.1998.

<sup>3</sup> OJ L 311, 28.11.2001, p. 67

to be placed on the market in Member States and either prepared industrially or manufactured by a method involving an industrial process.

### *Legal basis and procedure*

The proposal is based on Article 95 of the EC Treaty. Article 95, which prescribes the co-decision procedure described in Article 251, is the legal basis for achieving the aims set out in Article 14 of the Treaty, which includes the free movement of goods (Article 14(2)), in this case advanced therapy medicinal products for human use.

While taking account of the fact that any regulation on the manufacture and distribution of medicinal products must be fundamentally aimed at safeguarding public health, this aim must be achieved by means that do not impede the free movement of medicinal products within the Community. Since the Amsterdam Treaty came into force, all legislative provisions adopted by the European Parliament and the Council in this field have been adopted on the basis of that Article, since the differences between the national legislative, regulatory and administrative provisions on medicinal products tend to hinder intra-Community trade and therefore directly affect the operation of the internal market. Action to promote the development and authorisation of advanced therapy medicinal products is hence justified at a European level, with a view to preventing or eliminating these obstacles.

Given the particularities of advanced therapy products, it is essential to provide a robust and comprehensive regulatory framework, which is directly applicable in all Member States. A Regulation is therefore considered as the most appropriate legal instrument. It should indeed ensure uniform and timely application of the provisions, for the benefit of all actors, including patients, industry and other stakeholders involved in this emerging sector. In addition, the 'centralised' marketing authorisation procedure is also laid down in a Regulation (Regulation (EC) No 726/2004)<sup>4</sup>.

### **2.3. Subsidiarity and proportionality**

The proposal builds on the experience gained with the existing regulatory framework for medicines in Europe. On the basis of the available evidence, it is concluded that it is unlikely that the current public health issue regarding advanced therapy medicinal products, in particular tissue engineered products, will be resolved in the EU until a specific legislative system is put in place.

Community action allows the best possible use of the instruments set up in Community legislation (in particular in the pharmaceutical sector) to complete the internal market. In addition, authorisation and availability of innovative therapies is a Europe-wide issue. Nevertheless, Member States will have a crucial role in the fulfilment of the proposal's objectives.

The proposed rules aim at harmonising an area in which application of existing Community legislation and additional national measures have proven insufficient. However, the proposal will create additional regulatory requirements only when this appears necessary to achieve the intended objectives. In this respect, the scope of the proposal has been carefully designed and discussed with all stakeholders, in order to avoid imposing an unnecessary regulatory burden

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<sup>4</sup> OJ L 136, 30.4.2004, p. 1

on certain economic operators (*e.g.* hospitals, universities and research community). The proposal does not go beyond what is necessary to achieve the objectives pursued.

## 2.4. Legislative and administrative simplification

The proposed approach is based on a single, integrated regulatory framework for all advanced therapy products. The aim of this strategy is to avoid any re-drafting of already-existing and applicable concepts, while focusing exclusively on the key regulatory and technical specificities of the field.

The approach is based on 3 levels:

- (1) A Regulation on Advanced Therapy Medicinal Products, which lays down tailored regulatory principles for the evaluation and authorisation of these products: marketing authorisation procedure, post-authorisation vigilance, traceability, etc. Such Regulation builds on already-existing legislation, in particular:
  - Directive 2004/23/EC, which lays down quality and safety standards in respect of human tissues and cells<sup>5</sup>. It is important to bear in mind that these standards would apply to the donation, procurement and testing of human tissues and cells contained in advanced therapy products;
  - Regulation (EC) No 726/2004, which establishes the so-called ‘centralised procedure’ and the role/structure of the European Medicines Agency (EMA, hereinafter “the Agency”);
  - Directive 2001/83/EC on medicinal products;
  - Council Directive 93/42/EEC concerning medical devices<sup>6</sup> and Council Directive 90/385/EEC on active implantable medical devices<sup>7</sup>.
- (2) Technical requirements. It is well acknowledged that advanced therapy products are neither medical devices nor conventional medicines: therefore, the technical requirements necessary to demonstrate their quality, safety and efficacy (*e.g.* the type of pre-clinical and clinical data required) will be highly specific, and should depend on the level of risks associated with these products. As regards gene and somatic cell therapy products, those high-level requirements are already laid down in Annex I to Directive 2001/83/EC<sup>8</sup> (which is amendable by ‘comitology’) and further complemented by guidelines<sup>9</sup>. In order to provide for the same level of flexibility, it is proposed to follow a similar approach regarding tissue engineered products, *i.e.* to lay down the main technical requirements that are specific to these products in Annex I to Directive 2001/83/EC, and to further complement them with guidelines.
- (3) Detailed guidelines. As for gene and somatic cell therapy products, it is proposed to establish detailed technical guidance for tissue engineered products through

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<sup>5</sup> OJ L 102, 7.4.2004, p. 48

<sup>6</sup> OJ L 169, 12.7.1993, p. 1

<sup>7</sup> OJ L 189, 20.7.1990, p. 17

<sup>8</sup> Annex I to Directive 2001/83/EC, as amended by Directive 2003/63/EC, OJ L 159, 27.6.2003, p. 46.

<sup>9</sup> See <http://www.emea.eu.int/hums/human/itf/itfguide.htm>

guidelines. The fact that expertise is still scarce in this fast-growing, fast-evolving area highlights the importance of extensive and thorough consultation with all interested parties for the drafting of these guidelines.

It is important to note that the current, existing requirements for gene therapy medicinal products and somatic cell therapy medicinal products are not affected by the proposal. The only main change related to these products concerns the introduction of a new Committee (Committee for Advanced Therapies).

## **2.5. Consistency with other Community policies**

As described in Section 2.4, the proposed Regulation is consistent with Community policy in the field of public health (*e.g.* quality and safety of human tissues and cells) and medical devices. Consistency will also be sought with other activities related to health and consumer protection, as well as in the area of research and development.

## **2.6. Outside consultation**

All interested parties (patients associations, industry, hospitals, research community...) have been widely consulted on this proposal, through various means: internet-based consultation, workshops, bilateral meetings, interviews. Details on the consultations conducted by the Commission are included in the Impact Assessment attached to the proposal.

## **2.7. Evaluation of the proposal: Impact Assessment**

The proposed Regulation has been the subject of a Commission Impact Assessment, which is attached to the proposal.

# **3. PRESENTATION: KEY ELEMENTS OF THE PROPOSAL**

## **3.1. Definitions and Scope**

### *Definitions*

Advanced therapy products are defined as medicinal products being either:

- gene therapy medicinal products, as defined in Annex I to Directive 2001/83/EC; or
- somatic cell therapy medicinal products, as defined in Annex I to Directive 2001/83/EC; or
- tissue engineered products, as defined in the proposal.

Products which do not qualify as advanced therapy medicinal products, even if based on or consisting of tissues and cells, will not be regulated under this framework.

It must be acknowledged that even the best possible definition of advanced therapy medicinal products may not fully eliminate the risk of grey areas, given the highly innovative and rapidly evolving nature of the advanced therapies sector. To address this, the proposal foresees the possibility for applicants to request a scientific recommendation from the EMEA on the classification of any product based on cells or tissues, with a view to resolving borderline issues.

Within the Community legislation on pharmaceuticals, products intended for gene therapy and somatic cell therapy are already classified as biological medicinal products. Tissue engineered products are also considered from a legal viewpoint as medicinal products for at least one of the following reasons:

- They are presented as having properties for treating or preventing disease in human beings;
- They are used in or administered to human beings with a view to restoring, correcting or modifying physiological functions by exerting a pharmacological, immunological or metabolic action;
- In accordance with the jurisprudence of the European Court of Justice (ECJ) on the matter, they are capable of having a significant effect on the actual functioning of the body<sup>10</sup>.

Furthermore, the existence of health risks is traditionally one of the criteria employed by the ECJ for classifying a product as medicinal<sup>11</sup>. It follows from the aim of health protection pursued by the Community pharmaceutical legislation that products presenting potential health risks (as is clear for advanced therapy medicinal products) should be covered by the rigorous requirements of that legislation in case of doubt as to their classification<sup>12</sup>.

However, this does not mean that advanced therapy medicinal products will be subject to the same technical requirements as ‘conventional’ medicines. On the contrary, the type and amount of pre-clinical/clinical data necessary to demonstrate their quality, safety and efficacy should be highly specific, fully taking into account their biological, functional and structural characteristics.

#### *Scope*

The proposal addresses all advanced therapy medicinal products falling within the general scope of the Community legislation on medicinal products<sup>13</sup>, i.e. “*intended to be placed on the market in Member States and either prepared industrially or manufactured by a method involving an industrial process*”. Products which are both prepared in full and used in a single hospital, in accordance with a medical prescription for an individual patient, are excluded from the scope of the proposal. Detailed examples related to this aspect of the proposal are provided in the Impact Assessment.

### **3.2. Marketing Authorisation Procedure**

#### *General principles*

Experience gained in the area of modern biotechnology, where scientific expertise is often limited, highlights the necessity to establish centralised procedures for the authorisation of biotechnology-derived therapeutic products. This pooling of expertise from all Member States

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<sup>10</sup> See cases 227/82, Van Bennekom [1983] ECR 3883 ; C-369/88, Delattre [1991] ECR I-1487 ; C-60/89, Monteil and Samanni [1991] ECR I-1547 ; C-112/89, Upjohn [1991] ECR I-1703 ; C-290/90, Commission v Federal Republic of Germany [1992] ECR I-3317 ; C-219/91, Ter Voort [1992] ECR I-5485.

<sup>11</sup> Monteil and Samanni, paragraph 29; Delattre, paragraph 35; Commission v. Federal Republic of Germany, paragraph 17.

<sup>12</sup> See also Article 2(2) of Directive 2001/83/EC, as amended by Directive 2004/27/EC.

<sup>13</sup> Article 2(1) of Directive 2001/83/EC, as amended by Directive 2004/27/EC.

enables to guarantee a high level of scientific evaluation across the European Union, and thus to preserve the confidence of patients and medical practitioners in their evaluation. This is all the more important for advanced therapy medicinal products, which often result from highly innovative, not-yet-well-established processes and technologies.

The principle of a compulsory Community marketing authorisation is already established for gene therapy medicinal products and somatic cell therapy medicinal products resulting from any biotechnology process referred to in the Annex to Regulation (EC) No 726/2004. It is proposed to apply the same principle of a compulsory, ‘centralised’ Community marketing authorisation to all advanced therapy medicinal products, including tissue engineered products, in order to ensure the effective operation of the internal market in the biotechnology sector, and to enable undertakings to benefit from direct access to the Community market. As for other ‘centrally-authorized’ products, the scientific evaluation would be carried out by Member States experts, within the network coordinated by the EMEA.

#### *Committee for Advanced Therapies (CAT)*

Within the EMEA, the Committee for Medicinal Products for Human Use (CHMP) holds the responsibility for drawing up the Agency’s opinion on any scientific matter concerning the evaluation of medicinal products for human use, and for ensuring consistency in the risk-benefit assessment of all categories of medicinal products.

Nevertheless, the assessment of advanced therapy medicinal products often requires very specific expertise, which goes beyond the traditional pharmaceutical field and covers borderline areas related to other sectors, such as biotechnology or medical devices. For this reason, it is proposed to create, within the EMEA, a Committee for Advanced Therapies (CAT), which the CHMP should consult on the assessment of data related to advanced therapy medicinal products, whilst retaining responsibility for the final scientific opinions issued.

Thus, the main task of the CAT will be to advise scientifically on any data related to advanced therapy medicinal products.

The CAT will work in close cooperation with, and under the general supervision of, the CHMP. A clearly-defined procedure, with strict deadlines, is established in order to avoid any delays in the marketing authorisation of these products. The composition of this new Committee should reflect the multidisciplinary nature of the field and ensure appropriate coverage of the scientific areas relevant to advanced therapies. Patient associations and medical surgeons with scientific experience of advanced therapy medicinal products should also be represented.

#### *Evaluation procedure*

The CHMP will consult the CAT for any evaluation of advanced therapy medicinal products. A number of mechanisms are foreseen in the proposal to avoid divergent opinions between the CHMP and the CAT. The CAT may also be consulted for other medicinal products which, although not classified as advanced therapy medicinal products, may require specific, CAT-related expertise for the evaluation of their quality, safety or efficacy.



### **3.3. Marketing Authorisation Requirements**

#### *General principles*

Broadly speaking, advanced therapy medicinal products are biotechnology-derived products. They should therefore be subject to the same overarching regulatory principles as other types of biotechnology-derived medicines, such as products developed by means of recombinant DNA technology.

#### *Technical requirements*

‘Conventional pharmaceutical’ technical requirements are not directly relevant for advanced therapy medicinal products, due to their specific structural, functional and biological properties. Special considerations related to the viability or proliferation of cells, to the clinical circumstances where the products are used, or to their particular mode of action, may be required.

In respect of gene and cell therapy, the type and amount of quality-related, pre-clinical and clinical data necessary to demonstrate the quality, safety and efficacy of the products are already laid down in Annex I to Directive 2001/83/EC and through EMEA guidelines.

It is proposed to follow the same approach for tissue engineered products: to amend Annex I to Directive 2001/83/EC in order to lay down technical requirements that are specific to these particular products, and to further complement those requirements with guidelines, drawn up in consultation with all interested parties.

#### *Other requirements*

Directive 2004/23/EC lays down standards of quality and safety for the donation, procurement, testing, processing, preservation, storage and distribution of human tissues and cells. As for human tissues and cells contained in advanced therapy medicinal products, Directive 2004/23/EC should apply only as far as donation, procurement and testing are concerned, since the further aspects are regulated by the proposed Regulation.

Advanced therapy medicinal products may also include, as an integral part of the product, medical devices or active implantable medical devices, as defined in Directive 93/42/EEC and Directive 90/385/EEC, respectively. In that case, the ‘device’ part should meet the essential requirements laid down in those Directives. The EMEA, through the CAT, would provide a ‘one-stop shop’ system, by evaluating all aspects (including ‘device’ aspects) of the product. However, if the device part has already been evaluated and certified by a notified body, this certification should be fully taken into account by the CAT for the final evaluation of the concerned product.

### **3.4. Post-authorisation issues**

By their very nature, advanced therapy medicinal products can stay in the human body for a longer time than ‘conventional’ medicines. Thus, long-term patient follow-up and post-authorisation monitoring are crucial aspects of these products. It is hence essential to ensure, where justified on public health grounds, that the applicant puts in place a suitable risk management system, in order to address these critical issues.

Likewise, a system allowing complete traceability of the patient, as well as the product and its starting materials, is essential to monitor the safety of advanced therapy medicinal products in a long-term perspective, and should therefore be required. This traceability system should be compatible with the requirements laid down in Directive 2004/23/EC as regards the donation, procurement and testing of human tissues and cells, including the aspects related to data protection, confidentiality, and anonymity of both donor and recipient.

### **3.5. Ethical aspects**

#### *General principles*

The proposed Regulation respects fundamental human rights and observes the principles reflected in the Charter of Fundamental Rights of the European Union<sup>14</sup>. It also takes into account, as appropriate, 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 ('Oviedo' Convention<sup>15</sup>).

The issue of embryonic stem cells was extensively debated during the adoption of the Directive on the quality and safety of human tissues and cells (Directive 2004/23/EC). In this context, the legislators have recognised that there is, to date, no consensus among Member States upon which harmonised decisions at EU level could be taken on the use or prohibition of embryonic stem cells. Thus, regulating such use or prohibition should remain a national responsibility. If, however, any particular use of these cells is authorised in a given Member State, it should be ensured that all provisions necessary to protect public health and guarantee respect for fundamental rights are effectively applied, in a harmonised way throughout the Community<sup>16</sup>.

It is suggested to follow the same logic in this proposal. The proposed Regulation does not interfere with national legislation prohibiting or restricting the use of any specific type of human or animal cells, or the sale, supply or use of medicinal products based on such cells. Explicit provisions have been introduced in the proposal to clarify this point.

#### *Voluntary and unpaid donation*

As outlined in Directive 2004/23/EC, human tissue- and cell- based products should be founded on the philosophy of voluntary and unpaid donation, anonymity of both donor and recipient, altruism of the donor and solidarity between donor and recipient. Voluntary and unpaid tissue and cell donations are a factor which may contribute to high safety standards for tissues and cells, and hence to the protection of human health.

### **3.6. Competitiveness aspects**

The fact that advanced therapy medicinal products fall under the overall regulatory framework for medicinal products implies that all already-existing incentives and competitiveness-related provisions of this framework directly apply to these products. This includes:

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<sup>14</sup> OJ C 364, 18.12.2000, p. 1.

<sup>15</sup> <http://conventions.coe.int/treaty/en/treaties/html/164.htm>

<sup>16</sup> Recital (12) and Article 4(3) of Directive 2004/23/EC.

- Direct and harmonised access to the Community market through a Community marketing authorisation, without prejudice to national prohibitions as referred to in section 3.5;
- A harmonised data protection period (the so-called ‘8+2+1’ rule)<sup>17</sup>;
- The possibility to be designated as an orphan medicinal product<sup>18</sup>;
- The possibility of an accelerated assessment procedure<sup>19</sup>;
- The option to get conditional marketing authorisations or marketing authorisations in exceptional circumstances<sup>20</sup>;
- Specific financial incentives and administrative assistance in respect of small and medium-sized enterprises (SMEs)<sup>21</sup>.

Besides, the proposal foresees additional, specific incentives:

- a 90% fee reduction for the provision of scientific advice by the EMEA in respect of advanced therapies, regardless of the economic size of the applicant;
- A system of early evaluation and certification of quality and non-clinical safety data by the Agency, independently of any marketing authorisation application, for SMEs developing advanced therapy medicinal products. This system is designed to help SMEs which focus on the early development aspects, but do not conduct the subsequent clinical trials themselves. The certification of ‘early-development’ data by the Agency should provide an important selling argument to those companies who wish to license out their technology to bigger undertakings.

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<sup>17</sup> Article 14(11) of Regulation (EC) No 726/2004.

<sup>18</sup> Regulation (EC) No 141/2000, OJ L 18, 22/1/2000, p. 1

<sup>19</sup> Article 14(9) of Regulation (EC) No 726/2004.

<sup>20</sup> Article 14(7) and 14(8) of Regulation (EC) No 726/2004.

<sup>21</sup> Article 70(2) of 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 and Regulation (EC) No 726/2004**

**(Text with EEA relevance)**

THE EUROPEAN PARLIAMENT AND THE COUNCIL OF THE EUROPEAN UNION,

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

Having regard to the proposal from the Commission<sup>22</sup>,

Having regard to the opinion of the European Economic and Social Committee<sup>23</sup>,

Having regard to the opinion of the Committee of the Regions<sup>24</sup>,

Acting in accordance with the procedure laid down in Article 251 of the Treaty<sup>25</sup>,

Whereas:

- (1) New scientific progress in cellular and molecular biotechnology has led to the development of advanced therapies, such as gene therapy, somatic cell therapy, and tissue-engineering. This nascent field of biomedicine offers new opportunities for the treatment of diseases and dysfunctions of the human body.
- (2) Insofar as these advanced therapy products are presented as having properties for treating or preventing diseases in human beings, or that they may be used in or administered to human beings with a view to restoring, correcting or modifying physiological functions by exerting a pharmacological, immunological or metabolic action, they are biological medicinal products within the meaning of Article 1(2) and Annex I to Directive 2001/83/EC of the European Parliament and of the Council of 6 November 2001 on the Community code relating to medicinal products for human use<sup>26</sup>. Thus, the essential aim of any rules governing their production, distribution and use must be to safeguard public health.

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<sup>22</sup> OJ C , , p. .

<sup>23</sup> OJ C , , p. .

<sup>24</sup> OJ C , , p. .

<sup>25</sup> OJ C , , p. .

<sup>26</sup> OJ L 311, 28.11.2001, p. 67. Directive as last amended by Directive 2004/27/EC (OJ L 136, 30.4.2004, p. 34).

- (3) For reasons of clarity, complex therapeutic products need precise legal definitions. Gene therapy medicinal products and somatic cell therapy medicinal products have been defined in Annex I to Directive 2001/83/EC, but a legal definition of tissue engineered products remains to be laid down.
- (4) Because of the novelty, complexity and technical specificity of advanced therapy medicinal products, specially tailored and harmonised rules are needed to ensure the free movement of those products within the Community, and the effective operation of the internal market in the biotechnology sector.
- (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.
- (6) The regulation of advanced therapy medicinal products at Community level should not interfere with decisions made by Member States on whether to allow the use of any specific type of human cells, such as embryonic stem cells, or animal cells. It should also not affect the application of national legislation prohibiting or restricting the sale, supply or use of medicinal products containing, consisting of or derived from these cells.
- (7) This Regulation respects the fundamental rights and observes the principles reflected in the Charter of Fundamental Rights of the European Union<sup>27</sup> 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.
- (8) All other modern biotechnology medicinal products currently regulated at Community level are already subject to a centralised authorisation procedure, involving a single scientific evaluation of the quality, safety and efficacy of the product, which is carried out to the highest possible standard by the European Medicines Agency (hereinafter “the Agency”). This procedure should also be compulsory for advanced therapy medicinal products in order to overcome the scarcity of Community expertise, ensure a high level of scientific evaluation of these medicinal products in the Community, preserve the confidence of patients and medical professions in the evaluation, and facilitate Community market access for these innovative technologies.
- (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

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<sup>27</sup> OJ C 364, 18.12.2000, p. 1.

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.

- (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.
- (11) To ensure scientific consistency and the efficiency of the system, the Agency should ensure the coordination between the Committee for Advanced Therapies and other Committees, advisory groups and working parties of the Agency, notably the Committee for Medicinal Products for Human Use, the Committee on Orphan Medicinal Products, and the Scientific Advice Working Party.
- (12) Advanced therapy medicinal products should be subject to the same regulatory principles as other types of biotechnology medicinal products. However, technical requirements, in particular the type and amount of quality, pre-clinical and clinical data necessary to demonstrate the quality, safety and efficacy of the product, may be highly specific. While those requirements are already laid down in Annex I to Directive 2001/83/EC for gene therapy medicinal products and somatic cell therapy medicinal products, they need to be established for tissue engineered products. This should be done through a procedure that provides for sufficient flexibility, so as to easily accommodate the rapid evolution of science and technology.
- (13) Directive 2004/23/EC of the European Parliament and of the Council of 31 March 2004<sup>28</sup> lays down standards of quality and safety for the donation, procurement, testing, processing, preservation, storage and distribution of human tissues and cells. The proposed Regulation does not derogate from the basic principles laid down in this Directive, but supplements them with additional requirements where appropriate. Where an advanced therapy medicinal product contains human cells or tissues, Directive 2004/23/EC should apply only as far as donation, procurement and testing are concerned, since the further aspects are covered by this Regulation.
- (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.
- (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

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<sup>28</sup> OJ L 102, 7.4.2004, p. 48.

of clinical trials on medicinal products for human use<sup>29</sup>. 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<sup>30</sup>, in order to fully take into account the specific technical characteristics of advanced therapy medicinal products.

- (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<sup>31</sup>. Furthermore, guidelines specific to advanced therapy medicinal products should be drawn up, so as to properly reflect the particular nature of their manufacturing process.
- (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<sup>32</sup> 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<sup>33</sup>, respectively, in order to ensure an appropriate level of quality and safety.
- (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.
- (19) Long-term patient follow-up and pharmacovigilance are crucial aspects of advanced therapy medicinal products. Where justified on public health grounds, the holder of the marketing authorisation should therefore be required to put in place a suitable risk management system to address those aspects.
- (20) A system allowing complete traceability of the patient as well as of the product and its starting materials is essential to monitor the safety of advanced therapy medicinal products. The establishment and maintenance of that system should be done in such a way as to ensure coherence and compatibility with traceability requirements laid down in Directive 2004/23/EC in respect of human tissues and cells, and in Directive 2002/98/EC of the European Parliament and of the Council of 27 January 2003 setting standards of quality and safety for the collection, testing, processing, storage and distribution of human blood and blood components and amending Directive 2001/83/EC<sup>34</sup>. The traceability system should also respect the provisions laid down in Directive 95/46/EC of the European Parliament and of the Council of 24 October 1995

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<sup>29</sup> OJ L 121, 1.5.2001, p. 34.

<sup>30</sup> OJ L 91, 9.4.2005, p. 13.

<sup>31</sup> OJ L 262, 14.10.2003, p. 22.

<sup>32</sup> OJ L 169, 12.7.1993, p. 1. Directive as last amended by European Parliament and Council Regulation (EC) No 1882/2003 (OJ L 284, 31.10.2003, p. 1).

<sup>33</sup> OJ L 189, 20.7.1990, p. 17. Directive as last amended by European Parliament and Council Regulation (EC) No 1882/2003 (OJ L 284, 31.10.2003, p. 1).

<sup>34</sup> OJ L 33, 8.2.2003, p. 30.

on the protection of individuals with regard to the processing of personal data and the free movement of such data<sup>35</sup>.

- (21) As science evolves very rapidly in this field, undertakings developing advanced therapy medicinal products should be enabled to request scientific advice from the Agency, including advice on post-authorisation activities. As an incentive, the fee for that scientific advice should be kept at a minimal level.
- (22) The Agency should be empowered to give scientific recommendations on whether a given product based on cells or tissues meets the scientific criteria which define advanced therapy medicinal products, in order to address, as early as possible, questions of borderline with other areas such as cosmetics or medical devices, which may arise as science develops.
- (23) Studies necessary to demonstrate the quality and non-clinical safety of advanced therapy medicinal products are often carried out by small and medium-sized enterprises. As an incentive to conduct those studies, a system of evaluation and certification of the resulting data by the Agency, independently of any marketing authorisation application, should be introduced. This system should also aim at facilitating the evaluation of any future marketing authorisation application based on the same data.
- (24) In order to take into account scientific and technical developments, the Commission should be empowered to adopt any necessary changes regarding the technical requirements for applications for marketing authorisation of advanced therapy medicinal products, the summary of product characteristics, labelling, and package leaflet.
- (25) Provisions should be laid down to report on the implementation of this Regulation after experience has been gained, with a particular attention to the different types of advanced therapy medicinal products authorised.
- (26) The opinions of the Scientific Committee for Medicinal Products and Medical Devices concerning tissue engineering and that of the European Group on Ethics in Science and New Technologies have been taken into account, as well as international experience in this field.
- (27) The measures necessary for the implementation of this Regulation should be adopted in accordance with Council Decision 1999/468/EC of 28 June 1999 laying down the procedures for the exercise of implementing powers conferred on the Commission<sup>36</sup>.
- (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 a European Medicines Agency<sup>37</sup> should therefore be amended accordingly,

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<sup>35</sup> OJ L 281, 23.11.1995, p. 31. Directive as amended by Regulation (EC) No 1882/2003 (OJ L 284, 31.10.2003, p. 1).

<sup>36</sup> OJ L 184, 17.7.1999, p. 23.

<sup>37</sup> OJ L 136, 30.4.2004, p. 1



HAVE ADOPTED THIS REGULATION:

## **CHAPTER 1 SUBJECT MATTER AND DEFINITIONS**

### *Article 1*

#### **Subject matter**

This Regulation lays down specific rules concerning the authorisation, supervision and pharmacovigilance of advanced therapy medicinal products.

### *Article 2*

#### **Definitions**

1. In addition to the definitions laid down in Article 1 of Directive 2001/83/EC and in Article 3, points (a) to (l) and (o) to (q) of Directive 2004/23/EC, the following definitions shall apply for the purposes of this Regulation:

- (a) advanced therapy medicinal product means any of the following medicinal products for human use:
  - a gene therapy medicinal product as defined in Part IV of Annex I to Directive 2001/83/EC;
  - a somatic cell therapy medicinal product as defined in Part IV of Annex I to Directive 2001/83/EC;
  - a tissue engineered product as defined in point (b);
- (b) tissue engineered product means a product that:
  - contains or consists of engineered cells or tissues; and
  - is presented as having properties for, or is used in or administered to human beings with a view to, regenerating, repairing or replacing a human tissue;

A tissue engineered product may contain cells or tissues of human or animal origin, or both. The cells or tissues may be viable or non-viable. It may also contain additional substances, such as cellular products, bio-molecules, bio-materials, chemical substances, scaffolds or matrices;

- (c) engineered cells or tissues means cells or tissues which fulfil at least one of the points listed in Annex I;

- (d) combined advanced therapy medicinal product means an advanced therapy medicinal product that fulfils the following conditions:
- it must incorporate, as an integral part of the product, one or more medical devices within the meaning of Article 1(2)(a) of Directive 93/42/EEC or one or more active implantable medical devices within the meaning of Article 1(2)(c) of Directive 90/385/EEC;
  - 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.
2. An advanced therapy medicinal product containing both autologous (emanating from the patient himself) and allogeneic (coming from another human being) cells or tissues is considered to be for allogeneic use.
3. A product which may fall within the definition of a “tissue engineered product” and within the definition of a “somatic cell therapy medicinal product” shall be considered as a tissue engineered product.

## **CHAPTER 2 MARKETING AUTHORISATION REQUIREMENTS**

### *Article 3*

#### **Donation, procurement and testing**

Where an advanced therapy medicinal product contains human cells or tissues, the donation, procurement and testing of those cells or tissues shall be made in accordance with the provisions laid down in Directive 2004/23/EC.

### *Article 4*

#### **Clinical Trials**

1. The rules set out in Articles 6(7), 9(4) and 9(6) of Directive 2001/20/EC in respect of gene therapy and somatic cell therapy medicinal products shall apply to tissue engineered products.
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.

## *Article 5*

### **Good Manufacturing Practice**

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

## *Article 6*

### **Issues specific to medical devices**

1. A medical device which forms part of a combined advanced therapy medicinal product shall meet the essential requirements laid down in Annex I to Directive 93/42/EEC.
2. An active implantable medical device which forms part of a combined advanced therapy medicinal product shall meet the essential requirements laid down in Annex 1 to Directive 90/385/EEC.

## *Article 7*

### **Specific requirements for tissue engineered products**

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.

## *Article 8*

### **Technical requirements**

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.

## **CHAPTER 3 MARKETING AUTHORISATION PROCEDURE**

### *Article 9*

#### **Evaluation procedure**

1. The Committee for Medicinal Products for Human Use of the European Medicines Agency, hereinafter “the Agency”, shall consult the Committee for Advanced Therapies on any scientific assessment of advanced therapy medicinal products necessary to draw up the scientific opinions referred to in Article 5(2) and (3) of Regulation (EC) No 726/2004. The Committee for Advanced Therapies shall also be consulted in case of re-examination of the opinion pursuant to Article 9(2) of Regulation (EC) No 726/2004.
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.
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.
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.
5. The Agency shall draw up specific procedures for the application of paragraphs 1 to 4.

### *Article 10*

#### **Combined advanced therapy medicinal products**

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.
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.

The Agency may request the relevant notified body to transmit any information related to the results of its assessment. The notified body shall transmit the information within a period of one month.

## **CHAPTER 4 SUMMARY OF PRODUCT CHARACTERISTICS, LABELLING AND PACKAGE LEAFLET**

### *Article 11*

#### **Summary of Product Characteristics**

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

### *Article 12*

#### **Outer/immediate packaging**

By way of derogation from Articles 54 and 55(1) of Directive 2001/83/EC, the particulars listed in Annex III shall appear on the outer packaging of advanced therapy medicinal products or, where there is no outer packaging, on the immediate packaging.

### *Article 13*

#### **Special immediate packaging**

In addition to the particulars mentioned in Article 55(2) and (3) of Directive 2001/83/EC, the following particulars shall appear on the immediate packagings of advanced therapy medicinal products:

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

## *Article 14*

### **Package leaflet**

1. By way of derogation from Article 59(1) of Directive 2001/83/EC, the package leaflet for an advanced therapy medicinal product shall be drawn up in accordance with the summary of product characteristics and shall include the information listed in Annex IV, in the order indicated therein.
2. The package leaflet shall reflect the results of consultations with target patient groups to ensure that it is legible, clear and easy to use.

## **CHAPTER 5 POST-AUTHORISATION REQUIREMENTS**

## *Article 15*

### **Post-authorisation Risk Management**

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.
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.

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

Evaluation of the effectiveness of any risk management system and the results of any studies performed shall be included in the periodic safety update reports referred to in Article 24(3) of Regulation (EC) No 726/2004.

3. The Agency shall forthwith inform the Commission if it finds that the marketing authorisation holder has failed to comply with the requirements referred to in paragraph 2.
4. The Agency shall draw up detailed guidelines relating to the application of paragraphs 1, 2 and 3.

## *Article 16*

### **Traceability**

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.
2. The hospital, institution or private practice where the advanced therapy medicinal product is used shall establish and maintain a system for patient and product traceability. That system shall contain sufficient detail to allow linking of each product to the patient who received it and vice versa.
3. Where an advanced therapy medicinal product contains human cells or tissues, the marketing authorisation holder, as well as the hospital, institution or private practice where the product is used, shall ensure that the traceability systems established in accordance with the first and second paragraphs are complementary to, and compatible with, the requirements laid down in Article 8 and Article 14 of Directive 2004/23/EC as regards human cells and tissues other than blood cells, and Article 14 and Article 24 of Directive 2002/98/EC as regards human blood cells.
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.
5. In case of bankruptcy or liquidation of the marketing authorisation holder, and in the event that the marketing authorisation is not transferred to another legal entity, the data referred to in the first paragraph shall be transferred to the Agency.
6. In the event that the marketing authorisation is suspended, revoked or withdrawn, the holder of the marketing authorisation shall remain subject to the obligations laid down in the first, third and fourth paragraph.
7. The Commission shall draw up detailed guidelines relating to the application of paragraphs 1 to 6, in particular the type and amount of data referred to in paragraph 1.

## **CHAPTER 6 INCENTIVES**

### *Article 17*

#### **Scientific Advice**

1. The applicant or holder of a marketing authorisation may request advice from the Agency on the design and conduct of pharmacovigilance and of the risk management system referred to in Article 15.
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.

### *Article 18*

#### **Scientific recommendation on advanced therapy classification**

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.
2. The Agency shall publish summaries of the recommendations delivered in accordance with paragraph 1, after deletion of all information of commercial confidential nature.

### *Article 19*

#### **Certification of quality and non-clinical data**

Small and medium-sized enterprises developing an advanced therapy medicinal product may submit to the Agency all quality and, where available, non-clinical data required in accordance with modules 3 and 4 of Annex I to Directive 2001/83/EC, for scientific evaluation and certification.

The Commission shall lay down provisions for the evaluation and certification of such data, in accordance with the procedure referred to in Article 26(2).



## **CHAPTER 7 COMMITTEE FOR ADVANCED THERAPIES**

### *Article 20*

#### **Committee for Advanced Therapies**

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

### *Article 21*

#### **Composition of the Committee for Advanced Therapies**

1. The Committee for Advanced Therapies shall be composed of the following members:
  - (a) five members and five alternates of the Committee for Medicinal Products for Human Use, appointed by the latter;
  - (b) one member and one alternate appointed by each Member State whose national competent authority is not represented among the members and alternates appointed by the Committee for Medicinal Products for Human Use;
  - (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.
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.
3. The members of the Committee for Advanced Therapies shall be appointed for a renewable period of three years. At meetings of the Committee for Advanced Therapies, they may be accompanied by experts.

4. The Committee for Advanced Therapies shall elect its Chairman from among its members for a term of three years renewable once.
5. The names and scientific qualifications of the members shall be published by the Agency.

#### *Article 22*

#### **Conflicts of Interest**

1. Members of the Committee for Advanced Therapies and its experts shall undertake to act in the public interest and in an independent manner. They shall not have financial or other interests in the pharmaceutical sector, medical device sector or biotechnology sector that could affect their impartiality.
2. All indirect interests that could relate to the pharmaceutical sector, medical device sector or biotechnology sector shall be entered in the register referred to in Article 63(2) of Regulation (EC) No 726/2004.

#### *Article 23*

#### **Tasks of the Committee for Advanced Therapies**

The Committee for Advanced Therapies shall have the following tasks:

- (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;
- (b) at the request of the Committee for Medicinal Products for Human Use, to advise on any medicinal product which may require, for the evaluation of its quality, safety or efficacy, expertise in one of the scientific areas referred to in Article 21(2);
- (c) to provide advice on any question related to advanced therapy medicinal products, at the request of the Executive Director of the Agency or the Commission;
- (d) to assist scientifically in the elaboration of any documents related to the fulfilment of the objectives of this Regulation;
- (e) at the Commission's request, to provide scientific expertise and advice for any Community initiative related to the development of innovative medicines and therapies which requires expertise in one of the scientific areas referred to in Article 21(2).

## **CHAPTER 8 GENERAL AND FINAL PROVISIONS**

### *Article 24*

#### **Adaptation of Annexes**

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.

### *Article 25*

#### **Reporting**

Within 5 years of entry into force of this Regulation, the Commission shall publish a general report on its application, which shall include comprehensive information on the different types of advanced therapy medicinal products authorised pursuant to this Regulation.

### *Article 26*

#### **Committee procedure**

1. The Commission shall be assisted by the Standing Committee on Medicinal Products for Human Use set up by Article 121(1) of Directive 2001/83/EC.
2. Where reference is made to this paragraph, Articles 5 and 7 of Decision 1999/468/EC shall apply, having regard to the provisions of Article 8 thereof.

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

### *Article 27*

#### **Amendments to Regulation (EC) No 726/2004**

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

- (1) Article 56 is amended as follows:
  - (a) In paragraph 1, the following point (d)a is inserted:

“(d)a the Committee for Advanced Therapies;”
  - (b) In paragraph 2, in the first sentence of the first subparagraph, “paragraph 1(a) to (d)” is replaced by “paragraph 1(a) to (d)a”.
- (2) In the Annex, the following point 1a is inserted:

“1a. Advanced therapy medicinal products, as defined in Regulation (EC) No [.../of the European Parliament and of the Council (Regulation on Advanced Therapy Medicinal Products)\*].

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\* OJ L [...], [...], p. [...].”

#### *Article 28*

### **Amendments to Directive 2001/83/EC**

Directive 2001/83/EC is amended as follows:

(1) In Article 3, the following paragraph 7 is added:

“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.

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\* OJ L [...], [...], p. [...].”

(2) In Article 4, the following paragraph 5 is added:

“5. This Directive and all Regulations referred to therein shall not affect the application of national legislation prohibiting or restricting the use of any specific type of human or animal cells, or the sale, supply or use of medicinal products containing, consisting of or derived from these cells. The Member States shall communicate the national legislation concerned to the Commission.”

(3) In Article 6, the first subparagraph of paragraph 1 is replaced by the following:

“No medicinal product may be placed on the market of a Member State unless a marketing authorisation has been issued by the competent authorities of that Member State in accordance with this Directive or an authorisation has been granted in accordance with Regulation (EC) No. 726/2004 of the European Parliament and of the Council\*, read in conjunction with Regulation (EC) No [.../of the European Parliament and of the Council (Regulation on Advanced Therapy Medicinal Products)\*\*].

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\* OJ L 136, 30.4.2004, p. 1

\*\* OJ L [...], [...], p. [...].”

*Article 29*

**Transitional period**

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.
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.

*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 be binding in its entirety and directly applicable in all Member States.

Done at Brussels,

*For the European Parliament*  
*The President*

*For the Council*  
*The President*

**ANNEX I**  
**Points referred to in Article 2(1)(c)**

Cells or tissues shall be considered ‘engineered’ if they fulfil at least one of the following points:

- (1) The cells or tissues have been subject to substantial manipulation, so that their original biological characteristics, physiological functions or structural properties relevant for the intended regeneration, repair or replacement, are altered.

The following manipulations are not considered as substantial manipulations:

- cutting;
  - grinding;
  - shaping;
  - centrifugation;
  - soaking in antibiotic or antimicrobial solutions;
  - sterilization;
  - irradiation;
  - cell separation, concentration or purification;
  - filtering;
  - lyophilization;
  - freezing;
  - cryopreservation;
  - vitrification.
- (2) The cells or tissues are not intended to be used for the same essential function or functions in the recipient as in the donor;
- (3) The cells or tissues form part of a combined advanced therapy medicinal product.

**ANNEX II**  
**Summary of Product Characteristics**

1. Name of the medicinal product.
2. Composition of the product:
  - 2.1. general description of the product, if necessary with explanatory drawings and pictures.
  - 2.2. qualitative and quantitative composition in terms of the active substances and other constituents of the product, knowledge of which is essential for proper use, administration or implantation of the product. Where the product contains cells or tissues, a detailed description of these cells or tissues and of their specific origin shall be provided.
3. Pharmaceutical form.
4. Clinical particulars:
  - 4.1. therapeutic indications,
  - 4.2. dosage and detailed instructions for use, application, implantation or administration for adults and, where necessary, for children or other special populations, if necessary with explanatory drawings and pictures,
  - 4.3. contra-indications,
  - 4.4. special warnings and precautions for use, including any special precautions to be taken by persons handling such products and administering or implanting them to patients, together with any precautions to be taken by the patient,
  - 4.5. interaction with other medicinal products and other forms of interactions,
  - 4.6. use during pregnancy and lactation,
  - 4.7. effects on ability to drive and to use machines,
  - 4.8. undesirable effects,
  - 4.9. overdose (symptoms, emergency procedures).
5. Pharmacological properties:
  - 5.1. pharmacodynamic and pharmacokinetic properties, if applicable.
  - 5.2. preclinical safety data.
6. Quality particulars:
  - 6.1. list of preservative systems and excipients, if applicable

6.2. major incompatibilities, if applicable

6.3. shelf life, when necessary after reconstitution of the medicinal product or when the immediate packaging is opened for the first time,

6.4. special precautions for storage,

6.5. nature and contents of container and special equipment for use, administration or implantation,

6.6. special precautions and instructions for handling and disposal of a used advanced therapy medicinal product or waste materials derived from such product, if appropriate.

7. Marketing authorisation holder.

8. Marketing authorisation number(s).

9. Date of the first authorisation or renewal of the authorisation.

10. Date of revision of the text.



**ANNEX III**  
**Labelling**

- (a) The name of the medicinal product and, if appropriate, an indication of whether it is intended for babies, children or adults; the international non-proprietary name (INN) shall be included, or, if the product has no INN, the common name.
- (b) A description of the active substance(s) expressed qualitatively and quantitatively, including, where the product contains cells or tissues, the statement “This product contains cells of human/animal [*as appropriate*] origin” together with a short description of these cells or tissues and of their specific origin;
- (c) The pharmaceutical form;
- (d) A list of preservative systems and excipients, if applicable;
- (e) The method of use, application, administration or implantation and, if necessary, the route of administration. If applicable, space shall be provided for the prescribed dose to be indicated;
- (f) A special warning that the medicinal product must be stored out of the reach and sight of children;
- (g) Any special warning necessary for the particular medicinal product;
- (h) The expiry date in clear terms (month and year; and day if applicable);
- (i) Special storage precautions, if any;
- (j) Specific precautions relating to the disposal of unused medicinal products or waste derived from medicinal products, where appropriate, as well as reference to any appropriate collection system in place;
- (k) The name and address of the marketing authorisation holder and, where applicable, the name of the representative appointed by the holder to represent him;
- (l) The number of the authorization for placing the medicinal product on the market;
- (m) The manufacturer's batch number and the unique donation and product codes referred to in Article 8(2) of Directive 2004/23/EC;
- (n) In the case of advanced therapy medicinal products for autologous use, the unique patient identifier and the statement “For autologous use only”;

**ANNEX IV**  
**Package Leaflet**

(a) For the identification of the advanced therapy medicinal product:

(i) the name of the advanced therapy medicinal product and an indication of whether it is intended for babies, children or adults. The common name shall be included if the product contains only one active substance and if its name is an invented name;

(ii) the therapeutic group or type of activity in terms easily understandable for the patient;

(iii) where the product contains cells or tissues, a description of those cells or tissues and of their specific origin;

(b) The therapeutic indications;

(c) A list of information which is necessary before the medicinal product is taken or used, including:

(i) contra-indications;

(ii) appropriate precautions for use;

(iii) forms of interaction with other medicinal products and other forms of interaction (e.g. alcohol, tobacco, foodstuffs) which may affect the action of the medicinal product;

(iv) special warnings;

(v) if appropriate, possible effects on the ability to drive vehicles or to operate machinery;

(vi) the excipients, knowledge of which is important for the safe and effective use of the medicinal product and which are included in the detailed guidance published pursuant to Article 65 of Directive 2001/83/EC.

The list shall also take into account the particular condition of certain categories of users, such as children, pregnant or breastfeeding women, the elderly, persons with specific pathological conditions;

(d) The necessary and usual instructions for proper use, and in particular:

(i) the dosage,

(ii) a summary of the method of use, application, administration or implantation and, if necessary, the route of administration;

and, as appropriate, depending on the nature of the product;

(iii) the frequency of administration, specifying if necessary the appropriate time at which the medicinal product may or must be administered;

- (iv) the duration of treatment, where it should be limited;
  - (v) the action to be taken in case of an overdose (such as symptoms, emergency procedures);
  - (vi) information on what to do when one or more doses have not been taken;
  - (vii) a specific recommendation to consult the doctor or the pharmacist, as appropriate, for any clarification on the use of the product;
- (e) A description of the adverse reactions which may occur under normal use of the medicinal product and, if necessary, the action to be taken in such a case; the patient should be expressly asked to communicate any adverse reaction which is not mentioned in the package leaflet to his doctor or pharmacist;
- (f) A reference to the expiry date indicated on the label, with:
- (i) a warning against using the product after that date;
  - (ii) where appropriate, special storage precautions;
  - (iii) if necessary, a warning concerning certain visible signs of deterioration;
  - (iv) the full qualitative and quantitative composition;
  - (v) the name and address of the marketing authorisation holder and, where applicable, the name of his appointed representatives in the Member States;
  - (vi) the name and address of the manufacturer;
- (g) The date on which the package leaflet was last revised.

## LEGISLATIVE FINANCIAL STATEMENT

**Policy area: Internal Market (Art. 95 TEC).**

**Activities: The following policies are concerned:**

- To guarantee a high level of health protection for European patients treated with advanced therapies;
- To facilitate market access for advanced therapy products and the functioning of the internal market in this sector;
- To foster the competitiveness of European undertakings in this field, in particular small and medium-sized enterprises;

**TITLE OF ACTION: 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**

**1. BUDGET LINE(S) + HEADING(S)**

02 04 02 01 – European Medicines Agency — Subsidy under Titles 1 and 2

02 04 02 02 – European Medicines Agency — Subsidy under Title 3

**2. OVERALL FIGURES**

**2.1. Total allocation for action (Part B):**

The proposal has an impact on the EMEA, but not directly on the allocations for action of the Community budget. A detailed calculation of the impact on the EMEA is annexed.

**2.2. Period of application:**

The assumption is that the proposed Regulation would apply from the end of 2007. The impact has been calculated for 2008-2012; the impact for 2007 is assumed to be negligible.

**2.3. Overall multiannual estimate of expenditure:**

None (see Section 10 for the estimated impact on the EMEA)

#### 2.4. Compatibility with financial programming and financial perspective

Proposal may entail reprogramming of the relevant heading in the financial perspective.

#### 2.5. Financial impact on revenue:

Proposal has no financial implications on Community revenue

### 3. BUDGET CHARACTERISTICS

Type of expenditure		New	EFTA contribution	Contributions from applicant countries	Heading in financial perspective
Non-comp	Differentiated	NO	YES	NO	No 3 (1a)

### 4. LEGAL BASIS

- Treaty establishing the European Community and notably Article 95.
- Regulation (EC) No 726/2004 of the European Parliament and of the Council of 30 May 2004, laying down Community procedures for the authorisation and supervision of medicinal products for human and veterinary use and establishing a European Medicines Agency (OJ L136, 30.4.2004, p. 1).
- Directive 2001/83/EC of the European Parliament and of the Council of 6 November 2001, on the Community code relating to medicinal products for human use (OJ L311, 28.11.2001, p.67, as amended by OJ L136, 30.4.2004, p.34)
- Council Regulation (EC) No 297/95 of 10 February 1995 concerning fees payable to the European Agency for the Evaluation of Medicinal Products (OJ L035, 15.2.1995, p. 1, as amended by Council Regulation (EC) No 2743/98 of 14 December 1998, OJ L345, 19.12.98, p. 3 and by Commission Regulation (EC) No 494/2003 of 18 March 2003, OJ L73, 19.3.2003, p. 6; see also COM(2005)106).

## **5. DESCRIPTION AND GROUNDS**

### **5.1. Need for Community intervention**

#### *5.1.1. Objectives pursued*

The main objectives of the proposal are:

- To guarantee a high level of health protection for European patients treated with advanced therapy products;
- To facilitate market access for advanced therapy products;
- To foster the competitiveness of European undertakings operating in this field;
- To provide overall legal certainty.

The proposal contributes to the three strategic goals of the Community legislation on medicinal products:

- (1) Ensuring that public health is adequately protected across the Community;
- (2) Supporting the achievement of the internal market in the pharmaceutical sector;
- (3) Improving the competitiveness of the EU pharmaceutical and biotechnology industry.

#### *5.1.2. Measures taken in connection with ex ante evaluation*

An Impact Assessment was conducted on the Commission's proposal. It draws on:

- Experience with the existing EU legislation on medicinal products, medical devices and human tissues and cells;
- Experience with gene and somatic cell therapy products at the EMEA;
- Extensive consultation with all stakeholders;
- Two studies on human tissue engineering conducted by the Institute for Prospective Technological Studies (IPTS);
- Experience with legislation on human cells, tissues, and cellular and tissue-based products (HCT/Ps) in the United States (US); and
- Published literature on regenerative medicine in general.

There has been extensive consultation with all stakeholders in preparing the proposed Regulation. This included:

- Workshops and roundtable meetings;
- Stakeholders interviews;
- Public consultations on the internet.

Feedback from all stakeholders was carefully taken in consideration for the refinement of the proposal.

### 5.1.3. *Measures taken following ex post evaluation*

As regards gene and somatic cell therapy, the proposal draws on experience with the existing legislation on medicines, medical devices and human tissues and cells, experience with gene and somatic cell therapy products at the EMEA, and experience with legislation on HCT/PS in the US.

As regards tissue engineering, there is so far no Community framework covering these products. Therefore, no *ex-post* evaluation could be conducted at Community level. Nevertheless, experience at national level, in particular in the United Kingdom, France and Germany, was carefully analyzed and taken in consideration.

## 5.2. **Action envisaged and budget intervention arrangements**

Achievement of these objectives and results can easily be measured, for instance in terms of:

- Number of marketing authorisation applications for advanced therapy products.
- Number of requests for conditional marketing authorisations.
- Number of requests for accelerated assessment of marketing authorisation applications.
- Number of requests for scientific advice.
- Number of marketing authorisation applications granted.
- Percentage of applications coming from SMEs.
- Number of requests for post-marketing studies, post-authorisation plans and risk management systems and the delivery against those plans.

## 5.3. **Methods of implementation**

Centralised Management, indirectly by delegation to a body set up by the Communities as referred to in Art. 185 of the Financial Regulation (EMEA).

## **6. FINANCIAL IMPACT**

- The proposed Regulation has direct implications on the European Medicines Agency. (See Section 10).
- Advanced therapies represent a young sector, which is developing rapidly in Europe. Consequently, there are rather broad corridors of possible developments. The regulatory framework is only one of the factors influencing the future of this area. Only limited and static information is available in this fast-moving field. The figures provided here should hence be regarded as estimates only.

### **6.1. Total financial impact on Part B - (over the entire programming period)**

#### *6.1.1. Financial intervention*

None (see Section 10 for the estimated impact on the EMEA)

#### *6.1.2. Technical and administrative assistance, support expenditure and IT expenditure (commitment appropriations)*

None (see Section 10 for the estimated impact on the EMEA)

### **6.2. Calculation of costs by measure envisaged in Part B (over the entire programming period)**

None (see Section 10 for the estimated impact on the EMEA)

## **7. IMPACT ON STAFF AND ADMINISTRATIVE EXPENDITURE**

### **7.1. Impact on human resources**

None (see Section 10 for the estimated impact on the EMEA)

### **7.2. Overall financial impact of human resources**

None (see Section 10 for the estimated impact on the EMEA)

### **7.3. Other administrative expenditure deriving from the action**

None (see Section 10 for the estimated impact on the EMEA)

## **8. FOLLOW-UP AND EVALUATION**

### **8.1. Follow-up arrangements**

Most of the effects of the proposal lend themselves to direct measurement. Besides, Articles 67 to 70 of Regulation (EC) No 726/2004 lay down financial provisions for the



annual preparation, execution, monitoring and reporting of the EMEA budget, including revenues from fees paid by undertakings and costs entailed for the evaluation, supervision and post-authorisation vigilance of medicinal products. Adequate monitoring data regarding advanced therapies will be collected in the context of the implementation of these Articles and the provisions laid down in this proposal.

## **8.2. Arrangements and schedule for the planned evaluation**

The EMEA will provide annually an analysis of the experience acquired as a result of the application of this Regulation, through its Annual Report.

## **9. ANTI-FRAUD MEASURES**

The European Medicines Agency has specific budgetary control mechanisms and procedures. The Management Board, which comprises representatives of the Member States, the Commission and the European Parliament, adopts the budget (Article 66(f) of Regulation (EC) No 726/2004), as well as the internal financial provisions (Article 66(g)). The European Court of Auditors examines the execution of the budget each year (Article 68.3).

The provisions of Regulation (EC) No 1073/1999 of the European Parliament and of the Council of 25 May 1999 concerning investigations conducted by the European Anti-Fraud Office (OLAF) apply to the EMEA without restriction. A decision concerning cooperation with the OLAF was already adopted on 1 June 1999 (EMEA/D/15007/99).

Finally, the Quality Management System applied by the Agency supports a continuous review, whose objective is to ensure that the correct procedures are followed and that these procedures are pertinent and efficient. Several internal audits are undertaken each year as part of this process.

## **10. ANNEX: DETAILED CALCULATION OF THE PROPOSAL'S FINANCIAL IMPACT ON THE EMEA REVENUES AND COSTS**

### **Introduction**

The proposal entails various impacts on the EMEA, notably through:

- (1) The creation of a new Committee and the related infrastructure;
- (2) New applications submitted through the centralised procedure, for which applicants will have to pay a fee.

Costs related to point (1) can be estimated by analogy with already existing Committees.

Costs and revenues related to point (2) are more difficult to predict, as they will depend on external factors (e.g. development of the sector, venture capital investment in the field...) which lie outside the scope of the proposal.

## Methodology

### *Assumptions on the revenues*

- Fees amounts payable by applicants are normally based on average fees for 2004, as provided by the EMEA and based on Council Regulation (EC) No 297/95<sup>38</sup>. Inflation is not taken into account.
- The success rate for the marketing authorisation applications is assumed to be around 80%.
- The different types of services provided by the Agency are listed (*e.g.* evaluation of a marketing authorisation application, variations, scientific advice etc.). A distinction is made between designated orphan medicinal products, to which additional, specific fees reductions apply<sup>39</sup>, and other medicines. The fee for inspections is a flat-rate inspection fee, travel expenses are excluded.
- The calculation takes into account special fees reductions and deferrals for SMEs, as provided for in the Commission Regulation implementing Article 70(2) of Regulation (EC) No726/2004. The main provisions are:
  - Deferral of the marketing authorisation application fee until the end of the evaluation procedure. The fee for an application submitted in year N is hence allocated to the revenues of year N+1;
  - 90% reduction on scientific advice fee, inspection fee, and scientific services fee. The fee reduction on scientific advice also applies to non-SMEs undertakings;
  - 100% reduction on administrative service fee;
  - 100% fee reduction on scientific advice fee and scientific service fee for designated orphan medicinal products;
  - Conditional fee exemption for the marketing authorisation: if scientific advice has been requested and used prior to the submission of a marketing authorisation application, the fee for that application would be due only if the outcome is positive.
- The average fee for scientific services is estimated at 100 000 Euros.

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<sup>38</sup> OJ L035, 15.2.1995, p. 1, as amended by Council Regulation (EC) No 2743/98 of 14 December 1998, OJ L345, 19.12.98, p. 3 and by Commission Regulation (EC) No 494/2003 of 18 March 2003, OJ L73, 19.3.2003, p. 6. See also COM(2005)106.

<sup>39</sup> See Regulation (EC) No 141/2000 of the European Parliament and of the Council of 16 December 1999 on orphan medicinal products (OJ L18, 22.1.2000, p.1) and <http://www.emea.eu.int>.

- During the first two years, a number of applications may have to be evaluated free of charge. The figures vary from 4 applications (2008:2; 2009:2) in the conservative scenario, to 11 (2008:6; 2009:5) in the optimistic scenario. The evaluation of these applications does not entail revenues, but does entail costs (e.g. payment of rapporteurs, additional experts, etc.). Post-authorisation services related to these applications entail the same revenues and costs as other applications.

### ***Assumptions on the costs***

The following costs are assumed:

- CAT Members costs, based on 750 Euros per member per day, 2 days per meeting, 11 meetings per year;
- Secretariat costs, based on 1,5 to 2 Administrator FTEs (FTE: Full-time Equivalent Employee) and 1.5 to 3 Senior Assistant FTEs. Staff costs are usual EMEA standards, including overhead;
- Additional experts costs, on a *ad-hoc* basis depending on the number and novelty of applications to be evaluated by the Agency; and based on 750 Euros per expert per day, 2 days per meeting, 11 meetings per year;
- Meeting management and conference services costs, based on ~2500Euros per day per meeting, 2 days per meeting, 11 meetings per year;
- Evaluation costs, *i.e.* payment of the rapporteurs and co-rapporteurs, estimated to ~45% of the total fee revenues. This is in line with the usual evaluation costs for other types of medicinal products, as provided by the EMEA for the 2003-2005 period<sup>40</sup>.
- IT developments, databases and other costs related to the management of the dossiers and their maintenance at the Agency. At a given year N, those costs are assumed to be proportional to  $(1+\ln(A_N/A_{N-1}))$ , where  $A_N$  is the number of marketing authorisation applications in year N and  $A_{N-1}$  is the number of marketing authorisation applications in year N-1.
- EMEA workshops, trainings and missions related to the field. Given the pace at which science evolves in this area, these costs may not be negligible. A 10% increase per year is assumed.

As of 2007, the EMEA would most likely have to set up a task force to prepare the work and the procedures laid down in the proposal. It is assumed that this would require 1 Administrator FTE and 1 Senior Assistant FTE, but only through internal redeployment. These 2007 costs are hence assumed to be negligible.

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<sup>40</sup> See also Annex 7 of the EMEA 2004 Annual report.

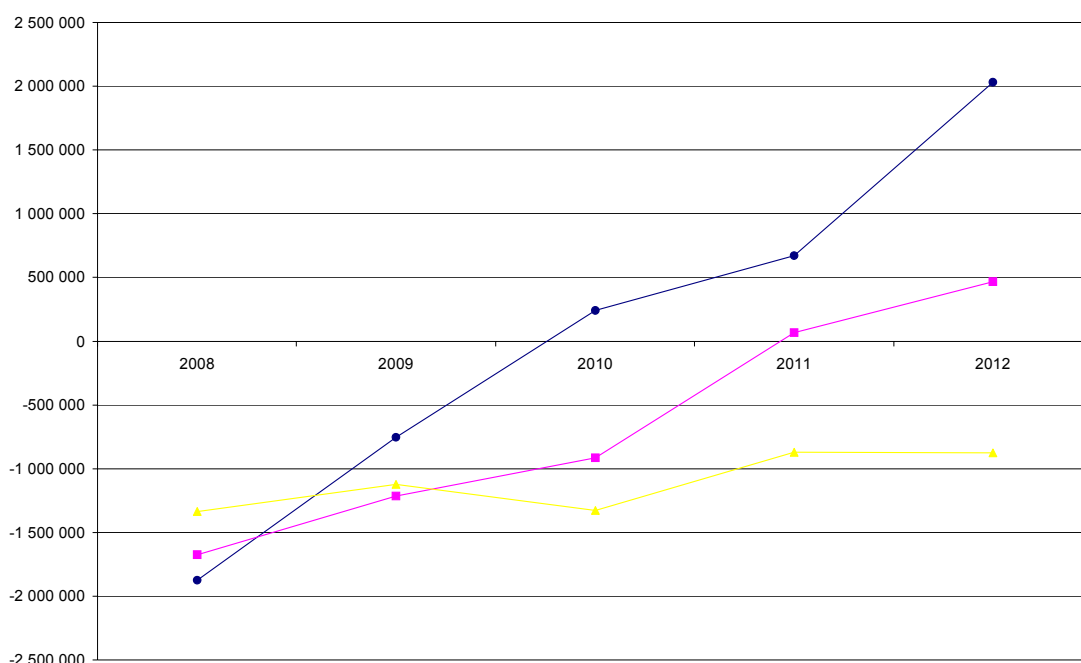
### *Assumptions on the scenarios*

Three scenarios (conservative, average, optimistic) are provided:

- Conservative scenario: the field of advanced therapies would develop very slowly. SMEs would mostly apply for scientific advice, with almost no marketing authorisation applications in the first three years. A few dossiers would nevertheless be submitted to the Agency by non-SMEs applicants.
- Optimistic scenario, based on an exponential development of the field. A significant number of applications, both at scientific advice and marketing authorisation level, would be submitted by SMEs and non-SMEs.
- Average scenario, based on a moderate development of the industry. A stationary state would be reached by 2011-2012.

### **Results**

The results are given in Figure 1. Detailed figures are given in Tables 1, 2 and 3.



**Figure 1:** Advanced Therapies: Revenues – Costs. The X-axis represents the years. The Y-axis represents the difference between the estimated revenues and costs, in Euros. The three scenarios are outlined: conservative (triangle dots), average (square dots), and optimistic (bullet dots).

The figures suggest that:

- During the first three years, the financial impact is overall negative in the three scenarios. This is essentially due to the costs entailed for the applications evaluated

free of charge under the 2-years 'Transitional period' foreseen in the proposal. However, the maximum annual deficit is capped below ~1.8 million Euros in 2008 and below ~1.3 million Euros in 2009 and 2010. In the optimistic scenario, equilibrium is reached in 2010 already.

- During the 2010-2012 period, the financial impact in the conservative scenario remains around -1 million Euros per year. In the optimistic scenario, the impact increases from ~+250 000 Euros surplus in 2010 to ~+2.1 million Euros surplus in 2012. In the average scenario, the financial impact reaches equilibrium in 2011 and stabilizes around ~+250 000 Euros surplus.
- Two financial incentives foreseen in the proposal may have a significant impact on the EMEA, by entailing costs without directly generating revenues: the 90% fee reduction on scientific advice, and the 2-years transitional period of free-of-charge assessment by the EMEA of products which were authorised before the entry into force of the Regulation. These two measures appear justified:
  - to support the growth of this emerging sector and thus the development of new products and treatments for patients;
  - to facilitate a smooth transition from the current regulatory picture to the one laid down in this Regulation, by alleviating the financial pressure put on applicants during this period.
- Whatever the scenario, the financial impact of the proposal is not negligible. It should therefore be fully taken into account in the budgetary procedures, when reviewing the Community contribution to the EMEA for the 2008-2012 period. This impact should not be considered alone but in a broader context, together with all other legislation that may have an impact on the EMEA budget, such as the Commission Regulation implementing Article 70(2) of Regulation (EC) No 726/2004.

Revenues	Fee	Special Fee reductions & deferrals	2008		2009		2010		2011		2012	
			N° applications	Financial Impact	N° applications	Financial Impact	N° applications	Financial Impact	N° applications	Financial Impact	N° applications	Financial Impact
Applications from transitional period	232.000	Free of charge	4.0	0	4.0	0						
<b>New Applications</b>												
<b>SMEs</b>												
Marketing Authorisation Applications - Non Orphan	232.000	Deferral	1.0	0	1.0	0	3.0	0	4.0	0	5.0	0
Positive outcome	232.000	0%	0	+0	1.0	+232.000	1.0	+232.000	3.0	+696.000	3.0	+696.000
Negative outcome, no Scientific Advice	232.000	0%	0	+0	0	+0	0	+0	0	+0	1.0	+232.000
Negative outcome with Scientific Advice	232.000	100%	0	+0	0	+0	0	+0	0	+0	0	+0
Marketing Authorisation Applications - Orphan	116.000	Deferral	0	+0	0	+0	1.0	+0	1.0	+0	2.0	+0
Positive outcome	116.000	0%	0	+0	0	+0	0	+0	1.0	+116.000	1.0	+116.000
Negative outcome without Scientific Advice	116.000	0%	0	+0	0	+0	0	+0	0	+0	0	+0
Negative outcome with Scientific Advice	116.000	100%	0	+0	0	+0	0	+0	0	+0	0	+0
Variations	50.000	0%	0	+0	2.0	+100.000	3.7	+183.333	5.4	+269.444	8.5	+424.537
Inspections	17.400	90%	3.8	+6.525	4.0	+6.960	5.0	+8.700	6.5	+11.310	9.0	+15.573
Annual Fee	80.000	0%	0	+0	2.4	+192.000	4.8	+384.000	7.6	+608.000	12.4	+992.000
Scientific Advice												
Non Orphan	52.200	90%	4.0	+20.880	10.0	+52.200	15.0	+78.300	18.0	+93.960	20.0	+104.400
Orphan	52.200	100%	2.0	+0	4.0	+0	4.0	+0	5.0	+0	5.0	+0
Scientific Services												
Non Orphan	100.000	90%	4.0	+40.000	6.0	+60.000	8.0	+80.000	12.0	+120.000	12.0	+120.000
Orphan	100.000	100%	0	+0	1.0	+0	3.0	+0	4.0	+0	4.0	+0
Administrative Services	5.800	100%	0	+0	0	+0	1.0	+0	2.0	+0	3.0	+0
<b>Non-SMEs</b>												
Marketing Authorisation Applications - Non Orphan	232.000	0%	1.0	+232.000	1.0	+232.000	3.0	+696.000	5.0	+1.160.000	5.0	+1.160.000
Marketing Authorisation Applications - Orphan	116.000	0%	0	+0	0	+0	0	+0	2.0	+232.000	1.0	+116.000
Variations	50.000	0%	0	+0	2.0	+100.000	3.7	+183.333	5.4	+269.444	8.5	+424.537
Inspections	17.400	0%	1.0	+17.400	3.0	+52.200	3.9	+67.860	8.2	+142.158	8.5	+147.047
Annual Fee	80.000	0%	0	+0	2.4	+192.000	4.8	+384.000	7.6	+640.000	12.4	+992.000
Scientific Advice												
Non Orphan	52.200	90%	4.0	+20.880	10.0	+52.200	15.0	+78.300	18.0	+93.960	20.0	+104.400
Orphan	52.200	100%	2.0	+0	2.0	+0	3.0	+0	3.0	+0	4.0	+0
Scientific Services												
Non Orphan	100.000	0%	5.0	+500.000	8.0	+800.000	10.0	+1.000.000	12.0	+1.200.000	13.0	+1.300.000
Orphan	100.000	0%	0	+0	2.0	+200.000	2.0	+200.000	3.0	+300.000	3.0	+300.000
Administrative Services	5.800	0%	0	+0	0	+0	2.0	+11.600	3.0	+17.400	3.0	+17.400
<b>Total Revenues (A)</b>				<b>837.685</b>		<b>2.271.560</b>		<b>3.587.427</b>		<b>5.937.677</b>		<b>7.261.894</b>
Marketing Authorisations Applications			6		6		7		12		13	
Marketing Authorisations granted			4.8		4.8		5.6		9.6		10.4	

Costs	Cost	2008		2009		2010		2011		2012	
		# FTEs	Impact	# FTEs	Financial Impact	# FTEs	Financial Impact	# FTEs	Financial Impact	# FTEs	Financial Impact
Evaluation costs (payment to (co-)rapporteurs)			-1.350.473		-2.319.750		-3.170.847		-4.442.376		-5.218.403
<b>Committee for Advanced Therapies</b>											
CAT member costs		31	-511.500	31	-511.500	31	-511.500	31	-511.500	31	-511.500
Secretariat costs											
Administrator Staff	150000	1.5	-225.000	1.5	-225.000	2.0	-300.000	2.0	-300.000	2.0	-300.000
Senior Assistant Staff	126000	1.5	-189.000	1.5	-189.000	2.0	-252.000	2.0	-252.000	3.0	-378.000
Additional experts costs		3	-49.500	3	-49.500	3.5	-57.750	6.0	-99.000	6.5	-107.250
Meeting management , and conference services			-55.000		-55.000		-55.000		-55.000		-55.000
IT developments & databases costs			-80.000		-80.000		-92.332		-142.099		-153.473
EMEA Workshops, trainings, missions			-50.000		-55.000		-60.500		-66.550		-73.205

<b>Total Costs (B)</b>				<b>-2.510.473</b>		<b>-3.484.750</b>		<b>-4.499.929</b>		<b>-5.868.525</b>		<b>-6.796.831</b>
<b>Total Impact (A+B)</b>				<b>-1.672.788</b>		<b>-1.213.190</b>		<b>-912.502</b>		<b>69 152</b>		<b>465.064</b>

**Table 1: (Average Scenario) Financial impact of the proposal on the EMEA. Financial figures are given in Euros. Figures should be regarded as indicative estimates only.**

**Table 2: (Conservative Scenario) Financial impact of the proposal on the EMEA. Financial figures are given in Euros. Figures should be regarded as indicative estimates only.**

Revenues	2008				2009		2010		2011		2012	
	Fee	Special Fee reductions & deferrals	N° applications	Financial Impact	N° applications	Financial Impact	N° applications	Financial Impact	N° applications	Financial Impact	N° applications	Financial Impact
Applications from transitional period	232.000	Free of charge	2,0	0	2,0	0						
<b>New Applications</b>												
<b>SMEs</b>												
Marketing Authorisation Applications - Non Orphan	232.000	Deferral	0	0	0	0	1	0	1,0	0	1,0	0
Positive outcome	232.000	0%	0	+0	0	+0	0	+0	1,0	+232.000	1,0	+232.000
Negative outcome, no Scientific Advice	232.000	0%	0	+0	0	+0	0	+0	0	+0	0	+0
Negative outcome with Scientific Advice	232.000	100%	0	+0	0	+0	0	+0	0	+0	0	+0
Marketing Authorisation Applications - Orphan	116.000	Deferral	0	+0	0	+0	1	+0	1,0	+0	1,0	+0
Positive outcome	116.000	0%	0	+0	0	+0	0	+0	1,0	+116.000	1,0	+116.000
Negative outcome without Scientific Advice	116.000	0%	0	+0	0	+0	0	+0	0	+0	0	+0
Negative outcome with Scientific Advice	116.000	100%	0	+0	0	+0	0	+0	0	+0	0	+0
Variations	50.000	0%	0	+0	0,7	+33.333	1,6	+77.778	2,3	+114.815	3,2	+162.346
Inspections	17.400	90%	1,5	+2.610	1,5	+2.610	1,5	+2.610	1,5	+2.610	1,5	+2.610
Annual Fee	80.000	0%	0	+0	0,8	+64.000	2,0	+160.000	3,2	+256.000	4,8	+384.000
Scientific Advice												
Non Orphan	52.200	90%	2,0	+10.440	4	+20.880	8,0	+41.760	11,0	+57.420	14,0	+73.080
Orphan	52.200	100%	0	+0	1,0	+0	2,0	+0	2,0	+0	3,0	+0
Scientific Services												
Non Orphan	100.000	90%	3,0	+30.000	3,0	+30.000	5,0	+50.000	7,0	+70.000	7,0	+70.000
Orphan	100.000	100%	0	+0	0	+0	1,0	+0	1,0	+0	2,0	+0
Administrative Services	5.800	100%	0	+0	0	+0	0	+0	1,0	+0	1,0	+0
<b>Non-SMEs</b>												
Marketing Authorisation Applications - Non Orphan	232.000	0%	0	+0	1,0	+232.000	1,0	+232.000	2,0	+464.000	3,0	+696.000
Marketing Authorisation Applications - Orphan	116.000	0%	0	+0	0	+0	0	+0	0,0	+0	0	0
Variations	50.000	0%	0	+0	0,7	+33.333	1,6	+77.778	2,3	+114.815	3,2	+162.346
Inspections	17.400	0%	0	+0	2,0	+34.800	2,0	+34.800	1,5	+26.100	3,0	+52.200
Annual Fee	80.000	0%	0	+0	0,8	+64.000	2,0	+160.000	3,2	+256.000	4,8	+384.000
Scientific Advice												
Non Orphan	52.200	90%	3,0	+15.660	5,0	+26.100	8,0	+41.760	10,0	+52.200	15,0	+78.300
Orphan	52.200	100%	0	+0	1,0	+0	1,0	+0	2,0	+0	3,0	+0
Scientific Services												
Non Orphan	100.000	0%	3,0	+300.000	4,0	+400.000	4,0	+400.000	5,0	+500.000	6,0	+600.000
Orphan	100.000	0%	0	+0	1,0	+100.000	1	+100.000	1,0	+100.000	1,0	+100.000
Administrative Services	5.800	0%	0	+0	0	+0	0	+0	1,0	+5.800	2,0	+11.600
<b>Total Revenues (A)</b>				<b>358.710</b>		<b>1.041.057</b>		<b>1.378.486</b>		<b>2.367.760</b>		<b>3.124.481</b>
Marketing Authorisations Applications			2,0		3,0		3,0		4,0		5,0	
Marketing Authorisations granted			1,6		2,4		2,4		3,2		4,0	
Costs	Cost		# FTEs	Impact	# FTEs	Financial Impact	# FTEs	Financial Impact	# FTEs	Financial Impact	# FTEs	Financial Impact
Evaluation costs (payment to (co-)rapporteurs)				-607.995		-1.046.595		-1.443.715		-1.945.093		-2.546.726
<b>Committee for Advanced Therapies</b>												
CAT member costs			31,0	-511.500	31,0	-511.500	31,0	-511.500	31,0	-511.500	31,0	-511.500
Secretariat costs												
Administrator Staff	150000		1,5	-225.000	1,5	-225.000	2,0	-300.000	2,0	-300.000	2,0	-300.000
Senior Assistant Staff	126000		1,5	-189.000	1,5	-189.000	2,0	-252.000	2,0	-252.000	3,0	-378.000
Additional experts costs			1,0	-16.5000	1,5	-24.750	1,5	-24.750	2,0	-33.000	2,5	-41.250
Meeting management , and conference services				-55.000		-55.000		-55.000		-55.000		-55.000
IT developments & databases costs				-50.000		-70.273		-70.273		-90.490		-110.682



EMEA Workshops, trainings, missions				-40.000		-44.000		-48.400		-53.240		-58.564
<b>Total Costs (B)</b>				<b>-1.694.995</b>		<b>-2.166.118</b>		<b>-2.705.638</b>		<b>-3.240.323</b>		<b>-4.001.722</b>
<b>Total Impact (A+B)</b>				<b>-1.336.285</b>		<b>-1.125.062</b>		<b>-1.327.153</b>		<b>-872.563</b>		<b>-877.241</b>

**Table 3: (Optimistic Scenario) Financial impact of the proposal on the EMEA. Financial figures are given in Euros. Figures should be regarded as indicative estimates only.**

Revenues	2008				2009		2010		2011		2012	
	Fee	Special Fee reductions & deferrals	N° applications	Financial Impact	N° applications	Financial Impact	N° applications	Financial Impact	N° applications	Financial Impact	N° applications	Financial Impact
Applications from transitional period	232.000	Free of charge	6,0	0	5,0	0						0
<b>New Applications</b>												
<b>SMEs</b>												
Marketing Authorisation Applications - Non Orphan	232.000	Deferral	2,0	0	2,0	0	4,0	0	7,0	0	7,0	0
Positive outcome	232.000	0%	0	+0	2,0	+464.000	1,0	+232.000	3,0	+696.000	6,0	+1.392.000
Negative outcome, no Scientific Advice	232.000	0%	0	+0	0	+0	0	+0	0	+0	1,0	+232.000
Negative outcome with Scientific Advice	232.000	100%	0	+0	0	+0	1,0	+0	1,0	+0	0	+0
Marketing Authorisation Applications - Orphan	116.000	Deferral	0	+0	1,0	+0	1,0	+0	2,0	+0	3,0	+0
Positive outcome	116.000	0%	0	+0	0	+0	1,0	+116.000	1,0	+116.000	2,0	+232.000
Negative outcome without Scientific Advice	116.000	0%	0	+0	0	+0	0	+0	0	+0	0	+0
Negative outcome with Scientific Advice	116.000	100%	0	+0	0	+0	0	+0	0	+0	0	+0
Variations	50.000	0%	0	+0	3,7	+183.333	7,7	+386.111	10,8	+538.426	15,3	+765.355
Inspections	17.400	90%	6,0	+10.440	6,0	+10.440	3,8	+6.525	6,8	+11.745	7,5	+13.050
Annual Fee	80.000	0%	0	+0	4,4	+352.000	10,0	+800.000	15,2	+1.216.000	22,8	+1.824.000
Scientific Advice												
Non Orphan	52.200	90%	8,0	+41.760	15,0	+78.300	20,0	+104.400	25,0	+130.500	30,0	+156.600
Orphan	52.200	100%	3,0	+0	5,0	+0	6,0	+0	8,0	+0	10,0	+0
Scientific Services												
Non Orphan	100.000	90%	5,0	+50.000	8,0	+80.000	9,0	+90.000	13,0	+130.000	14,0	+140.000
Orphan	100.000	100%	1,0	+0	2,0	+0	3,0	+0	5,0	+0	7,0	+0
Administrative Services	5.800	100%	0	+0	0	+0	2,0	+0	3,0	+0	4,0	+0
<b>Non-SMEs</b>												
Marketing Authorisation Applications - Non Orphan	232.000	0%	3,0	+696.000	5,0	+1.160.000	7,0	+1.624.000	8,0	+1.856.000	7,0	+1.624.000
Marketing Authorisation Applications - Orphan	116.000	0%	0	+0	1,0	+116.000	1,0	+116.000	2,0	+232.000	2,0	+232.000
Variations	50.000	0%	0	+0	3,7	+183.333	7,7	+386.111	10,8	+538.426	15,3	+765.355
Inspections	17.400	0%	2,3	+39.150	4,5	+78.300	7,0	+121.800	10,0	+174.000	10,0	+174.000
Annual Fee	80.000	0%	0	+0	4,4	+352.000	10,0	+800.000	15,2	+1.216.000	22,8	+1.824.000
Scientific Advice												
Non Orphan	52.200	90%	8,0	+41.760	15,0	+78.300	18,0	+93.960	22,0	+114.840	25,0	+130.500
Orphan	52.200	100%	2,0	+0	4,0	+0	6,0	+0	7,0	+0	8,0	+0
Scientific Services												
Non Orphan	100.000	0%	7,0	+700.000	10,0	+1.000.000	12,0	+1.200.000	13,0	+1.300.000	13,0	+1.300.000
Orphan	100.000	0%	1,0	+100.000	2,0	+200.000	4,0	+400.000	4,0	+400.000	5,0	+50.000
Administrative Services	5.800	0%	0	+0	1,0	+5.800	2,0	+11.600	3,0	+17.400	5,0	+29.000
<b>Total Revenues (A)</b>				<b>1.679.110</b>		<b>4.341.807</b>		<b>6.488.507</b>		<b>8.687.337</b>		<b>11.333.860</b>
Marketing Authorisations Applications			11,0		14,0		13,0		19,0		19,0	
Marketing Authorisations granted			8,8		11,2		10,4		15,2		15,2	

Costs	2008		2009		2010		2011		2012		
	Cost	# FTEs	Impact	# FTEs	Financial Impact	# FTEs	Financial Impact	# FTEs	Financial Impact	# FTEs	Financial Impact
Evaluation costs (payment to (co-)rapporteurs)			-2.336.288		-3.829.935		-4.849.413		-6.531.976		-7.683.304
<b>Committee for Advanced Therapies</b>											
CAT member costs		31,0	-511.500	31,0	-511.500	31,0	-511.500	31,0	-511.500	31,0	-511.500
Secretariat costs											
Administrator Staff	150000	1,5	-225.000	1,5	-225.000	2,0	-300.000	2,0	-300.000	2,0	-300.000
Senior Assistant Staff	126000	1,5	-189.000	1,5	-189.000	2,0	-252.000	2,0	-252.000	3,0	-378.000
Additional experts costs		4,0	-66.000	5,1	-84.000	4,7	-78.000	6,9	-114.000	6,9	-114.000
Meeting management , and conference services			-55.000		-55.000		-55.000		-55.000		-55.000
IT developments & databases costs			-100.000		-124.116		-114.918		-158.528		-158.528

EMEA Workshops, trainings, missions				-70.000		-77.000		-84.700		-93.170		-102.487
<b>Total Costs (B)</b>				<b>-3.552.788</b>		<b>-5.095.551</b>		<b>-6.245.531</b>		<b>-8.016.174</b>		<b>-9.302.820</b>
<b>Total Impact (A+B)</b>				<b>-1.873.678</b>		<b>-753.745</b>		<b>242.977</b>		<b>671.163</b>		<b>2.031.040</b>

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