## Basic information

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|---|---|
| **2005/0227(COD)**<br><br>COD - Ordinary legislative procedure (ex-codecision procedure)<br>Regulation | Procedure completed |
| Advanced therapy medicinal products<br><br>Amending Directive 2001/83/EC 1999/0134(COD)<br>Amending Regulation (EC) No 726/2004 2001/0252(COD)<br>Amended by 2008/0257(COD)<br><br>**Subject**<br><br>4.20.04 Pharmaceutical products and industry<br>4.60.08 Safety of products and services, product liability | |

## Key players

### European Parliament

| Committee responsible | Rapporteur | Appointed |
|---|---|---|
| ENVI Environment, Public Health and Food Safety | MIKOLÁŠIK Miroslav (PPE-DE) | 14/12/2005 |

| Committee for opinion | Rapporteur for opinion | Appointed |
|---|---|---|
| ITRE Industry, Research and Energy | CHICHESTER Giles (PPE-DE) | 20/06/2005 |
| IMCO Internal Market and Consumer Protection | The committee decided not to give an opinion. | |
| JURI Legal Affairs<br>(Associated committee) | BREYER Hiltrud (Verts/ALE) | 19/04/2006 |

### Council of the European Union

| Council configuration | Meetings | Date |
|---|---|---|
| Employment, Social Policy, Health and Consumer Affairs | 2803 | 2007-05-30 |
| Employment, Social Policy, Health and Consumer Affairs | 2733 | 2006-06-01 |
| Environment | 2826 | 2007-10-30 |

### European Commission

| Commission DG | Commissioner |
|---|---|
| Internal Market, Industry, Entrepreneurship and SMEs | VERHEUGEN Günter |

## Key events

| Date | Event | Reference | Summary |
|---|---|---|---|

| | | | |
|---|---|---|---|
| 16/11/2005 | Legislative proposal published | COM(2005)0567 | Summary |
| 30/11/2005 | Committee referral announced in Parliament, 1st reading | | |
| 18/05/2006 | Referral to associated committees announced in Parliament | | |
| 01/06/2006 | Debate in Council | | |
| 30/01/2007 | Vote in committee, 1st reading | | Summary |
| 07/02/2007 | Committee report tabled for plenary, 1st reading | A6-0031/2007 | |
| 23/04/2007 | Debate in Parliament | CRE link | |
| 25/04/2007 | Decision by Parliament, 1st reading | T6-0144/2007 | Summary |
| 25/04/2007 | Results of vote in Parliament | | |
| 30/10/2007 | Act adopted by Council after Parliament's 1st reading | | |
| 13/11/2007 | Final act signed | | |
| 13/11/2007 | End of procedure in Parliament | | |
| 10/12/2007 | Final act published in Official Journal | | |

## Technical information

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|---|---|
| **Procedure reference** | 2005/0227(COD) |
| **Procedure type** | COD - Ordinary legislative procedure (ex-codecision procedure) |
| **Nature of procedure** | Legislation |
| **Legislative instrument** | Regulation |
| | Amending Directive 2001/83/EC 1999/0134(COD)<br>Amending Regulation (EC) No 726/2004 2001/0252(COD)<br>Amended by 2008/0257(COD) |
| **Legal basis** | EC Treaty (after Amsterdam) EC 095 |
| **Stage reached in procedure** | Procedure completed |
| **Committee dossier** | ENVI/6/31976 |

## Documentation gateway

**European Parliament**

| Document type | Committee | Reference | Date | Summary |
|---|---|---|---|---|
| Committee draft report | | PE374.157 | 16/05/2006 | |
| Amendments tabled in committee | | PE374.231 | 29/05/2006 | |
| Committee draft report | | PE371.745 | 30/05/2006 | |
| Committee opinion | ITRE | PE371.930 | 20/06/2006 | |
| Amendments tabled in committee | | PE374.483 | 22/06/2006 | |
| Amendments tabled in committee | | PE376.369 | 27/06/2006 | |
| Committee opinion | JURI | PE374.450 | 17/07/2006 | |
| Committee draft report | | PE380.740 | 08/11/2006 | |
| Amendments tabled in committee | | PE382.323 | 19/12/2006 | |
| Committee report tabled for plenary, 1st reading/single reading | | A6-0031/2007 | 07/02/2007 | |

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|---|---|---|---|---|
| Text adopted by Parliament, 1st reading/single reading | | T6-0144/2007 | 25/04/2007 | Summary |

**Council of the EU**

| Document type | Reference | Date | Summary |
|---|---|---|---|
| Draft final act | 03627/2007/LEX | 13/11/2007 | |

**European Commission**

| Document type | Reference | Date | Summary |
|---|---|---|---|
| Document attached to the procedure | SEC(2005)1444 | 16/11/2005 | Summary |
| Legislative proposal | COM(2005)0567 | 16/11/2005 | Summary |
| Follow-up document | COM(2014)0188 | 28/03/2014 | Summary |

**National parliaments**

| Document type | Parliament /Chamber | Reference | Date | Summary |
|---|---|---|---|---|
| Contribution | PT_PARLIAMENT | COM(2014)0188 | 20/10/2014 | |

**Other institutions and bodies**

| Institution/body | Document type | Reference | Date | Summary |
|---|---|---|---|---|
| ESC | Economic and Social Committee: opinion, report | CES0951/2006 | 05/07/2006 | |

**Additional information**

| Source | Document | Date |
|---|---|---|
| European Commission | EUR-Lex | |

**Final act**

Regulation 2007/1394
OJ L 324 10.12.2007, p. 0121 Summary

Corrigendum to final act 32007R1394R(01)
OJ L 087 31.03.2009, p. 0174 Summary

# Advanced therapy medicinal products

2005/0227(COD) - 28/03/2014 - Follow-up document

The Commission presents a report in accordance with Regulation (EC) No 1394/2007 of the European Parliament and of the Council on advanced therapy medicinal products (ATMP) and takes stock of the situation of ATMPs in the EU and analyses the impact of the Regulation on advanced therapies.

The cornerstone of the Regulation is that a marketing authorisation must be obtained prior to the marketing of ATMPs. The marketing authorisation can only be granted if, after a scientific assessment of the quality, efficacy and safety profile, it is demonstrated that the benefits outweigh the risks.

The Commission states that the contribution of the ATMP Regulation to public health could be measured against two parameters: (1) the extent to which new ATMPs have become available in the EU; and (2) the extent to which authorised ATMPs are efficacious and safe.

**Availability of new ATMPs**: the report stresses that the regulation of ATMPs has been an important step to protect patients from scientifically unsound treatments. In addition, the ATMP Regulation has created a common framework for the assessment of advanced therapies in the EU. However, it is still the early days of the development of advanced therapies and **only four ATMPs have been granted a marketing authorisation**.

The much higher activity of the Committee for Advanced Therapies in the area of scientific advice and classification, as well as the high number of clinical trials involving ATMPs, is a signal of a dynamic research sector.

The Commission feels that **advanced therapies have the potential to bring major benefits to patients.** However, there are still many unknowns and it is therefore important to put in **place adequate controls** to prevent detrimental consequences for public health.

**Requirements for authorisation**: the ATMP Regulation protects patients by requiring that an independent review of the ATMP is done by the best available experts in the EU according to high standards of quality, efficacy and safety before the product is made available to patients.

**The report** states, however, that too burdensome requirements could have **detrimental consequences for public health** as it could prevent the appearance of valid treatments for unmet medical needs.

**Regulation** in this area should contribute to creating conditions that facilitate the appearance of new medicinal products, while ensuring a high level of public health protection. It is also important that the regulatory framework is adapted to rapid scientific progress.

**Conclusions and recommendations**: experience accumulated since the entry into force of the ATMP Regulation shows that some options to help the translation of research into ATMPs available to patients across the EU while maintaining a high level of public health protection can be identified, including:

- clarification of **the scope** of the ATMP Regulation by fine-tuning the current definitions of ATMPs and by reflecting on the appropriate regulatory framework for new innovative products that many not be captured by existing provisions;
- considering measures to avoid disparities in the **classification** of ATMPs in the EU;
- clarification of the conditions for the application of the **hospital exemption (**which allows the use of custom-made ATMPs under controlled conditions in the absence of a marketing authorisation), as well as the role of data obtained therefrom in the context of marketing authorisation procedures. If the hospital exemption became the normal route to market advanced therapies, there would be detrimental consequences for public health ;
- revising the **requirements for the authorisation of ATMPs** with a view to ensuring that requirements applicable are proportionate and well-adapted to the specific characteristics thereof, having specific consideration to autologous products (in the latter case, the cells/tissues are harvested from a patient, then treated or expanded, and finally they are introduced back into the same patient;
- streamlining **the marketing authorisation procedures** (scientific evaluation involves up to five committees) which is perceived as too cumbersome, particularly for SMEs and non-for-profit organisations ;
- extending **the certification procedure** and clarification of the link between the certification and the marketing authorisation procedure ;
- creating a more favourable environment for **ATMP developers working in an academic or non-for-profit setting**, including by promoting early contacts with the authorities through the application of the fee reduction for scientific advice and by extending the certification scheme to these developers;
- considering possible **fee incentives** to reduce the financial impact of post-marketing obligations.

# Advanced therapy medicinal products

2005/0227(COD) - 13/11/2007 - Final act

PURPOSE: to establish specific rules concerning the authorisation, supervision and pharmacovigilance of advanced therapy medicinal products.

LEGISLATIVE ACT: Regulation (EC) No 1394/2007 of the European Parliament and of the Council concerning advanced therapy medicinal products and amending Directive 2001/83/EC as well as Regulation (EC) No 726/2004.

CONTENT: the Council adopted the Regulation, unanimously accepting all the amendments suggested by the Parliament on first reading.

The main objective of this Regulation is to create a single legal framework for three types of advanced therapies (gene therapy, somatic cell therapy and tissue engineering), for which scientific and technical evolution has been very rapid due to scientific progress in cellular and molecular biotechnology.

The main elements of the Regulation are as follows:

- **setting up a centralised authorisation procedure in the market**, enabling a gathering of expertise at European level and direct access to the EU market;

- **definition of customised technical requirements**, adapted to the specificities of these products;

- **definition of stricter requirements concerning risk management and traceability**: in order to ensure the efficacy of the risk management system, efficacy and adverse reactions of medicinal products must be followed up. The Commission will have to demand necessary action when there is a particular cause for concern. Moreover, in order to ensure better traceability, the marketing authorisation holder shall keep the data referred to by the Directive for a minimum of 30 years after the expiry date of the product, or longer if required by the Commission as a term of the marketing authorisation;

- **special incentives for small and medium-sized enterprises (SMEs)**: by way of derogation from Regulation (EC) No 297/95, a 90% reduction for small and medium-sized enterprises (and 65% for other applicants) shall apply to the fee payable to the Agency for any scientific advice given in respect of advanced therapy medicinal products. The fees for marketing authorisation shall be reduced by 50% for SMEs and hospitals;

- **creation of a committee of experts from many disciplines (Committee for Advanced Therapies)** within the European Medicines Agency (EMEA), responsible for evaluating advanced therapy medicinal products and following up scientific progress in this field. When formulating a draft opinion for final approval by the Committee for Medicinal Products for Human Use, the Committee for Advanced Therapies shall strive to reach a scientific consensus.

  This new Committee will be composed of representatives of Member States' competent authorities, and those representing patients and clinicians. The European Parliament shall be consulted regarding the nomination of members, representing clinicians and patient associations, to the Committee for Advanced Therapies. At least two members and two alternates of the Committee for Advanced Therapies shall have scientific expertise in medical devices. Finally, members and alternates of the Committee shall have no financial or other interests in the biotechnology sector and medical device sector.

- **comitology**: future amendments with be made in respect of the new rules of comitology, that is, controlled by Parliament (regulatory procedure with scrutiny).

- **report and review**: by 30 December 2012, the Commission shall publish a general report on the application of this Regulation, which shall include comprehensive information on the different types of advanced therapy medicinal products authorised pursuant to this Regulation. In this report, the Commission will examine the impact of technical progress and review the scope of this Regulation, including in particular the regulatory framework of combined advanced therapy medicinal products.

- **transitional period**: advanced therapy medicinal products, other than tissue engineered products, legally on the Community market in accordance with national or Community legislation on 30 December 2008, shall comply with this Regulation no later than 30 December 2011.

ENTRY INTO FORCE: 30/12/2007

APPLICATION: from 30/12/2008.

# Advanced therapy medicinal products

2005/0227(COD) - 16/11/2005 - Legislative proposal

PURPOSE: to propose new rules concerning advanced therapy medicinal products.

PROPOSED ACT: European Parliament and Council Regulation

CONTENT: 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.

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), 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.

The main features of the proposal are as follows:

- a centralised marketing authorisation procedure, to benefit from the pooling of expertise at European level and direct access to the EU market;

- a new and multidisciplinary expert Committee (Committee for Advanced Therapies), within the European Medicines Agency (EMEA), to assess advanced therapy products and follow scientific developments in the field;

- tailor-made technical requirements, which are adapted to the particular characteristics of these products;

- strengthened requirements for risk management and traceability;

- a system of low-cost, top-quality scientific advice provided by EMEA;

- special incentives for small and medium-sized enterprises.

- ethical aspects. The proposed Regulation respects fundamental human rights and observes the principles reflected in the Charter of Fundamental Rights of the European Union1. 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). 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.

In addition, 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.

The Commission is of the opinion that 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.

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

**For more details concerning the financial implications of this proposal, please refer to the financial statement.**

# Advanced therapy medicinal products

2005/0227(COD) - 13/11/2007 - Corrigendum to final act

PURPOSE: **corrigendum** to Regulation (EC) No 1394/2007 of the European Parliament and of the Council of 13 November 2007 on advanced therapy medicinal products and amending Directive 2001/83/EC and Regulation (EC) No 726/2004 (Regulation initially published in the Official Journal L 324 of 10 December 2007).

The aim of the Regulation is to establish specific rules concerning the authorisation, supervision and pharmacovigilance of advanced therapy medicinal products.

The corrigendum relates to **Article 28 of the Regulation** (Amendments to Directive 2001/83/EC, point 4):

- in Article 6(1), the first subparagraph shall be 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, read in conjunction with Regulation (EC) No 1901/2006 of the European Parliament and of the Council of 12 December 2006 on medicinal products for paediatric use and Regulation (EC) No 1394 /2007.

# Advanced therapy medicinal products

2005/0227(COD) - 25/04/2007 - Text adopted by Parliament, 1st reading/single reading

The European Parliament adopted a resolution based on the draft by Miroslav **MIKOLÁŠIK** (EPP-ED, SK) and made some amendments to the proposed regulation on advanced therapy medicinal products. Parliament voted by 403 votes for, 246 against and 11 abstentions in favour of the compromise package submitted by the PSE, ALDE and GUE/NGL Groups, reflecting an agreement found between the three Shadow Rapporteurs from these Groups, against the wish of the Rapporteur. The main amendments were as follows:

- the "ethical" amendments (submitted originally by the Legal affairs Committee and taken over by the Environment in the framework of enhanced cooperation) were rejected. These amendments stipulated that the regulation should not apply to advanced therapy medicinal products that contain or are derived from human embryonic or foetal cells, primordial germ cells or cells derived from those cells;

- a number of definitions were clarified. On "tissue engineered product", Parliament stated that products containing or consisting exclusively of non-viable human or animal cells and/or tissues, which do not contain any viable cells or tissues and which do not act principally by pharmacological, immunological or metabolic action, shall be excluded from this definition. It felt that the Medical Devices Directives (MDD) provide a regulatory framework which is readily adapted to the control of devices containing or made of tissue engineered products. If a tissue engineered product falls within the definition of 'medical device' in Article 1 of the MDD (and therefore does not have a mode of action which is primarily pharmacological, immunological or metabolic), it should be regulated under the MDD;

- cells or tissues shall be considered "engineered" if they fulfil at least one of the following points: the cells or tissues have been subject to substantial manipulation, so that biological characteristics, physiological functions or structural properties relevant for the intended regeneration, repair or replacement are achieved. The manipulations listed in Annex I, in particular, shall not be considered as substantial manipulations; or the cells or tissues are not intended to be used for the same essential function or functions in the recipient as in the donor;

- according to Directive 2001/83/EC and the Medical Device Directives the basis for deciding which regulatory regime is applicable to combinations of medicinal products and medical devices is the principal mode of action of the combination product. However, the complexity of combined advanced therapy medicinal products containing viable cells or tissues requires a specific approach. For these products, whatever the role of the medical device, the pharmacological, immunological or metabolic action of these cells or tissues should be considered to be the principal mode of action of the combination product. Such combination products must always be regulated under this Regulation;

- Member States should be urged to take all necessary steps to encourage a strong public and non-profit sector involvement in the procurement of human cells or tissues;

- the fee for scientific advice from the Agency should be kept at a minimal level for small and medium-sized enterprises, and should also be reduced for other applicants. The 90% reduction in the fee payable to the EMEA for scientific advice, which the Commission was proposing in order to boost innovation in the field of advanced therapy medicinal products, should be granted only to SMEs; other firms should get a maximum reduction of 65%. Parliament also introduced new articles providing for financial incentives for biotech SMEs, a reduction of 50% in the marketing authorisation fee they pay;

- Parliament emphasised that the Commission should consult the European Medicines Agency (EMEA) on drawing up guidelines;

- the European Parliament should be consulted on the appointment of members of the CAT representing clinicians. There will also be two members and two alternates appointed by the Commission, on the basis of a public call for expressions of interest and after consultation of the European

Parliament, in order to represent patients associations. At least two members and two alternates of the Committee for Advanced Therapies shall have scientific expertise in medical. One amendment spelled out more clearly that members and alternate members of the committee must "have no financial or other interests in the biotechnology sector and medical device sector";

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

- Parliament was concerned about the notification of adverse reactions, and stipulated that the follow-up of efficacy and adverse reactions is a crucial aspect of the regulation of advanced therapy medicinal products. The applicant should therefore detail in its marketing authorisation application whether and, if so, which measures are envisaged to ensure such follow-up. If serious adverse events or reactions occur in relation to a combined advanced therapy medicinal product, the Agency shall inform the relevant national competent authorities responsible for implementing the requirements of Directive 2004/23/EC, Directive 93/42/EEC and Directive 90/385/EEC;

- on comitology, a new clause states that the regulatory procedure with scrutiny provided for in Article 5a of that Decision will apply to the adoption of amendments to Annexes I to IV to this Regulation and to Annex I to Directive 2001/83/EC. Since these measures are essential for the proper operation of the whole regulatory framework, they should be adopted as soon as possible;

- in its report, the Commission must assess the impact of technical progress on the application of this Regulation. It shall also review the scope of the Regulation, including in particular the regulatory framework of combined advanced therapy medicinal products;

- advanced therapy medicinal products, other than tissue engineered products, which were legally on the Community at the time of application of this Regulation will comply with this Regulation no later than 3 years after its application. Tissue engineered products which were legally on the Community market at the date of application of the Regulation shall comply with it no later than 4 years after its application. The Regulation must apply from 1 year after entry into force.

# Advanced therapy medicinal products

2005/0227(COD) - 30/05/2007

The Council unanimously accepted all the amendments voted by the European Parliament plenary on 25 April 2007 concerning a draft Regulation on advanced therapy medicinal products. Thus, an agreement at first reading was reached with the European Parliament. The text now agreed will be formally adopted as soon as it has been legally and linguistically finalised in all the official languages.

# Advanced therapy medicinal products

2005/0227(COD) - 16/11/2005 - Document attached to the procedure

**COMMISSION'S IMPACT ASSESSMENT**

*For further information regarding the context of this issue, please refer to the summary of the Commission's initial proposal for a Regulation on Advanced Therapy Medicinal Products - COM(2005)0567.*

**1- POLICY OPTIONS AND IMPACTS**: Six options were considered by the Commission.

**1.1- Option 1 - Status quo – no new regulation at European level:** In the absence of a clear and comprehensive regulatory framework at European level, the application of different legal requirements in the Member States results in legal uncertainty for economic operators, as well as obstacles to the free circulation of tissue engineered products (TEPs). Fragmentation of the European market may deprive patients' access to a number of innovative therapies using TEPs.

**1.2- Option 2 - Extension of the Medical devices legislation to include TEPs**: However, although TEPs may incorporate medical device elements, they raise inherent and specific issues due to the presence of manipulated tissues and cells and the associated risks, *e.g.* viral safety and the transmission of infectious diseases, as well as pyrogenicity.

**1.3- Option 3 - "New approach" legislation**: The Commission also looked into the possibility of proposing separate legislation based on the regulatory principles of the "new approach" (similar approach as the one used to regulate medical devices). Under the "new approach" concept, conformity of the product with the technical 'essential requirements' laid down in legislation is assessed by a notified body (public or private) officially designated by the Member States. However, expertise in tissue engineered products, although increasing, remains limited in Europe.

**1.4- Option 4 - Semi-centralised and 2-tier authorisation procedure:** This would consist in setting up a specific regulatory framework based on semi-centralised procedures. Under this framework, applications for authorisation of TEPs would be submitted to and processed by the competent authorities of the Member States, passed on to a central scientific committee for evaluation, and eventually approved by the Community. This would have introduced two layers of bureaucracy and may have been considerably time-consuming.

**1.5- Option 5 - 'Third pillar' approach:** The Commission services assessed the opportunity to establish a new, independent regulatory framework, which would specifically and exclusively address TEPs ('third pillar'). It implied that the European Medicines Agency (EMEA) would be responsible for assessing TEPs, through the involvement of a newly created Committee on TEPs but presented one major shortcoming, insofar as it addressed TEPs in isolation from other cell-based, advanced therapies. The common scientific and economic characteristics that TEPs, somatic cell therapy and gene therapy share were overlooked in this option.

**1.6- Option 6- 'Advanced Therapies' approach:** The Commission then investigated the option of a more global and integrated approach, building upon existing legislation. This approach consists in addressing all advanced therapies (gene therapy, somatic cell therapy, tissue engineering) within a single and coherent framework, taking into account their regulatory and technical specificities.

*CONCLUSION*: Option 6, in the form of a Regulation, is therefore considered as the most appropriate legal instrument. Such a global approach presents the advantage of meeting the main objectives of the proposal (*i.e.* it **fills the current regulatory gap** with respect to tissue engineered

products in order to achieve a functioning internal market, taking as a base a high level of health protection), **while ensuring legal clarity, consistency and coherence with the existing legislative framework.** Also, in the absence of specific national legislation on TEPs in a number of Member States, a Regulation will facilitate the application of common rules without requiring any transposition measures at national level.

**IMPACTS**: Although the proposal addresses all advanced therapy products, the **most significant impact is in the tissue engineering sector**, which at present is not regulated at all by Community legislation. The impact on gene therapy and cell therapy sectors, which have been regulated for many years under the legislation on medicinal products, is considered to be less significant.

**Legal uncertainties** for manufacturers will be **reduced** by facilitating the classification of TEPs and providing transparent legislation. On the other hand, the regulatory framework for TEPs may become more stringent than some current national regimes, resulting in increased costs for some companies.

A clear improvement can be expected compared to the current situation regarding **costs related to the product classification process.** There may be increased costs in comparison to the present situation, e.g. compliance with good manufacturing practice (GMP) or the obligation to provide clinical data may require adaptations for some companies. However, the rise in costs will vary between Member States as well as between individual applicants. Implementation of the proposed Regulation is likely to demand tighter post-market surveillance and long-term traceability. Thus, costs related to the post-approval phase are likely to increase).

As the proposed approach builds on existing Community law, all incentives and competitiveness-related provisions which are already laid down would directly impact on companies developing advanced therapies. They should have a **strong positive economic impact** on the tissue engineering sector.

A **single EU market for TEPs** is likely to have positive effects on economic operators in the short term, due to reduced risks in accessing new markets, as well as less demanding procedures for marketing products in several countries. In the longer term, additional positive effects are expected due to increased trust in the products, higher demand and, consequently, higher sales. These improvements are of vital importance, in particular for the development of SMEs in this sector.

Another effect of the proposal is that the EU could become more attractive market for non-EU companies. This would increase competition in the field, which might have negative effects on companies that are less developed in terms of innovation capabilities.

In the short term, manufacturers will need to adapt to **new and tighter requirements for market authorisation**. This will bind resources and might lead to some companies exiting the market. For SMEs, the level of R&D investment and innovation activities may decline in a first phase. This may lead to concentration on fewer products, increased cooperation with larger companies for marketing products and financing R&D and vertical specialisation.

The short to mid-term impact of the proposed Regulation on **employment** will most likely be very modest due to the early development stage of the tissue engineering and advanced therapies sector.

Generally, environmental risks are considered to be low, because of the low production volume, the use of readily degradable substances, the limited survival of cells outside controlled laboratory environment and strict manufacturing conditions. The same holds true for gene and somatic cell therapy.

**2- FOLLOW-UP** : The draft Regulation includes a proposal for, within five years of entry into force, a general report on experience acquired as a result of the application of the Regulation. Through this report, *ex-post* evaluation is already planned. Furthermore the need for a designated independent study to support the general report might be considered. Such an independent study could include within its scope the financial and social impacts for which prospective data collection is problematic.