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Annex to the **:**

PROPOSAL FOR A REGULATION ON ADVANCED THERAPY MEDICINAL PRODUCTS

IMPACT ASSESSMENT

{COM(2005) 567 final}

EXECUTIVE SUMMARY

Tissue engineering is an emerging biotechnology sector at the interface between medicine, cellular/molecular biology, materials science and engineering. It aims at developing cell- or tissue-based products to replace, repair or regenerate human tissues. Together with other advanced therapies like gene therapy or cell therapy, this emerging and fast-growing biotechnology sector paves the way for new, highly promising treatment opportunities for European patients.

However, the development of this sector is currently hampered by the lack of a harmonised and tailored regulatory environment. While the other advanced therapy products have been regulated as medicinal products for many years within the Community, tissue-engineered products currently lie outside of any EU legislative framework. This leads to divergent national approaches as to their legal classification and authorisation, which impair the free movement of these products, hinder patients' access to innovative therapies, and ultimately affect the EU competitiveness in this key biotechnology area.

In order to bridge this regulatory gap, the European Commission proposes to establish specific procedures and requirements for the authorisation, supervision and vigilance of tissue engineered products, in the broader context of advanced therapies. This initiative is part of the Commission Legislative Work Programme for 2005[1]. Objective is to ensure the free movement of these products, while guaranteeing an equal high level of safety for patients throughout Europe.

In accordance with the principles set out in the Communication '***Better Regulation for Growth and Jobs in the European Union***'[2], this impact assessment report provides a detailed overview of the policy options envisaged by the European Commission to meet its objective. It is based, in particular, on wide-ranging consultation with all stakeholders, including patients, industry, hospitals, doctors, regulators, and the research community.

Outcome of the impact assessment suggests that the proposed Regulation should be of significant benefit for all actors in the field, by providing legal clarity and certainty, harmonising quality, safety and efficacy standards for the placing on the Community market of these products, improving the competitiveness of the concerned economic operators and increasing the confidence of patients and healthcare practitioners.

In practice, the success of this proposal will depend on particular attention paid to certain categories of stakeholders –most notably hospitals and small and medium-sized enterprises (SMEs)– so as to ensure a high level of health protection without imposing an unnecessary regulatory burden. The subsequent establishment of technical requirements for tissue engineered products, and the related scientific guidelines, will also be important to ensure that the overall regulatory framework on advanced therapies is balanced, tailored, and can keep the pace with new scientific developments.

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1 http://europa.eu.int/comm/off/work_programme/index_en.htm

2 COM(2005) 97 final, 16.3.2005. See also: http://europa.eu.int/comm/enterprise/regulation/better_regulation/index_en.htm

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This impact assessment report provides a detailed overview of the policy options envisaged by the European Commission with a view to establishing a harmonised regulatory framework for tissue engineered products (**TEPs**), in the broader context of advanced therapies. It outlines the background to the proposal and presents an in-depth analysis of all legislative options available and possible impacts that may derive from them.

Impact Assessment is one of the key tools put forward by the Commission to promote Better Regulation for Growth and Jobs in the European Union[3]. The Commission's commitment to integrated impact assessment is based on the principle of sustainable development and is designed to allow policy makers to make choices on the basis of careful analysis of the potential economic, social and environmental impacts of new legislation. This integrated approach is based upon the principle of a thorough and balanced appraisal of all impacts and allows the presentation of a comprehensive analysis and the identification of trade-offs, where relevant. A key idea is that the depth and scope of an impact assessment, and hence the resources allocated to it, are proportionate to the expected nature of the proposal and its likely impacts. Finally, Impact Assessments must go hand in hand with wide-ranging consultation allowing for sufficient time to receive the views of all stakeholders who wish to contribute to the shaping of new rules.

This Impact Assessment is based primarily on:

– Experience with existing EU legislation on medicinal products, medical devices and human tissues and cells;

– Experience with gene therapy and somatic cell therapy products at the European Medicines Agency (EMEA);

– Extensive consultation with all stakeholders;

– Two studies on human tissue engineering conducted by the Institute for Prospective Technological Studies (IPTS)[4];

– Experience with legislation on human cells, tissues, and cellular and tissue-based products (HCT/Ps) in the United States (US); and

– Published literature on scientific, economic, regulatory and ethical aspects of tissue engineering and 'regenerative medicine' in general.

This document is to be read together with the proposal for a Regulation on Advanced Therapy Medicinal Products, and the accompanying Legislative Financial Statement.

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3 COM(2005) 97 final, 16.3.2005. See also: http://europa.eu.int/comm/enterprise/regulation/better_regulation/index_en.htm

4 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 - http://www.jrc.es/home/publications/publication.cfm?pub=1127. and "Human tissue-engineered products: Potential socio-economic impacts of a new European regulatory framework for authorisation, supervision and vigilance", 2005, to be published.

1. INTRODUCTION

Tissue engineering is an emerging biotechnology sector at the interface between medicine, cellular/molecular biology, materials science and engineering. It aims at developing cell or tissue-based products to replace, repair or regenerate human tissues. TEPs are manufactured on the basis of cells of human (human TEPs) or animal (xenogeneic TEPs) origin, before being implanted in, applied on or administered to the patient (usually *via* a surgical operation).

Current applications of this nascent field of "regenerative medicine" include treatment for skin, cartilage and bone diseases or injuries. More complex products – such as heart valves, blood vessels or heart muscle tissue – are currently in pre-clinical and clinical development, and could reach the Community market in a near future.

From a regulatory and scientific viewpoint, TEPs lie within a spectrum of advanced therapies, which includes other cell-based therapies like gene or somatic cell therapy, with which they share a number of scientific and economic features:

– They are based on complex, innovative manufacturing processes aiming at modifying genetic, physiological or structural properties of cells and tissues. The specificity of the product precisely lies *in* the process.

– Regulatory and scientific expertise for the evaluation of advanced therapies, although increasing, remains limited;

– Traceability from the donor to the patient, long-term patient follow-up and a thorough 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 (SMEs), highly-specialised divisions of larger operators in the Life Science industry (biotechnology, medical devices and pharmaceuticals), hospitals or tissue banks. They are subject to rapid and often radical innovation.

Advanced therapies herald new forms of medical treatment. Tissue engineering, through its focus on the regeneration of human tissues, is expected to have a major impact on future medical practice. One of the longer term perspectives is to be able to regenerate full organs and hence to tackle the issue of donor shortages. Thus, the development of this novel biotechnology area paves the way for new and highly promising treatment opportunities for patients.

TEPs have already been present on the European market for several years. Current sales do not exceed 60 million euros per year worldwide. However, market growth is expected to be substantial in the coming years, with an estimated market potential roughly around 100 billion euros worldwide[5].

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[5] Bock, A.K., Ibarreta, D., Rodriguez-Cerezo, E.: "Human tissue-engineered products - Today's markets and future prospects".

2. WHAT ISSUE IS THE PROPOSAL EXPECTED TO TACKLE ?

Tissue engineering uses cells or tissues for the regeneration of human body parts, sometimes with the help of supporting scaffolds and/or biomolecules such as growth factors. Despite the commonalities with other advanced therapies like gene or cell therapy, which are already regulated under existing Community legislation, TEPs currently lie outside of any EU legislative framework.

2.1. A fragmented and incomplete regulatory framework

The EU has established an important set of legislative rules to promote an effective internal market for safe and efficacious health products: medicinal products, medical devices, etc., and for the safeguard of public health in respect of human cells and tissues. However, at present, tissue engineered products are not adequately covered by any existing Community legislation (

Figure):

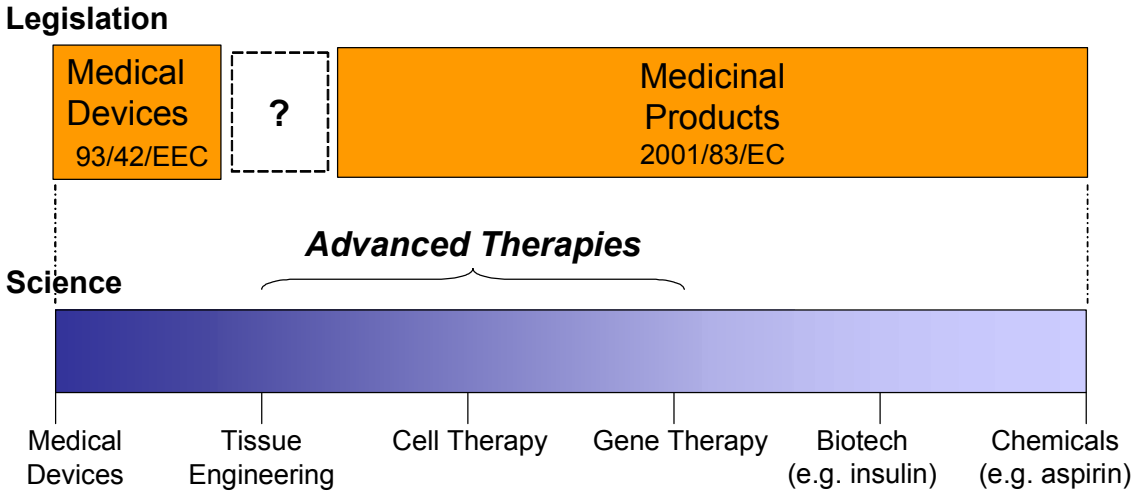

Figure f products and corresponding. 1: o

The main Directive on medical devices is Dir. 93/42/EEC. The main Directive on medicinal products is Dir. 2001/83/EC.

– Products incorporating or derived from tissues or cells of human origin, such as human TEPs, are explicitly excluded from the scope of Directive 93/42/EEC on medical devices[6];

– Directive 2001/83/EC on the Community code relating to medicinal products for human use[7] regulates gene therapy and somatic cell therapy products, but not TEPs.

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6 Directive 93/42/EEC of the Council concerning medical devices - Article 1, paragraph 5, point f), OJ L169, 12.7.1993, p.1. See also http://europa.eu.int/comm/enterprise/medical_devices/index_en.htm

7 Directive 2001/83/EC of the European Parliament and of the Council on the Community code relating to medicinal products for human use, OJ L311, 28.11.2001, p. 67. Directive as amended by Commission Directive 2003/63/EC, OJ L159, 27.06.2003, p 46, and Directive 2004/27/EC, OJ L136, 30.4.2004, p.34.

No legal definition of 'tissue engineering' is laid down, although one may argue that the current definition of somatic cell therapy partly encompasses tissue engineering. Specific requirements for the demonstration of the quality, safety and efficacy of tissue engineered products are also missing;

– Directive 2004/23/EC provides for quality and safety standards for the donation, procurement, testing, processing, preservation, storage and distribution of human tissues and cells[8]. However, it does not address efficacy aspects, does not lay down rules for the evaluation and marketing authorisation of tissue/cell-based manufactured products, and also does not cover products based on animal cells. More broadly, Directive 2004/23/EC is based on Article 152 of the Treaty establishing the European Community (EC Treaty), which aims at establishing a high level of human health protection but does not pursue an 'internal market' objective. As such, it does not ensure the free movement of TEPs within the Community.

2.2. A disrupted internal market

In the absence of a specific and comprehensive legal framework at Community level, Member States often authorise TEPs on an *ad hoc* basis. National authorities tend to rely on existing legislation, in particular provisions on medical devices or medicinal products. In addition, some Member States have adopted specific measures or defined guidelines to regulate the production, authorisation and use of TEPs. This results in divergent national approaches and creates discrepancies regarding both the legal classification of TEPs and the conditions under which such products may be manufactured and placed on the market in Member States (**Figure 2**).

	Country	Austria	Belgium	Bulgaria	Cyprus	Finland	France	Germany	Ireland	Netherlands	Poland	Slovakia	Spain	Sweden	UK
framework	not at all			●●	●●				●●	●●	●●	●			
	as medicinal product (MP)	●●	●●			●●		●●							
	as medical device (MD)														
	as MP or MD, decided on case-by-case basis												●●	●●	●●
	specific national guidance						●●								●●
	other regulations	●●										●			
authorisation	by product authorisation (PA)		●					●							
	by manufacturing authorisation (MA)	●●	●					●●							
	by accreditation... of the tissue establishment		●●									●			
	by PA and MA						●●	●					●●		
import	from EU MS mandatory through accredited... tissue establishment in your country		●●				●●					●	●●		
	from non-EU country mandatory through accredited... tissue establishment in your country		●●				●●					●	●●		

Figure 2: Regulation for autologous and allogeneic human TEPs in EU Member States

[8] Directive 2004/23/EC of the European Parliament and of the Council on setting standards of quality and safety for the donation, procurement, testing, processing, preservation, storage and distribution of human tissues and cells, OJ L102; 7.4.2004, p. 48.

(as of March 2004; ref.: See Footnote 2)

The diversity of national approaches creates obstacles to the free movement of TEPs. For each country where a tissue engineered product is planned to be marketed, different requirements must be complied with and, in many instances, a specific authorisation procedure needs to be completed. Manufacturers often consider these procedures as opaque and lengthy, making it difficult for them to place their products on the market. This situation could prevent patients' access to innovative therapies in some EU countries, although such therapies are readily available in others. Regulatory differences may also act as barriers to guaranteeing a high level of public health protection across the European Union. Finally, divergent approaches in the Member States could impede the development of a strong tissue engineering sector in Europe and affect the European Union's competitiveness in this key biotechnology area.

In a recent European Commission's study on the human tissue engineering market in Europe, the lack of a harmonised and comprehensive legal framework was identified as one of the main challenges which this emerging sector is facing[9]. This study notably demonstrated that, while European companies are at the same level of scientific and technological excellence as their world competitors, they are disadvantaged by the fragmentation of the European market. Obviously, this situation is also detrimental to European patients.

3. MAIN OBJECTIVES OF THE PROPOSAL

The overall policy objective is to bridge the existing regulatory gap, in order to improve patients' safe access to tissue engineered products and other advanced therapies by increasing the research, development and authorisation of these products.

More specifically, the main objectives are:

- To guarantee a **high level of health protection** for European patients treated with advanced therapies;
- To **harmonise market access** for advanced therapies 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 these 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.

Beyond these policy objectives, it is also essential to ensure consistency between the proposal and other legal instruments already in place in the Community, most notably the legislation on medical devices, human tissues and cells, and medicinal products.

[9] See footnote 2, 1st report.

4. MAIN POLICY OPTIONS AVAILABLE TO REACH THE OBJECTIVE

Different regulatory approaches were considered and discussed with interested parties during the preparatory phase leading to this proposal.

Given the potential health risks associated with TEPs, it is essential to provide a coherent and stable regulatory framework, which is strictly enforced in all Member States where these products are manufactured, imported or put on the market. A Regulation is therefore considered as the most appropriate legal instrument. It will ensure uniform and timely application of the provisions, for the benefit of all actors involved in the sector. Moreover, 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.

4.1. Regulatory options considered

4.1.1. 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 TEPs. Fragmentation of the European market may deprive patients' access to a number of innovative therapies using TEPs.

Existing legislation on medical devices, human tissues and cells and medicinal products does not appear sufficient to properly cover TEPs and address the above issue of lack of harmonisation (see also Section 2.1). Besides, all consultations highlighted a broad consensus in favour of a specific EU regulatory framework, covering tissue engineered products as well as other cell/tissue based products. Maintaining the *status quo* does therefore not appear as an acceptable option.

4.1.2. Extension of the Medical devices legislation

The opportunity to extend the scope of Directive 93/42/EEC on medical devices to include TEPs was considered early in the process. 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. These aspects were also recognised by the Council during the adoption process of Directive 98/79/EC on *in vitro* diagnostic medical devices: the Council agreed that "*in view of the many problems (existing and future) raised by substances of human origin, much more careful study was required of all the safety and ethical aspects of the question*"[10].

[10] OJ C 178 , 10.6.1998, p.7

4.1.3. "New approach" legislation

The Commission services also addressed the possibility of proposing separate legislation based on the regulatory principles of the "new approach"[11] (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. In this context, it is questionable whether any single public or private entity would, at national level, possess the required expertise and capacity to evaluate such highly complex products which include biological, physical and chemical aspects. In order to ensure true harmonisation of requirements across the EU, pooling of scientific expertise also appeared more adequate than the designation of scientific bodies spread over various Member States.

4.1.4. Semi-centralised and 2-tier authorisation procedure

One of the options envisaged consisted in setting up a specific regulatory framework based on a semi-centralised procedure (see also Section 11.3). 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 option presented a major advantage in that applicants could introduce applications in their own language and have as a main interlocutor the national authorities they are accustomed to work with. However, this procedure would have introduced two layers of bureaucracy and may have been considerably time-consuming. Results of public consultation conducted in 2002 also revealed a clear majority against this policy option.

Another possible policy choice consisted in establishing a mechanism in which the Community and the Member States would share the responsibility of granting marketing authorisations. During the stakeholders' consultation process, the Commission services investigated the opportunity to establish a procedure along this line (see also Section 11.4). A "two-tier" approach was envisaged, whereby allogeneic products (based on tissues and cells from another human being) would be authorised exclusively by the Community, whereas autologous products (based on tissues and cells from the same person) could be authorised either by the Member States' competent authorities or by the Community, at the choice of the manufacturer. The impact of this approach was thoroughly analysed in collaboration with the IPTS (see also Section 11.1).

The two-tier approach was initially contemplated with a view to limiting the regulatory and administrative burden on small operators, in particular hospitals, tissue banks and small and medium-sized enterprises (SMEs). It was based on the observation that those operators tend to produce autologous products for local or regional use, or for their own patients in the case of hospitals. On the other hand, allogeneic products are more likely to be produced in batches and placed on the market in several Member States.

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[11] More information on the New Approach to technical harmonisation can be found at: http://europa.eu.int/comm/enterprise/newapproach/index.htm

However, field research carried out in relation to the proposal demonstrates that very few hospitals and tissue banks currently produce – or are planning to produce – TEPs[12]. When they are involved in tissue engineering, health institutions do not usually manufacture products on a large, industrial-type scale. Their activities are rather focused on research and, in some cases, on the development of products intended for the in-house treatment of particular patients. Besides, a registration process already applies to those establishments[13]: the requirement for a marketing authorisation, be it at national or Community level, would only add another layer of bureaucracy, for little public health benefit. Therefore, it would appear more appropriate to introduce a specific exemption for these tailor-made, in-house produced and patient-specific products.

The two-tier approach was also reconsidered in light of the 2004 public consultation results (see Section 11.4). A number of interested parties pointed out that:

– A regulatory approach based on the autologous vs. allogeneic criterion would create an artificial distinction between products which may indeed carry the same level of risk. In both cases, a thorough scientific assessment, based on uniform criteria, should be required.

– Scientific expertise on TEPs is scarce, and may not be evenly distributed in all Member States. Pooling of that expertise is therefore crucial, not only to guarantee a high level of scientific evaluation, but also to preserve the confidence of patients and medical practitioners in the system.

– In a decentralised procedure, all Member States, irrespective of the development of a national tissue engineering sector and respective applications, would be required *by law* to build up the necessary infrastructure and expertise for the evaluation of autologous products, thus increasing the overall complexity and the costs of the proposal.

– A decentralised system would require, in one way or another, mutual recognition of authorisations granted at national level. The establishment of a genuine internal market and access to the whole Community market would hence depend directly on the actual functioning of such recognition system.

These findings were further confirmed during the 2005 public consultation (see Section 11.5).

Two other options were further explored by the Commission services:

– *('Third pillar' approach)* Introducing a third, new regulatory framework solely for TEPs, independent from existing legislation on medical devices and medicinal products, and based on a fully centralised authorisation procedure; or

– *('Advanced Therapies' approach)* Designing a comprehensive regulatory framework which encompasses all advanced therapies based on genes, cells and tissues (*i.e.* gene therapy, somatic cell therapy and tissue engineering). Such framework would build on

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12 See REF 2nd IPTS REPORT, Section 0

13 See Article 6 of Directive 2004/23/EC.

existing legislation (medicinal products, medical devices, human tissues and cells) and applicable regulatory principles, while adapting to the technical specificities of the products and to the particularities of the economic operators concerned.

4.1.5. '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'). This approach was advocated by certain stakeholders, in particular amongst industry, during the public consultation process. It implied that the European Medicines Agency (EMEA) would be responsible for assessing TEPs, through the involvement of a newly created Committee on TEPs. Nevertheless, specific procedures and technical requirements would be established for these products. The rationale behind such a 'third pillar' was to emphasise the specificity of TEPs compared to medical devices and "conventional" medicinal products.

However, this approach presented one major shortcoming, insofar as it addressed TEPs in isolation from other cell-based, advanced therapies. Common scientific and economic characteristics that TEPs, somatic cell therapy and gene therapy do share (see Section 1) were overlooked in this option.

From the consultation process, it appeared that most of, if not all the overarching regulatory principles applicable for the evaluation and authorisation of gene and cell therapy are equally relevant to tissue engineered products: concept of marketing authorisation, demonstration of quality, safety and efficacy, post-authorisation vigilance and risk management, variations to the marketing authorisation dossier in case of changes in the manufacturing process, traceability, etc. At best, the establishment of a separate and specific regulatory framework for TEPs would hence create an unnecessary duplication of these legislative provisions, by introducing essentially similar principles twice, in different 'pillars'. This approach was likely to entail confusion and legal uncertainty. The risk of borderline issues and legal conflicts between the different regulatory instruments was high, while one the primary objectives of the initiative is precisely to ensure legal certainty.

4.1.6. 'Advanced Therapies' approach

As an alternative to a completely new legal framework designed for the sole purpose of regulating TEPs, the Commission 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 (Figure 3).

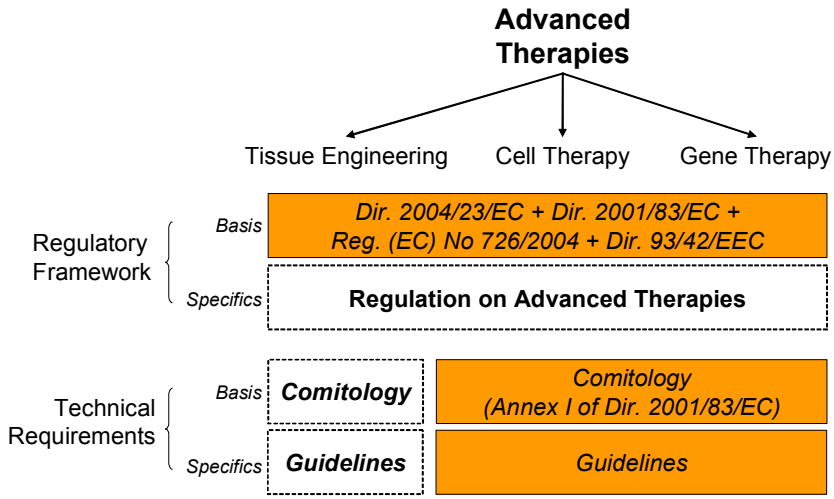

Figure 3: The 'Advanced Therapies' regulatory strategy.
Existing elements are highlighted in grey; elements to be established are highlighted in white, dashed boxes.

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.

Concretely, the approach is based on 3 levels (Figure 3):

1. A tailored **Regulation on Advanced Therapy Medicinal Products**, covering gene therapy, cell therapy, and tissue engineered products, which would lay down tailored regulatory principles for the evaluation and authorisation of these products: marketing authorisation procedure, post-authorisation vigilance, traceability, etc. Such Regulation would build on already-existing legislation, in particular:

   – Directive 2004/23/EC, which lays down basic quality/safety requirements on human tissues and cells;

   – Regulation (EC) No 726/2004, which establishes the so-called 'centralised procedure' and the role/structure of the European Medicines Agency (EMEA)[14];

   – Directive 2001/83/EC on medicinal products;

   – Council Directive 93/42/EEC concerning medical devices.

   As in the 'third pillar' option, the EMEA would be responsible for assessing TEPs, through the involvement of a newly created Committee (Committee for Advanced Therapies, see Sections 8.2.5 and 9).

2. Technical requirements. It is well acknowledged that advanced therapy products are neither standard medical devices, nor conventional medicines: therefore, the

[14] OJ L136, 30.4.2004, p.1

technical requirements necessary to demonstrate their quality, safety and efficacy (*e.g.* the type of pre-clinical and clinical data required, control of the manufacturing process, etc.) would be highly specific.

As regards gene and somatic cell therapy products, those high-level requirements are already laid down in Annex I to Directive 2001/83/EC[15] (which is amendable *via* a so-called 'comitology' procedure), and further complemented by guidelines[16]. In order to provide for the same level of flexibility, it would be proposed to follow a similar approach regarding tissue engineered products (Figure 3), *i.e.* to lay down the main technical requirements that are specific to these products through a 'comitology' procedure, and to further complement them with guidelines.

3. Detailed guidelines. As for gene and somatic cell therapy products, detailed technical guidance would be drawn up for tissue engineered products through guidelines, drawn up either by the EMEA or by the Commission (Figure 3). 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, in particular the industry, for the drafting of these guidelines.

Such a global approach presents the advantage of meeting the main objectives of the proposal (*i.e.* fill 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.

In addition, the assessment of advanced therapy products often requires very specific expertise, which goes beyond the traditional pharmaceutical field and extend to other sectors such as biotechnology, medical devices, materials science and engineering, cell biology, etc. In this context, an integrated approach offers the opportunity to bring together the scientific expertise which is necessary for assessing the quality, safety and efficacy of all advanced therapy medicinal products (rather than just TEPs).

However, it would be critical in this option to ensure that:

– a fully centralised approach does not entail an unnecessary regulatory overburden on certain stakeholders (e.g. hospitals, universities and research community);

– the existing legislation is properly adapted to meet the specificities and corresponding requirements of advanced therapies, in particular tissue engineered products.

4.2. Regulatory option retained

Figure 4 provides an overview of the pros and cons of all regulatory options envisaged. In light of these elements, the Commission considered the 'Advanced Therapies' option as

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15 Annex I to Directive 2001/83/EC, as amended by Directive 2003/63/EC, OJ L159, 27.6.2003, p.46.

16 See http://www.emea.eu.int/htms/human/itf/itfguide.htm

the most sensible and practical way forward towards an effective regulatory framework for TEPs in particular and other advanced therapies in general.

	Pros	Cons
Status Quo	Does not require any change	–Current situation is unharmonised –Stakeholders in favour of a specific EU framework
Extension of the Medical Devices legislation	Existing framework with demonstrated practicability	–Tissues/cells raise specific safety, efficacy and ethical issues –Scarcity of expertise / Notified bodies –Community harmonisation may not be ensured
'New Approach' legislation	–Concept of 'New approach' has worked well in other sectors –'Essential requirements' system provides for flexibility	–Scarcity of expertise / Notified bodies –Community harmonisation may not be ensured
Semi-centralised and 2-tier auhtorisation	–Flexible system, match the need of local/national producers –Use of existing resources and expertise at national level	–Scarcity of expertise –National authorisation implies mutual recognition; Community harmonisation might not be ensured –2 layers of bureaucracy; overall complexity of the system
'3rd pillar'	–Specificity of TEPs emphasised and addressed –New framework allows flexibility	–Creates artificial border between TEPs and other, 'similar' products (e.g. cell therapy) –Duplication of existing and applicable regulatory concepts; 'reinvent the wheel' risk
'Advanced Therapies' approach	–Builds on existing and applicable frameworks –Focus on specificities –Allows for flexibility	–Need for special attention to small/local actors –Existing framework need to be adapted to match specificities

Figure 4: Overview of all regulatory options envisaged.

4.3. Subsidiarity and proportionality

The European Commission's proposal carefully takes into account the principles of subsidiarity and proportionality. The proposed rules aim at harmonising an area in which application of existing Community legislation and additional national measures have proven insufficient. Lack of Community action would hamper the functioning of the internal market and may act as a barrier to guaranteeing a high level of public health protection (see Section 4.1.1). However, Member States will have a crucial role in the fulfilment of the objectives of the proposal.

In accordance with the proportionality principle, 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 stakeholders, in order to avoid imposing an unnecessary regulatory burden on certain economic operators (*e.g.* hospitals, universities and research community).

5. ECONOMIC, SOCIAL AND ENVIRONMENTAL IMPACTS

The following section considers the main economic, social and environmental impacts of the proposed option compared to a *status quo* situation, in which the Commission would not take action to recommend the adoption of common rules for TEPs. 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. Indeed, the technical requirements applying to gene therapy and cell therapy medicinal products, which are already laid down in Annex I to Directive 2001/83/EC, will not be modified by the proposal. The only main change related to these products concerns the introduction of a new Committee (Committee for Advanced Therapies, see Sections 8.2.5 and 9). Consequently, the impact analysis primarily focuses on the tissue engineering sector, and addresses other advanced therapies only where relevant.

The analysis of potential economic, social and environmental impact on tissue engineering is largely –but not exclusively– based on two studies carried out by the Joint Research Centre's Institute for Prospective Technological Studies (JRC-IPTS) in 2003 and 2004[17]. Both studies were conducted in collaboration with the European Science and Technology Observatory (ESTO), in particular by the Fraunhofer Institute for Systems and Innovation Research based in Karlsruhe, Germany.

This impact analysis focuses on the commercial, human tissue engineering sector. It also takes into account hospitals and tissue banks insofar as they are involved – or may become involved – in tissue engineering. However, little data is available regarding the scope and extent of hospitals and tissue banks tissue engineering activities in Europe. A qualitative survey was therefore carried out in three countries where the tissue engineering sector is well developed, namely: France, Germany and the United Kingdom (UK). The key findings are included in this analysis[18].

It is important to keep in mind that tissue engineering in particular, and advanced therapies in general, represent a young and dynamic sector, which is developing rapidly in Europe. Consequently, there are rather broad corridors of possible developments. The regulatory framework is only one of the key factors influencing the future of this biotechnology area. In addition, only limited and static information is available in this fast-moving field. The impact analysis therefore concentrates on the identification of possible trends and the evaluation of the overall impacts of the proposed Regulation.

The level of additional costs companies will face, as well as the ability to cope with these costs, mainly depends on the applicant's profile. In addition, future implementing measures and guidelines, to be adopted on the basis of the Regulation, will play a crucial role in helping certain categories of operators (*e.g.* smaller structures such as SMEs, hospitals and tissue banks) to adapt to the new requirements. According to estimates by tissue engineering experts, the majority of companies will be able to cope well or may need some adaptations which can be overcome (about 50% and 30%, respectively). Substantial adaptations might be required for around 20% of the companies[19]. Companies which have already implemented high levels of quality and safety, have acquired experience with authorisation procedures, produce TEPs in large quantities and have

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17 See footnote 2.

18 The complete reports are available in the Annex to this assessment. They can also be downloaded from the JRC-IPTS website at http://www.jrc.es.

19 See footnote 2, 2nd report.

sufficient resources will most probably encounter little or hardly any difficulties to cope with the proposed Regulation. Even though large companies are more likely to be in this situation, a number of smaller companies are already well established in the tissue engineering sector and should be able to adapt well to the new situation.

5.1. The tissue engineering sector in the EU

The commercial tissue engineering sector in the European Union is currently concentrated in the "old" Member States (EU-15). It is characterised by small, research-based and technology-oriented biotechnology companies. Many companies have less than 50 full-time equivalent employees (FTEs). A total of 113 tissue engineering companies were identified in the European Union in 2003. At this date, 35 TEPs were available on the European market, 90% of which were autologous products (consisting mainly of skin replacements and knee cartilage, as well as a few bone products)[20]. Survey results indicate that the majority of new products due to come on the market in the next five years will be autologous.

Currently, most TEPs are marketed at least on the home market of the company which produces them. The vast majority of SMEs and large companies involved in this sector are keen on marketing their products beyond their national market, up to the whole Community market. It seems that allogeneic products are always marketed in more than one country, whereas a few autologous products are only proposed in the company's home market. There is no tissue engineered product available in all EU Member States to date.

In addition to tissue engineering companies, some hospitals and tissue banks have engaged in tissue engineering activities. They mostly produce engineered cells and tissues for their own patients (in-house use) or for supply at a local level. Surveys conducted in France, Germany and the UK show that only a limited number of hospitals and tissue banks are currently involved in tissue engineering or intend to become active in this area in the future. Three different types of operators can be distinguished:

– *Research-driven hospitals* are integrated in, or affiliated with, national academic "centres of excellence" in tissue engineering or linked to tissue engineering companies. They carry out preclinical research with plans to proceed to the early stages of clinical trials. Their activities are restricted to research purposes. Products under development are mainly autologous, but research-driven hospitals are also carrying out research on allogeneic products. As far as placing on the market of TEPs is concerned, collaboration with companies or out-licensing is envisaged. Thus, applications for marketing authorisation are not part of these hospitals' strategy.

– *Treatment-driven hospitals* are often specialised hospitals, which focus on providing optimal treatments to their patients. Their research activities usually do not include the development of new TEPs, but rather concentrate on optimisation of treatments and comparison with other treatment options. In these hospitals, manufacturing activities concentrate on autologous products to be used for the hospital's own patients. However, some of the bigger institutions could envisage an extension of their

[20] See footnote 2, 1st report.

production. These products would be intended for in-house, as well as for use in other local or national hospitals. In contrast, smaller treatment-driven hospitals perceive the establishment of own manufacturing facilities as too demanding with the current technical possibilities.

– *Strategy-driven tissue banks* consider tissue engineering as a potential strategic option for their future development. However, the survey carried out in France, Germany and the United Kingdom indicates that no tissue bank currently produces TEPs on a genuine routine basis. Research is focused on specific technologies, such as the use of tissue derivatives and decellularised/demineralised matrices of allogeneic origin to be seeded with autologous cells. These research activities are partly carried out in cooperation with leading tissue engineering research groups.

5.2. Economic and competitiveness impacts

This section looks successively at the impact of the proposal on the various stakeholders. It also analyses its consequences on public expenditure.

5.2.1. Commercial undertakings, in particular SMEs

The proposed Regulation will provide a binding, harmonised legal framework, based on common requirements, for placing TEPs on the market throughout the European Community. On the one hand, it will reduce legal uncertainties for manufacturers by facilitating the classification of TEPs and providing transparent legislation. On the other hand, the regulatory framework for TEPs may become more stringent than current national regimes in some Member States, resulting in increased costs for some companies.

The introduction of a new piece of legislation by the Community is always susceptible to reduce flexibility for companies operating on the market, especially in an emerging and dynamic sector such as tissue engineering. However, this risk needs to be balanced with public health concerns. Furthermore, the benefits of an effective internal market, with direct access to it, must also be considered when assessing the economic impact of the proposal.

5.2.1.1. Marketing costs

On the basis of the IPTS reports, three groups of cost drivers have been identified for placing TEPs on the market:

– costs related to the product classification process;

– costs related to compliance with regulatory requirements; and

– costs related to the post-approval phase.

As far as product classification is concerned, a clear improvement can be expected compared to the current situation, with corresponding cost reductions for applicants. Identification of the appropriate regulatory framework, the responsible authorities and the relevant data requirements will be less time-consuming and resource-intensive. The process will have to be carried out only once and not for each Member State where the

product is planned to be marketed. The integration of all advanced therapies within the same framework should not only reduce the number of borderline cases, but also have a synergistic effect on companies developing several types of advanced therapy products, such as somatic cell therapy products *and* tissue engineered products (one single regulatory framework instead of several). Besides, the option to request a scientific recommendation from the Agency on the classification of any cell/tissue-based product (as foreseen in the proposal) should help in resolving borderline issues. This approach is relatively similar to the 'Tissue Reference Group' system in place in the US[21].

Compliance with regulatory requirements may entail increased costs in comparison to the present situation. For instance, 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. Currently, requirements differ widely in the EU, depending on national product classifications, country-specific approaches (for instance on safety issues, donor selection, good manufacturing practice) and the nature of the applicants (company, hospital etc.). The level of compliance costs will also depend on the detailed technical requirements to be laid down on the basis of the proposal (*i.e.* nature of the tests and studies to be carried out to demonstrate the quality, safety and efficacy of TEPs) compared to existing national rules. Fees for authorisations will be those applied by the EMEA in accordance with existing legislation, with specific reductions for SMEs. These fees will have to be paid only once, instead of several times for each authorisation in different EU countries (as is often the case currently).

Finally, 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. Moreover, costs for regular inspections might rise in countries where such controls were not required before the introduction of common requirements.

5.2.1.2. Competitiveness

As the proposed approach builds on existing Community legislation, in particular the legislation on medicinal products, all incentives and competitiveness-related provisions which are already laid down in this legislation would directly impact companies developing advanced therapies. This includes, *inter alia*:

– A harmonised data protection period (the so-called '8+2+1' rule), relating in particular to pre-clinical tests and clinical trials[22];

– The possibility to be designated as an orphan medicinal product, and hence to benefit from a 10 years market exclusivity period, protocol assistance and special financial incentives[23];

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21 See http://www.fda.gov/cber/tissue/trg.htm

22 See Article 14(11) of Regulation (EC) No 726/2004.

23 See Regulation (EC) No 141/2000, OJ L18, 22/1/2000, p.1

– An accelerated ('fast-track') assessment procedure, in the case of advanced therapy products which are of major public health interest, in particular from the viewpoint of therapeutic innovation[24];

– The option to get conditional marketing authorisations or marketing authorisations in exceptional circumstances[25].

Besides, the proposal foresees 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.

All these provisions should have a strong positive economic impact on the tissue engineering sector.

5.2.1.3. Access to the EU market

The establishment of 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. It can be expected that the time required for the first entry into the market will increase due to certain time consuming requirements, such as the obligation to conduct clinical trials. However, a reduction in time to access other national markets in the EU is likely to occur, based on effective harmonisation of requirements and authorisation procedures. This could result in an advantage for companies which are internationally oriented.

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. The expansion of the potential customer-base due to a larger market might also contribute to increased sales. However, pricing and reimbursement is a prerequisite for the full exploitation of market potentials. This aspect falls outside the scope of the proposal, as responsibility for pricing and reimbursement schemes in national healthcare systems remains with the Member States.

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. However, issues such as understanding of the market or the pricing and reimbursement mechanisms, awareness of public sensitivities, necessary proximity and training of medical staff will leave EU companies with an initial advantage in their home markets compared to non-EU competitors.

5.2.1.4. Specific provisions for SMEs

A vast proportion of economic operators in the field of advanced therapies are innovative SMEs. These companies can significantly benefit from the pooling of scientific expertise at Community level, but often lack experience and regulatory resources to cope with the

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[24] See Article 14(9) of Regulation (EC) No 726/2004.

[25] See Article 14(7) and 14(8) of Regulation (EC) No 726/2004.

centralised procedure and the EMEA as an administrative organisation. Without any adaptations, a fully centralised marketing authorisation procedure might have a negative impact on these economic operators.

Within the proposed approach, SMEs would nevertheless benefit directly from the incentives foreseen in the legislation on medicinal products (Article 70(2) of Regulation (EC) No 726/2004), i.e. *'establishing the circumstances in which small and medium-sized enterprises may pay reduced fees, defer payment of the fee, or receive administrative assistance'*. As it currently stands, the draft proposal for a Commission Regulation implementing this Article lays down three types of provisions[26]:

– Significant fee reductions, especially for scientific advice and inspections;

– Deferral of the fee for marketing authorisation application until the end of the procedure (*i.e.* until the notification of the final decision on the marketing authorisation is issued, or the application is withdrawn), in order to avoid that the financial condition of undertakings is weakened during the assessment phase;

– Administrative assistance: first, the EMEA would make appropriate arrangements to provide for the translations of all documents (summary of product characteristics, labelling and package leaflet etc.) which accompany the marketing authorisation. Secondly, a dedicated SME office would be created within the EMEA, with the sole remit of offering administrative assistance to SMEs. This office should provide a single interface between applicants and the Agency, so as to facilitate communication and to answer practical or procedural enquiries. More specifically, it would undertake the following tasks:

    - advising applicants on the administrative and procedural steps necessary to comply with the regulatory framework for the centralised procedure;

    - ensuring that all requests and applications submitted by the same applicant and related to a particular product are monitored within the SME Office, which would act as a facilitator for communication between the EMEA and the applicant;

    - organising workshops and training sessions for applicants on the administrative and procedural aspects of the regulatory framework for the centralised procedure.

As outlined in **Figure 5**, the estimated impact of the financial incentives may be very substantial.

[26] For more details, see http://pharmacos.eudra.org/F2/pharmacos/new.htm, 15/10/2004 and 10/01/2005.

	Standard application non-SME developing conventional pharmaceutical	Standard application SME developing TEPs	
Scientific Advice	*70 000 EUR*	7 000 EUR **(-90%)**	
Inspection	*17 000 EUR*	1 700 EUR **(-90%)**	*Payment deferred until the end of the procedure*
Marketing Autorisation Application	*232 000 EUR*	232 000 EUR if success 0 EUR **(-100%)** if failure	
Total	*320 000 EUR*	241 000 EUR if success **(-25%)** 8 700 EUR if failure **(-97%)**	

Figure 5: Estimated impact of financial incentives for SMEs.
Calculation is based on standard EMEA fees[27]. Fee reductions and deferrals are based on the current draft Regulation on SMEs incentives implementing Art. 70(2) of Reg. (EC) No 726/2004. It is assumed that the company would ask for one scientific advice, and would be subject to one inspection (within the EU) during the course of the evaluation of the marketing authorisation application. 'Success' means that the marketing authorisation is granted. 'Failure' means that the marketing authorisation is not granted.

The impact of the administrative assistance provisions (translations, SME Office etc.) is more difficult to assess quantitatively. Nevertheless, those provisions are expected to considerably reduce the regulatory burden faced by SMEs developing advanced therapies (*e.g.* translations, which are often seen as a major bottleneck by small actors).

The proposal also foresees a system of early evaluation and certification of quality and non-clinical safety data by the Agency, for SMEs developing advanced therapy products. This system primarily aims at facilitating the evaluation of future marketing authorisation applications based on the same data. It might thus lead to substantial reduction in approval times. It may also impact positively on SMEs which focus on the early development aspects (quality of the technology and manufacturing, pre-clinical safety studies) but do not conduct the subsequent clinical trials themselves. The certification of those 'early-development' data by the Agency might provide a strong selling argument to those companies who wish to license out their proprietary technology to bigger undertakings.

5.2.1.5. Investment capacity

In the short term, investments might be shifted from R&D to adapting the company to the new regulatory requirements, especially in the case of SMEs. Some companies might be at risk if they are unable to adapt to the new regulatory framework. Their innovative capacity might be reduced or might be taken over by other players. On the other hand, the proposed regulatory framework could help new tissue engineering companies to enter

[27] For more details, see http://www.emea.eu.int/htms/general/admin/fees/feesfaq.htm

the market. In addition, current players will be able to expand their tissue engineering business, for the reasons already outlined above.

Small companies, due to increased compliance costs, might reduce their portfolio and focus on fewer, more promising products. The increase in regulatory security, potentially higher revenues due to a large market and growing demand, as well as an improved protection of intellectual property, will make tissue engineering more attractive for investors. This could improve the situation of SMEs by making it easier for them to obtain financial support.

5.2.1.6. Increased competition

The proposed Regulation aims at creating a level playing field for all actors throughout the European Community. This might result in an intensification of competition as more companies – including from third countries – will try to take advantage of the internal market, also with a view to recovering higher compliance costs. This applies especially to large companies with sufficient internal resources for an international distribution strategy.

In the medium to long term, a structure similar to other biopharmaceutical sectors could emerge, with highly innovative research being performed by SMEs, which bring tissue engineered products to the phase of clinical testing. For clinical trials, authorisation procedures and marketing, these SMEs cooperate with or are taken over by larger companies. The provision for certification of quality/non-clinical safety data would be particularly beneficial if such structure develops.

For optimisation of the product portfolio, it is expected that large companies will increasingly focus on allogeneic products (together with some autologous products), targeting larger markets in the EU and in third countries such as the US. Their product range could be extended through licensing or take over of SMEs. As a result, their market share could increase. Smaller players, such as SMEs, might reduce the variety of their product development pipeline and focus on a few products, probably targeted at niche markets, which are unattractive for larger companies.

5.2.2. Hospitals and tissue banks

As regards hospitals and tissue banks, the proposed Regulation will potentially concern two of the three categories identified (see Section 5.1). It is expected that research-driven hospitals will not be affected by the new rules set out in the proposal. Only treatment-driven hospitals and strategy-driven tissue banks might be required to comply with these rules, as soon as they start providing TEPs for other-than-in-house use and fall within the scope of the framework. According to the data currently available, this represents only a very minor fraction of hospitals and tissue banks in the EU. In general, those stakeholders are confident that they would be able to comply with future legal standards, since efforts have already been made to conform to current national or international standards and regulatory requirements, including the recent Directive 2004/23/EC on the quality and safety of human cells and tissues.

5.2.2.1. Research-driven hospitals

Leading research-driven hospitals do not expect major impacts from the proposed Regulation. Research activities would only be affected by provisions on the conduct of clinical trials[28]. Commercial strategies requiring marketing authorisations would be approached in collaboration with other, strategic partners (spin-off companies, out-licensing etc.).

5.2.2.2. Treatment-driven hospitals

Leading treatment-driven hospitals with dedicated manufacturing facilities for tissue engineering are similar to tissue engineering companies in terms of technical equipment, quality assurance, qualification of staff and manufacturing capacity. However, most of the hospitals are public institutions that do not commercialise TEPs and often operate on a non-profit, cost-recovery basis.

The vast majority of treatment-driven hospitals, which produce cell-based products for in-house use, would not fall within the scope of the proposal and should hence not be subject to any impact. Indeed, a centralised marketing authorisation procedure might impose a regulatory overburden on these stakeholders.

For those treatment-driven hospitals which fall within the scope of the proposal, the centralised marketing authorisation procedure and the related requirements may entail additional costs linked to regulatory compliance. Should requirements for a marketing authorisation be established, these institutions would generally prefer a national authorisation process. However, it seems that not all treatment-driven hospitals have yet devised precise strategies for their future positioning in a harmonised regulatory environment. Some facilities might develop into elements of a national manufacturing and distribution infrastructure with regional manufacturing centres.

5.2.2.3. Strategy-driven tissue banks

While small entities are unlikely to engage into tissue engineering activities, larger strategy-driven tissue banks currently comply with high technical standards and have the potential to become relevant players in this field. Similarly to larger treatment-driven hospitals, these organisations could develop in the future into nation-wide tissue engineering infrastructures. A marketing authorisation is considered problematic for certain actors in the tissue banking. For tissue banks relying on altruistic tissue donation, the feeling is that such a procedure could interfere with the non-profit image of their activities and negatively influence the willingness to donate organs or tissues.

Similarly to hospitals, tissue banks active in tissue engineering and advanced therapies are often public, non-profit institutions with a local or potentially national scope of activity. Most of these operators would fall outside the scope of the proposal. For the others, the advantage of being able to access other European markets, improved planning security and increased trust of investors in the field have a lower relevance compared to companies and might not always offset the compliance costs.

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[28] Directive 2001/20/EC, OJ L121, 1.05.2001, p. 34.

5.2.2.4. Competition with tissue engineering companies

A few hospitals and tissue banks have developed, or are planning to develop, large-scale tissue engineering manufacturing facilities. They can, therefore, be regarded as competitors to tissue engineering companies. This is true in particular for institutions which intend to rely on industrial processes and to make their products available to patients and/or to other operators on their home market or beyond national borders.

In terms of future market developments, the outcome of potential competition between tissue engineering companies and hospitals/tissue banks is open due to the often public, non-profit character of the latter. The fixed production costs are considered to be similar for both types of actors. However, hospitals and tissue banks normally have less marketing costs and do not calculate profit margins. On the other hand, tissue engineering companies might be able to exploit economies of scale due to a national or international orientation and have more incentives for a rationalised production process. More efforts into R&D might result in a more advanced product portfolio, thus improving the companies´ market position. Private tissue banks, in contrast to public, non-profit organisations, behave in a similar way to tissue engineering SMEs.

Competition between tissue engineering companies and health institutions is expected to remain limited in the short to medium term. Many hospitals do not intend to develop important facilities for producing a large number of TEPs. Their main interest is in providing optimal treatments to their own patients, on a non-industrial scale. This will be done either through cooperation with tissue engineering companies, or through the development of tailored tissue engineering treatments.

5.2.3. Research

Research activities in the preclinical stage are excluded from the scope of the proposed Regulation. The proposal has therefore no direct impact on this sector. Clinical research on TEPs will be affected by the regulatory requirements of Directive 2001/20/EC and Directive 2005/28/EC on good clinical practice (GCP)[29], with necessary and substantial adaptation as laid down in the proposal. At present, depending on national legislation and available facilities, manufacturing of TEPs for clinical trials may not always be carried out in compliance with GCP. The need for adaptation to the proposed Regulation will depend largely on current national rules, the situation of individual actors, and the guidelines on GCP foreseen in the proposal.

Research activities in companies, especially those with limited resources, will be affected in the short term by the need to invest in infrastructure in order to adapt to the proposed Regulation. In the mid- to long term, based on increased trust in tissue engineering and a more mature market, investment in research might increase in companies as well as in the academic and hospital/tissue bank sectors.

5.2.4. Upstream players

Providers of cells and tissues will have to comply –if they haven't already- with the provisions laid down in Directive 2004/23/EC as far as donation, procurement and

[29] Directive 2001/20/EC, OJ L 121, 1.05.2001, p. 34; Directive 2005/28/EC, OJ L91, 9.4.2005, p.13

testing of cells and tissues are concerned. There will be no additional requirements on the basis of the proposed Regulation.

Other upstream players, such as providers of equipment or consumables, will need to adapt to provide their customers with materials or services in compliance with the requirements of the proposed Regulation. They can expect improved sales opportunities in the short term due to increased demand (*e.g.* GMP-conform equipment).

5.2.5. Downstream players

Downstream 'players', such as medical staff, patients and health insurers might face increased product and treatment prices, if manufacturers of TEPs refinance increased compliance costs *via* higher product prices. On the other hand, costs might be reduced due to increased competition, economies of scale, and a more transparent market[30]. The scientific assessment to be carried out during the authorisation process will enable to provide important information to medical practitioners and patients, mainly through the validation of labelling and leaflets.

5.2.6. Public expenditure

Public budgets will be affected by the proposed Regulation through the costs incurred by the mandatory manufacturing authorisation[31] and the post-authorisation surveillance for TEPs. There are three cost categories to consider: adaptation of the national infrastructures responsible for manufacturing authorisations and market surveillance, maintenance of these infrastructures and operational expenditures. At present, the costs in these categories cannot be specified for the EU as a whole because of the heterogeneous systems in place in the different Member States.

It is expected that initial efforts will be required to adapt the necessary infrastructures in the Member States. Once this set-up phase has been completed, maintenance costs will occur continuously (maintenance of infrastructures, salaries, education and training of employees). The operational expenditures, *i.e.* costs directly connected to applications and inspections of manufacturing facilities, will depend on the number of applications to be assessed. They might increase as the tissue engineering sector develops. In the medium to long term, increases in efficiency can be expected due to the experience gained.

Lastly, there may also be a potential indirect impact on public expenditure through pricing and reimbursement of advanced therapy products. This 'pricing and reimbursement' aspect falls under the responsibility of Member States.

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30 Nanotechnology would also be an interesting way to achieve significant cost reduction and improved product performance.

31 See Title IV of Directive 2001/83/EC.

5.3. Social impacts

5.3.1. Employment and education

At present, the tissue engineering sector, and more broadly the advanced therapies field, has a minor effect on employment in the EU due to its early stage of development. Exact figures on the current employment effect of tissue engineering are not available. Nevertheless, rough estimations based on staff numbers for several tissue engineering companies and figures from the German biotechnology sector indicate that current employment could be around 10,000 full time equivalent employees. The short to mid-term impact of the proposed Regulation on the employment level will most likely be very modest due to the early development stage of the tissue engineering and advanced therapies sector.

Advanced therapies, however, require highly qualified staff in research and development, production, regulatory supervision and hospitals. The sector, as well as the regulatory authorities, might face the problem of staff shortage because they have to 'compete' with other sectors (*e.g.* the 'conventional' pharmaceutical or medical devices industry) for the same workforce. The proposed Regulation will entail considerable training needs for all actors concerned with its implementation. Training of medical practitioners is currently provided by the respective companies, but it might be desirable to define, in the future, standards for education and training on a general basis.

5.3.2. Other social impacts

Specific risks are connected to the sourcing of cells and tissues, their handling during the production, the preservation or storage of the products, the implantation process and the long-term implantation in the patient. Due to the diverse regulatory situation in Europe (different or non-existent standards for safety, quality and efficacy of TEPs, lack of agreed scientific assessment procedures, discrepancies in post-authorisation surveillance), there is a risk that potential safety gaps result in incidents or adverse events, with possible severe consequences for the patient. This could also entail a negative public perception and limited trust in TEPs. With strict and harmonised standards, patients' safety should be improved by considerably reducing the risk of adverse health effects. Increased market transparency should push substandard manufacturers of TEPs out of the market, contributing to higher trust levels in the products, as well as increased demand and investment in the longer term. The overall impact of the proposed Regulation on the health status and quality of life of patients, and on EU populations in general, should be assessed in the longer-term. It will mostly depend on scientific progress and on the development of advanced therapy treatments.

The completion of a single market for TEPs will most probably lead to increased availability of these products for European patients. The proposed Regulation should indeed facilitate the placing on the market of TEPs in different Member States. However, effective patients' access to treatments also depends on other factors, for example pricing and reimbursement policies. Currently, TEPs are significantly more costly than more conventional treatment options. Prices might rise at first due to higher regulatory compliance costs, but increased competition and economies of scale should help to reduce the price of tissue engineered products in the longer term. At present, there is no general coverage of tissue engineering treatments by statutory or private health insurance

bodies in the Member States. The proposed Regulation will obviously not have a direct impact on pricing and reimbursement policies, but it might provide a favourable environment for improving pricing and reimbursement conditions.

5.4. Environmental impacts

Environmental impacts can be envisaged during the manufacturing of TEPs or during their use. The European Union has already established a regulatory framework to prevent, minimise and treat emissions from industrial production processes, which will also cover tissue engineered production[32]. Generally, environmental risks are considered to be low, because of the low production volume, the use of readily degradable substances, limited survival of cells outside controlled laboratory environment and strict manufacturing conditions. The same holds true for gene and somatic cell therapy.

In the framework of the legislation on medicinal products, an environmental risk assessment is required in marketing authorisation applications relating to products containing or consisting of genetically modified organisms (GMOs)[33]. Although it is not the case at present, it cannot be excluded that some TEPs might include genetically modified cells in the future. The same requirement for an environmental risk assessment would therefore be required for TEPs.

5.5. Impacts outside the Union

With the establishment of an EU-wide regulatory framework, manufacturers from third countries may find it easier and more attractive to access the European market, thus increasing competition in Europe. However, existing obstacles to market penetration, such as pricing and reimbursement policies and training needs of medical staff, will also affect third country companies operating in the EU.

Conversely, a harmonised regulatory framework, based on a high level of quality, safety and efficacy, could positively influence EU companies' access to third country markets, if international convergence and mutual recognition of regulatory frameworks are actively strived for. Commonalities between the US legislation on human cells, tissues, and cellular and tissue-based products (HCT/Ps) and the proposed EU framework (tiered approach, pre-market approval, demonstration of quality, safety and efficacy…) should notably enhance the competitiveness of EU companies and their ability to enter the US market.

More broadly, the strict criteria for marketing authorisation in Europe will most likely increase trust in tissue engineered products, thus facilitating exports to non-EU markets. Nevertheless, pricing and reimbursement conditions in non-EU countries will also influence the ability of EU companies to access international markets.

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[32] National laws for approval and inspection of production facilities; Directive 96/61/EC on integrated pollution prevention control (OJ L257, 10.10.1996, p.26); Directive 75/442/EEC on waste (OJ L194 25.7.1975); Directive 91/689/EEC on hazardous waste (OJ L377, 31.12.1991, p.20); Directive 90/219/EEC as amended by Directive 98/81/EC on the contained use of genetically modified micro-organisms (OJ L117, 8.05.1990, p.1 and OJ L330, 05.12.1998, p.13)

[33] See Annex I to Directive 2001/83/EC as amended by Directive 2003/63/EC, OJ L159, 27.6.2003, p.46; see also Directive 2001/18/EC OJ L106 , 17.4.2001, p.1

5.6. Impacts over time

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. A structure similar to other biopharmaceutical sectors could develop. This might apply not only to companies but also to hospitals and tissue banks active in tissue engineering.

In the mid- to long term, an increased attractiveness of the sector due to legal clarity and certainty and harmonisation should compensate or reverse these effects.

6. ETHICAL ASPECTS

This section is based on consultations with the European Group on Ethics in Science and New Technologies (EGE)[34]. At the Commission's request, the EGE has examined the potential ethical issues raised by the introduction of a common framework for TEPs. These issues were analysed in light of previous opinions of the Group, as well as other reference documents such as the European Charter of Fundamental Rights[35] and 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)[36].

The main ethical aspects identified by the independent experts of the EGE are presented below. Some of them relate to the specific issues of donation and procurement of human cells and tissues and, as such, are addressed in the framework of Directive 2004/23/EC, as the proposal foresees that donation, procurement and testing of human cells and tissues shall be carried out in accordance with this Directive.

6.1. Information and consent of the donor

This question has been addressed in two opinions of the EGE. In Opinion 11 on ethical aspects of human tissue banking[37], the Group considered that:

> *"The procurement of human tissues requires, as a principle,* ***the prior, informed and free consent*** *of the person concerned. (…)*
>
> *In order to be informed, the donor's consent must have been given on the basis of information provided in as clear and precise lay terms as possible by the doctor supervising the procurement.*
>
> *The information provided to the donor should concern:*

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34 http://europa.eu.int/comm/european_group_ethics/index_en.htm

35 OJ C 364, 18.12.2000, p. 1.

36 See http://www.legal.coe.int/bioethics/gb/pdf/convention.pdf

37 See point 2.3 - http://europa.eu.int/comm/european_group_ethics/docs/avis11_en.pdf

– *the procurement arrangements, in particular concerning the free nature of the donation, and the extent of its anonymity.*

– *possible tissue storage time and conditions, and conditions of registration of data in databases, in conformity with requirements of private life protection and medical confidentiality;*

– ***foreseeable use of the tissues*** *(diagnostic, allograft or autograft,* ***pharmaceutical products****, research,* ***production of cellular lines*** *for various uses, etc.). The donor may at any time withdraw her/his consent."*

Opinion 16 on ethical aspects of patenting inventions involving human stem cells[38] notably underlined that *"when the donated cells may become part of a patent application, donors should be informed of the possibility of patenting and they are* ***entitled to refuse such use"****.* In addition, the European Union Charter of Fundamental Rights states in its Article 3 that *"the free and informed consent of the person concerned must be respected".*

When examining the ethical aspects of the proposal, the EGE recalled that all relevant facts which could affect the donor's decision to consent or refuse donation should ideally be presented to the donor. The "free nature" of the donation entails the right to refuse and refusal should not have any negative consequences on the person asked to donate. The EGE considers that the possibility of unforeseeable future uses should be made clear to the donor and different options of consent should be proposed. The point where withdrawing of consent becomes impossible should also be explicit.

The proposal foresees that the donation and procurement of human tissues and cells must be made in accordance with the provisions of Directive 2004/23/EC. All aspects related to donor consent, including with respect to tissues and cells used in the manufacture of TEPs, are therefore addressed by the said Directive. Article 13 notably refers to the legal requirements applicable in the Member States as regards donor consent. It also aims at ensuring that donors, their relatives or any persons granting authorisation on behalf of the donors are provided with all appropriate information.

6.2. Free donation and financial benefits by private undertakings

When consulted on the proposal, the EGE referred to Opinion 11 on ethical aspects of human tissue banking. Point 1.10 stresses that all Member States of the European Union adhere to the principle that donations of human tissues must be free. Furthermore, Article 3 of the Charter of Fundamental Rights includes a *"prohibition on making* ***the human body and its parts as such*** *a source of financial gain".*

As regards **engineered products derived from human tissues and cells**, the Group acknowledged in opinion 11 that the issue of commercialisation of human tissues which have been processed and prepared for therapeutic purposes may be controversial (point 1.10). However, it considered in point 2.8 that *"it is difficult to exclude tissue banking activities by commercial organisations, such as large private laboratories. This is*

[38] See points 1.20 and 2.6 - http://europa.eu.int/comm/european_group_ethics/docs/avis16_en.pdf

particularly true where human tissues are used as a basis for "engineered" products requiring the use of sophisticated medical techniques."

6.3. Privacy, data protection and traceability

There may be conflicting interests between, on the one hand, respect of the donor's privacy, anonymity and confidentiality of information collected during tissue procurement and, on the other hand, safety of treatment for the recipient, which implies traceability requirements. Based on Opinion 11 (point 2.4), the EGE recalled that strict data protection rules, with the use of appropriate coding systems, are necessary to reconcile both donor's and recipient's interests and prevent misuse of personal data or/and transmission of health data to third parties. As far as traceability is concerned, the Group underlined that traceability systems must be complete in order to be effective. Precise traceability requirements are key in achieving a high level of safety.

A number of issues concerning privacy and data protection (*e.g.* anonymity of donors) relate directly to the donation and procurement of tissues. These aspects are already addressed in Directive 2004/23/EC, whose provisions apply to the donation, procurement (and testing) of human tissues and cells used for manufactured products. In addition, the proposed Regulation foresees detailed provisions with regard to the traceability of products and patients.

6.4. Safety

Guaranteeing the safety of donors, recipients and health-care professionals is a major ethical responsibility for policy-makers. In Opinion 11 on human tissue banking[39], the EGE highlighted that:

> *"The issue of safety is also vital, as the European Union has set itself the objective of guaranteeing each citizen a "high level of human health protection". This protection must extend to tissue donors and recipients, and to all health care professionals – whose work involves collecting, manipulating and using human tissues" and that "No substance of human origin is free from the risk of disease transmission. Thus tissues, in particular those intended for transplantation to third parties or for the preparation of pharmaceutical specialities, must undergo advance testing to provide maximum health guarantees in accordance with the state of the art."*

Directive 2004/23/EC on the quality and safety of human cells and tissues contributes to establishing a high level of human health protection, as foreseen in the Treaty and as called upon by the EGE in Opinion 11. 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 products.

The provisions of the proposed Regulation apply equally to TEPs manufactured in the Community, including products intended for export, and to products imported from third countries. This is also in line with Opinion 11, which stated that *"tissue imports or*

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[39] See points 1.8 and 2.1 - http://europa.eu.int/comm/european_group_ethics/docs/avis11_en.pdf

exports should be licensed by public authorities. Authorisation should be subject to at least equivalent ethical and health rules to those outlined above".

When examining the ethical aspects of the proposal, the EGE mentioned that the use of genetically modified organisms in tissue engineering may require particular attention, as it can raise specific safety problems. However, this remains a theoretical issue for the moment, as research in this area is still in an infant stage. The tissue engineering sector currently does not manufacture products containing genetically modified cells and it does not intend to do so in the coming years. Nevertheless, monitoring of scientific progress in tissue engineering and of product development will be necessary in order to adapt the proposed regulatory framework if and where necessary.

6.5. Priorities of access

In Opinion 11, the EGE considered that the principle of justice makes it *"necessary to define the criteria for priority access to […] tissue products in the most transparent manner possible […]"* (point 2.9). The competence for defining such criteria currently lies with the Member States. Consequently, the proposal does not touch upon this aspect.

6.6. Research and clinical trials

Opinion 15 of the EGE on ethical aspects of human stem cell research and use[40] addresses the ethical aspects relating to clinical trials (in particular points 2.10 to 2.14). The EGE considers that, although they focus on stem cells, the principles outlined in this opinion – free and informed consent, risk-benefit assessment, protection of the health of subjects involved in clinical trials, scientific evaluation, anonymity of the donation – could also apply to TEPs.

The proposed Regulation takes due account of ethical issues related to clinical trials. It notably includes provisions for the protection of persons involved in clinical trials, as laid down in Directive 2001/20/EC.

6.7. Use of embryonic stem cells

The EGE has addressed issues related to human embryo in the context of invention patents involving human stem cells. Opinion 16[41] states that:

> *"The Group is well aware that all procedures involving directly or indirectly the human embryo are controversial in the sense that they are based on presuppositions for instance concerning the beginning of human life and the question whether there should be an absolute or a relative protection of human life in its different stages. Political and legal decisions in these ethical matters may change the self understanding of what it means to be a human being in a given epoch and society.*
>
> *The question of the dignity and the moral status of the embryo remain indeed highly controversial in a pluralistic society as the European Union. Those who*

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40 http://europa.eu.int/comm/european_group_ethics/docs/avis15_en.pdf

41 See point 1.21 - http://europa.eu.int/comm/european_group_ethics/docs/avis16_en.pdf

are opposed to human embryo research, cannot, a fortiori, consider any patenting in that field. Among those who consider research on embryos ethically acceptable, some may feel great reluctance towards patenting the resulting inventions, while others consider patenting inventions derived from embryo research as acceptable, especially given their potential medical benefits."

The issue of embryonic stem cells was already debated during the adoption of Directive 2004/23/EC. In this context, the legislators have recognised that there is, to date, no consensus in Europe upon which harmonised decisions could be taken on the use or prohibition of embryonic stem cells. Thus, decisions on such use or prohibition should remain a national responsibility. However, it was also agreed that, if 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[42].

The same logic as outlined above should apply to the proposed Regulation on advanced therapy medicinal products. This Regulation will not interfere with decisions made by Member States on the use or prohibition of these cells as starting materials; nevertheless, if a company develops advanced therapy products based on embryonic stem cells in a Member State where such use is authorised, then the Regulation should apply to these products. The resulting marketing authorisation would only be valid in those Member States where embryonic stem cells are not prohibited. Following the stakeholders consultation, explicit provisions have been introduced in the draft to clarify this point.

6.8. Patenting

The EGE raised the issue of profit obtained with an invention resulting from the use of donated tissues. The Group is of the opinion that the file to be completed in order to obtain a patent should always include a proof of the informed consent of the donor[43]. Nevertheless, the proposal is not intended to address patent aspects, which fall outside its scope.

7. MONITORING AND EVALUATION OF IMPACTS

Advanced therapies represent a young field of biotechnology. It is expected to evolve profoundly in the coming decades, with scientific and technological progress. Many of the products that will be subject to the proposed Regulation are yet to be developed. It is therefore difficult at this early stage to evaluate the impact of the proposal in the medium to long term.

The impact, both financial and social, of improved health of EU patients treated with advanced therapies is very difficult to measure. Unless there is major investment in the central collection of indices of EU health on this particular matter, this difficulty will most likely remain when attempting to measure the impact of the draft Regulation in the future.

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42 Recital (12) and Article 4(3) of Directive 2004/23/EC.

43 However, this does not necessarily reflect the views of the Commission, nor the current patent legislation in force.

7.1. Monitoring indicators

Many of the effects of the draft Regulation lend themselves to measurement and some of these can be directly related to the objectives set out in Section 3. For instance, collection of the following data is possible:

– The dates on which the Committee for Advanced Therapies is established and TEPs technical requirements and guidelines are adopted.

– The number of clinical trials on advanced therapies initiated and completed (broken down by country and type of trial).

– The number of marketing authorisation applications for advanced therapies (TEPs, gene therapy, somatic cell therapy) submitted for assessment.

– The number of requests for conditional marketing authorisation of advanced therapies.

– The number of requests for accelerated assessment ('fast-track') of marketing authorisation applications of advanced therapies.

– The number of requests for scientific advice.

– The numbers of marketing authorisation applications granted.

– The percentage of applications (marketing authorisations, scientific advice, variations etc.) coming from SMEs.

– The number of requests for post-marketing studies, post-authorisation plans and risk management systems and the delivery against those plans.

– Impact on the budget of the EMEA.

– Impact on the pricing and reimbursement of advanced therapies at national level.

These data will provide a robust measure of the impact of the draft Regulation in terms of stimulating research, development and authorisation of advanced therapies. They will also provide some measure of the financial impacts on the EMEA and impact on the price of the products at national level.

7.2. Arrangements for *ex-post* evaluation

The draft Regulation includes a proposal for, within five years of entry into force, a general report on experienced acquired as a result of the application of the Regulation.

Through this report, *ex-post* evaluation is already planned. The report will likely be based on the indices listed in section 7.1. 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.

8. STAKEHOLDERS CONSULTATION

8.1. Means of consultation

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

– Workshops and roundtable meetings

– Stakeholders interviews by the IPTS (see also Section 11.1)

– Public consultation

8.1.1. Workshops and roundtable meetings

The Commission has held a series of workshops and bilateral meeting with stakeholders on the issue of tissue engineering and on its proposals for a draft Regulation on advanced therapies. Section 11.2 of the Annex provides a summary list of the workshops and bilateral meetings held. In particular, two large stakeholders' workshops took place on 16 April 2004 and 7 June 2005. They involved all social and economic actors concerned, including health and patients organisations, industry, hospitals and doctors, tissue banks, research community, health insurance representatives and ethics groups.

Member States were also widely and actively consulted, through:

– Experts meetings on 11 July, 7 August, 9 September 2003, 19 February 2004 and 25 May 2005;

– Formal consultation of the 25 Member States' regulatory authorities on 23 September 2003, 29 April 2004 and 1 June 2005.

8.1.2. Stakeholders interviews by the IPTS

Questionnaire-guided interviews (1 hour to 1.5 hours duration) were carried out by the IPTS with 28 stakeholders from tissue engineering companies and national authorities as well as other experts. Twelve representatives from national authorities from Austria, Denmark, France, Germany (3 interview partners), Ireland, Italy, Spain, Sweden, the Netherlands and the United Kingdom were interviewed. Ten interviews were carried out with company representatives from Austria, Belgium, Germany, France and The Netherlands. Additionally, representatives from some hospitals and other experts were interviewed.

For hospitals and tissue banks a limited survey was carried out. Twenty-one questionnaire-guided interviews (30 – 60 minutes duration) were performed in Germany (8 interviews), United Kingdom (7) and France (6) with relevant experts and representatives from hospitals and tissue banks.

For the 2nd IPTS report[44], a written survey targeted at tissue engineering companies and national competent authorities was used to obtain more information on the status-quo situation of tissue engineering in Europe. 117 companies from 14 countries were approached, from which 29 answered. 20 questionnaires were completed. This corresponds to an answer rate of 17%, covering 8 countries (Austria, Belgium, Denmark, Germany, Slovenia, Sweden, the Netherlands, United Kingdom). The 20 companies are representative for the tissue engineering sector in terms of distribution of SMEs and large companies. The majority of these companies describe their activity as concerning tissue engineering, 8 are also active in the sector of medical devices, and 9 in medicinal products. Six partly or totally work as tissue banks or other tissue establishment. 13 companies describe themselves as actively monitoring the field of human TEPs, 17 are doing R&D and 1 company reported not to be active in tissue engineering. 14 out of 20 participating companies stated having products on the market. Compared with the earlier study[45], which identified 20 European companies having products on the market, about 70% of these companies are represented in the survey.

60 questionnaires were sent out to national authorities from 26 countries (EU-27 without Slovenia). 25 contacts had been provided by DG Enterprise of the European Commission and were complemented by further 35 contacts identified through an internet search. 20 completed questionnaires (33%) were received from 16 countries (Austria, Belgium (3 answers), Bulgaria, Cyprus, Finland, France (2), Germany (2), Ireland, Italy, Latvia, Malta, the Netherlands, Poland, Slovakia, Spain, Sweden).

8.1.3. Public consultation[46]

The Commission's public consultation was split in three parts:

A first round started in July 2002 and included, as a main component, a web-based questionnaire on key aspects of a future proposal. 51 written contributions were received.

As a second step, a non-paper outlining the main architecture and elements of a future proposal was submitted for public consultation in March-April 2004. 35 written contributions were received.

Finally, a draft Regulation on Advanced Therapies together with an accompanying Consultation document, were publicly released for comments in May-June 2005. More than 170 written contributions were received.

8.2. Outcome of the consultation and impact on the proposal

Detailed summaries of outcome of the 2002, 2004 and 2005 public consultations are provided in Annexes (see Sections 11.3, 11.4 and 11.5).

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44 See footnote 2.

45 See footnote 2.

46 All results of public consultation are available at: http://pharmacos.eudra.org/F2/advtherapies/index.htm

8.2.1. Overall strategy

Overall, consultations highlighted a broad consensus in favour of a specific, harmonised and coherent EU regulatory framework covering tissue engineered products, as well as other cell/tissue based products. A majority of interested parties advocated a piece of legislation that would take into account the specificity of TEPs compared to medical devices and "conventional" medicinal products. Stakeholders, in particular the industry, stressed the need to establish legal certainty in that emerging field, as rapidly as possible. They also recommended that any new initiative should comprehensively address not only existing, but also future cell/tissue based products. Finally, they provided valuable input on key procedural and technical aspects (notably the scope, definitions, marketing authorisation requirements and borderline issues) that any proposal for a Regulation in this area should address. Many of the detailed comments on the draft Regulation on Advanced Therapies have been taken on board for the final proposal.

8.2.2. Legal basis, procedure and choice of legal instrument

The proposed approach for a Regulation based on Article 95 of the EC Treaty was supported by the vast majority of stakeholders. 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, in particular the free movement of goods, taking as a basis a high level of health protection.

The suggested 3-tier regulatory strategy (1: overarching principles through co-decision; 2: technical requirements through 'comitology'; 3: detailed requirements through guidelines) was also felt to be a sensible approach, provided that technical requirements can be adapted in a flexible manner.

8.2.3. Definitions and Scope

8.2.3.1. Definitions

The definition of tissue engineered products has been subject to a number of modifications, in the light of stakeholders' comments. TEPs are defined in the proposal as:

"Any product which:

- *contains or consists of engineered cells or tissues; and*
- *is presented as having properties for, or is used in, applied on or administered to human beings with a view to, regenerating, repairing or replacing a human tissue."*

Although some TEPs include a medical device part (a matrix, scaffold etc.), and other substances (*e.g.* growth factors), these features are not always present in all TEPs (*e.g.* autologous cultured chondrocytes) and were therefore not included as *mandatory* criteria in the definition.

A number of stakeholders called for an accurate and scientific definition of the term 'engineered cells or tissues'. The approach finally retained is relatively similar to the one

used in the US to distinguish between products which require premarket approval and products which do not. 'Engineered cells or tissues' are defined as cells or tissues which meet at least one of the following criteria:

(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;

(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 advanced therapy medicinal product which contains or consists of the referred cells or tissues is a combined advanced therapy medicinal product (*i.e.* a cells or tissues/device combination).

Annex I to the proposal gives examples of manipulations which, from a scientific viewpoint, are not considered as 'substantial manipulations' as referred to in the first criterion, like: cutting; grinding; shaping; centrifugation; soaking in antibiotic or antimicrobial solutions; sterilization; irradiation; cell separation, concentration or purification; filtering; lyophilization; freezing; cryopreservation; and vitrification. Those examples are similar to the ones outlined by the US Food and Drug Administration (FDA)[47] for 'minimal manipulation'. For example, a tissue bank or a hospital that separates, decontaminates, sterilises and preserves (drying and/or freezing) cells and tissues would not be considered to produce tissue engineered products, and would thus not be subject to the requirements laid down in the proposal.

Criterion 2 is equivalent to the 'homologous use' criterion used in the US. For example, non-substantially manipulated cartilage used to replace cartilage, even elsewhere in the body, is for homologous use and can reasonably be expected to function appropriately. This is obviously not tissue engineering, but transplantation; this type of product would therefore not be regulated under the proposed Regulation (but would be covered by Directive 2004/23/EC).

On the other hand, a tissue used in a non-homologous way, *e.g.* amniotic membrane used to heal a damaged corneal epithelium by growing new corneal epithelial cells, a function it does not normally perform *in utero*, would be considered as 'engineered' (not by manipulation, but by virtue of the intended use and the therapeutic claim associated with the product). This type of product would be considered as a tissue engineered product.

Criterion 3 is self-explanatory. Indeed, the vast majority of stakeholders recognised that cells combined with devices should always be considered as engineered, as the association with the device can significantly influence the properties of the cells and the overall safety of the product. Following the public consultation, the definition has been slightly amended in order to cover both medical devices within the meaning of Directive 93/42/EEC, and active implantable medical devices within the meaning of Directive 90/385/EEC[48].

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47 See http://www.fda.gov/cber/tissue/docs.htm

48 Directive 90/385/EEC, OJ L189, 20.7.1990, p.17.

Some stakeholders have expressed concerns on potential overlap between the definition of TEPs and the definition of somatic cell therapy medicinal product[49]. A provision has therefore been introduced to address products falling within both definitions. In any case, both types of products would anyway be subject to the same marketing authorisation procedure. On the long-term, and after experience has been gained, the definition of somatic cell therapy could also be revised.

Even if the proposal seeks to avoid grey areas and legal uncertainties, it must be acknowledged that even the best possible definition may not fully eliminate the risk of grey areas with other Community legislation, given the highly innovative and rapidly evolving nature of the advanced therapies sector. If doubts remain, the provision on an EMEA scientific recommendation on classification of any cell/tissue-based products should ultimately ensure that the product is regulated within the appropriate legal framework.

Another issue raised during the consultation process was the inclusion of TEPs and other advanced therapy products within the overarching definition of (biological) medicinal products. The detailed scientific and legal rationale for choosing this approach is outlined in the Explanatory Memorandum of the proposal.

8.2.3.2. Scope

The proposal addresses all advanced therapy products falling within the global scope of the Community legislation on medicinal products[50], 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"*. This should cover, *inter alia*:

– any 'mass production' of advanced therapy products for allogeneic use (batch production, 'on the shelf' products etc.);

– any advanced therapy product for autologous use which, although being patient-specific by definition, is manufactured in accordance with a standardised and industrial process.

The consultation process outlined the necessity to better define what 'industrial process' means. It was agreed that products which are which are both prepared in full and used in a single hospital, in accordance with a medical prescription for an individual patient, should not be subject to a marketing authorisation procedure. In any case, those products would still be regulated under the accreditation/registration system and the quality and safety standards laid down in Directive 2004/23/EC as regards human tissues and cells.

It should be borne in mind that the 'scope' aspects are to be read in conjunction with the definitions provided in the proposal. For example, if a product based on tissues and cells *is* industrially produced but is neither a gene therapy product, a somatic cell therapy product nor a TEP, it would *not* be subject to the requirements laid down in the proposal.

Examples:

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[49] See Annex I to Directive 2001/83/EC as amended by Directive 2003/63/EC, Part IV.

[50] See Article 2(1) of Directive 2001/83/EC, as amended by Directive 2004/27/EC.

– A hospital developing an in-house, non-industrial technology based on autologous cells to repair/regenerate cardiovascular tissue for a given patient, treated in the same hospital. In this case:

  - the resulting product may be considered as an advanced therapy product, if the cells are substantially manipulated;
  - however, it is prepared in full and used in a hospital, in accordance with a medical prescription for an individual patient.
  - This case would therefore not be covered by the proposed Regulation, as it falls outside its scope.

– A small and medium-sized biotech company (SME), developing a skin substitute product based on substantially manipulated allogeneic cells, produced *via* a standardised, GMP-compliant large-scale process. In this case:

  - the product is a tissue engineered product (substantial manipulation);
  - it is clearly *"prepared industrially"*: it should therefore be covered by the proposed Regulation.

– A large operator developing a product based on substantially manipulated autologous cultured chondrocytes, which is produced *via* a well validated and controlled industrial process. In this case:

  - the product is a tissue engineered product (substantial manipulation);
  - it is "*manufactured by a method involving an industrial process"*; it should therefore be covered by the proposed Regulation.

– A tissue bank processing tissues or cells for transplantation, through non-substantial manipulation (*e.g.* sterilisation and preservation (drying and/or freezing)), on a very large scale and *via* an industrial process. In this case, the product is *not* an advanced therapy product, and is therefore not covered by the proposed Regulation, no matter how industrial the process is.

8.2.4. Cells of animal origin and xenogeneic TEPs

Tissue engineered products derived from cells or tissues of animal origin raise specific safety and ethical issues. It was initially proposed to exclude them from the scope of the Regulation, with the proviso that this scope be re-assessed at a later stage, to consider their inclusion. The Regulation would have applied only to human tissue engineered products for which tissues and cells of animal origin are used in the manufacture without being present in the final product, or, if present, only in trace amounts and without being viable.

However, a number of stakeholders have challenged that exclusion, on the following grounds:

– Cell therapy medicinal products based on animal cells are already covered, since 2003, by the legislation on medicinal products[51];

– Medical devices incorporating (non viable) animal cells are already covered, since 1993, by the legislation on medical devices[52];

– Xenogeneic tissue engineered products are already in clinical development in Europe, and more are expected in a near future. To exclude them may hamper such developments;

– It may be difficult to argue that xenogeneic TEPs are totally excluded from the Regulation, while even more controversial products (*e.g.* based on embryonic stem cells) are not;

– If excluded, xenogeneic TEPs would not be regulated under Community legislation. The issues of unharmonisation, market segmentation and, more importantly, access to innovative and sometimes life-saving treatments would most likely remain.

For all these reasons, xenogeneic TEPs have been re-included in the scope of the proposal, but without prejudice to national legislation prohibiting or restricting:

(1) the use of such cells;

(2) the sale, supply or use of products containing, consisting of or derived from these cells.

Consequently, a marketing authorisation granted for a xenogeneic TEP would be valid only in the Member States where such marketing authorisation does not contradict national legislation.

8.2.5. Authorisation Procedure and Committee for Advanced Therapies

The principle of a fully centralised marketing authorisation procedure was welcomed and supported by a vast majority of stakeholders. According to the feedback received during the consultation process, even SMEs usually seek access to a market that is not only national, but multi-Member States if not Community-wide or even international. To achieve this, a centralised procedure is considered appropriate. Besides, pooling of expertise from all Member States appeared necessary to guarantee a high level of scientific evaluation across the European Union, and thus to preserve the confidence of patients and medical practitioners in this evaluation.

No stakeholder had objections against the use of the European Medicines Agency for the scientific evaluation of advanced therapy products. However, it was already clear in the first round of consultation (2002) that the existing structure of the EMEA would have to be adapted: specific, multidisciplinary expertise would need to be brought in, and a new Committee would need to be established.

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[51] Part IV, Section 2 of Annex I to Directive 2001/83/EC, as amended by Directive 2003/63/EC, OJ L159, 27.6.2003, p.46

[52] Directive 93/42/EEC, OJ L169, 12.7.1993, p.1

On these grounds, it was proposed to create, within the EMEA, a Committee for Advanced Therapies (CAT), which would advise scientifically on any data related to advanced therapy products (Figure 6).

The composition of the CAT should reflect the multidisciplinary nature of the field and ensure appropriate coverage of the scientific areas relevant to advanced therapies, like medical devices, tissue-engineering, gene therapy, cell therapy, biotechnology, and pharmacovigilance and risk management. The ethical dimension is also an important element, which should be appropriately represented at the CAT level.

There was no consensus amongst stakeholders as to an ideal composition of the CAT. It was nevertheless agreed that:

– The CAT should be a scientific Committee;

– All members of the CAT should be chosen on the basis of their scientific experience of advanced therapies;

– The CAT should not be oversized.

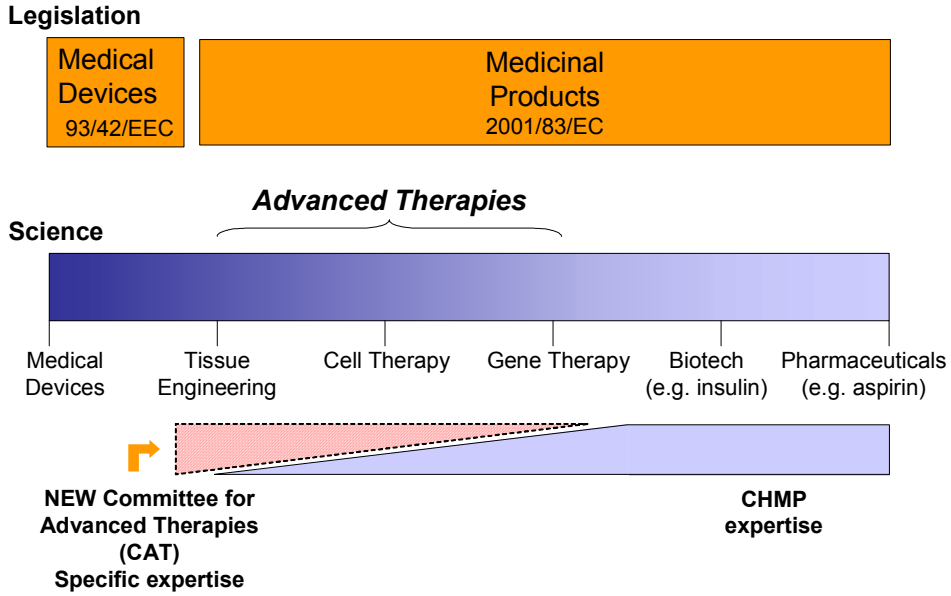

Figure 6: The Committee for Advanced Therapies

The proposal for a CAT where only certain Member States would be represented was rejected, for a number of reasons. In particular, as the marketing authorisation resulting from the evaluation would be valid in the whole Community[53], it was felt important that all Member States are appropriately represented. Besides, an equal opportunity to share experience and develop expertise as far as science progresses should be ensured. In practice, it is certainly expected that some Member States would develop specific expertise in certain scientific areas and categories of products.

[53] without prejudice to national legislation prohibiting or restricting the use of specific type of cells.

The interaction between the CAT and other Committees of the Agency, especially the Committee for Medicinal Products for Human Use (CHMP), is an important issue which was raised by various stakeholders. The system laid down in the proposal takes into account those comments, based on the following rationale:

– All existing and future Committees of the Agency dealing with medicinal products for human use (COMP (Orphan drugs), HMPC (Herbals), Paediatrics Committee etc.) are linked to the CHMP. The same is true for all scientific advisory groups and working parties. There seems to be no particular reason to derogate from this rule in the case of advanced therapies;

– It is key to ensure consistency, for all medicinal products, of the evaluation of the benefit/risk ratio, in particular at clinical level. The CHMP warrants this consistency;

– The CHMP has already expertise in gene therapy and somatic cell therapy, through scientific advice and products evaluation;

– Tissue-engineered products represent a total market of about 60 Millions Euros today, *i.e.* significantly less than the average annual turnover of a single drug approved by the CHMP. From this 'cost-effectiveness' viewpoint, it would clearly be disproportionate to create a totally independent Committee.

Nevertheless, a series of mechanisms are foreseen to avoid divergent opinions between the CHMP and the CAT, as outlined in the proposal. For example:

– Five members of the CAT are also members of the CHMP;

– The rapporteur or the co-rapporteur appointed by the CHMP will be a member of the CAT. This member will also act as rapporteur or co-rapporteur for the CAT, thereby preventing any inconsistency;

– The Executive Director of the Agency is expressly required, in the proposed Regulation, to ensure appropriate co-ordination between the Committee for Advanced Therapies and the other Committees of the Agency, in particular the CHMP;

– Where the final opinion of the CHMP is not in accordance with the opinion of the CAT, the CHMP will have to explicitly detail the scientific grounds for the differences.

8.2.6. Marketing Authorisation Requirements

The proposed Regulation mainly addresses procedural and legal aspects. According to the 3-tier strategy (see Section 4.1.6), technical requirements are adopted and revised through a 'comitology' procedure, and through guidelines. In such an evolving area, this approach appears crucial to ensure that those requirements are established in a way that provides for sufficient flexibility.

From the beginning of the consultation process, stakeholders agreed that 'conventional pharmaceutical' technical requirements, as laid down in Annex I to Directive 2001/83/EC, are not directly relevant to advanced therapy products, due to their specific structural, functional and biological properties. For example, in some cases it may not be

possible to perform 'conventional' clinical trials: the clinical development will hence have some special features owing to the complex nature of the products, and will most likely require considerations related to the viability, proliferation, migration and differentiation of cells, to the special clinical circumstances where the products are used, or to their particular mode of action.

The specific technical requirements as regards gene and somatic cell therapy are already laid down in Annex I to Directive 2001/83/EC (Part IV of the Annex) and through EMEA guidelines54. It is not foreseen to amend them at this stage, but they obviously may be in the future.

As regards tissue engineered products, it is proposed to follow the same approach: to amend Annex I to Directive 2001/83/EC in order to lay down technical requirements that are specific to these particular products (e.g. related to their mechanical, physical and structural properties), and to further complement those requirements with guidelines, drawn up in consultation with all interested parties. This approach was clearly agreed by the vast majority of stakeholders.

In the light of comments received during the public consultation, it is also foreseen in the proposal to draw up guidelines on the application of good manufacturing55 and good clinical practice56 for advanced therapy products. The objective is to fully take into account the inherent technical specificities of these products, while respecting the general regulatory principles laid down in Directive 2003/94/EC57 and Directive 2001/20/EC. Again, those guidelines should be drafted in close consultation with all interested parties, in particular the industry.

Lastly, advanced therapy 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 'medical device' part should meet the essential requirements laid down in these Directives.

In order to address the concerns expressed by stakeholders, a flexible system is provided to ensure that those essential requirements are met:

(1) either the device part has already been certified by a notified body. As foreseen in the proposal, this certification should be taken into account by the CAT for the evaluation of the concerned product. If necessary, the referred notified body may be requested to transmit relevant documents to the Agency;

(2) or the device part has not been certified already. In this case, the Committee for Advanced Therapies, with its unique expertise, would provide a 'one-stop shop' system, by evaluating all aspects (including medical devices aspects) of the product.

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54 See http://www.emea.eu.int/htms/human/itf/itfintro.htm

55 OJ L262, 14.10.2003, p.22.

56 OJ L121, 1.5.2001, p.34.

57 Directive 2003/94/EC, OJ L262, 14.10.2003, p.22.

8.2.7. Post-authorisation issues

The consultation process highlighted the necessity to devote special attention to post-authorisation issues in respect of advanced therapy products, in particular the risk management aspects and the traceability aspects.

A system allowing complete traceability of the patient, as well as the product and its starting materials[58], appeared essential to monitor the safety of advanced therapy products in a long-term perspective. However, various types of stakeholders (industry, hospitals, regulators…) highlighted that, while such a system was agreed in principle, the responsibilities of all parties involved across the traceability chain should be clearly defined: from the sourcing of the starting materials, the manufacture, transport, delivery, up to the actual hospital, institution or private practice where the product is used. The system should be fully compatible with other traceability provisions laid down in Directive 2004/23/EC and Directive 2002/98/EC, and should also respect data protection, confidentiality, and anonymity of both donor and recipient. New provisions have been introduced in the proposal to reflect these comments.

8.2.8. Other provisions

Three other provisions were integrated in the proposal, which were directly derived from stakeholders' feedback:

– the option for any applicant to request scientific advice, not only on pre-authorisation developments but also on pharmacovigilance and risk management systems;

– the option for any applicant developing a product based on cells or tissues to request a scientific recommendation of the Agency with a view to determining whether the product falls, on scientific grounds, within the definition of an advanced therapy product. This provision establishes within the Agency a system similar to the Tissue Reference Group system in the US (see also Section 5.2.1). It aims at resolving borderline issues, e.g. between somatic cell therapy and tissue engineering, between non-substantially manipulated tissues and tissue engineered products, etc;

– the possibility for an SME to get a certification of the quality and non-clinical safety data related to its product (see also Section 5.2.1).

9. COMMISSION PROPOSAL AND JUSTIFICATION

Please refer to the proposal and its Explanatory Memorandum

10. CONCLUSION

Overall, outcome of the impact assessment suggests that the proposed Regulation should, on the long term, be of significant benefit for all actors in the field, by providing legal

[58] The issue of traceability of starting materials may be of particular relevance in the case of advanced therapy products which include nanomaterials.

clarity and certainty, harmonising quality, safety and efficacy standards for the placing on the Community market of these products, improving the competitiveness of the concerned economic operators and increasing the confidence of patients and healthcare practitioners.

In practice, the success of the proposal will however depend on particular attention paid to certain categories of stakeholders, in order to avoid imposing an unnecessary regulatory burden, with little public health benefit. This especially concerns:

– Hospitals (and, to a lesser extent, tissue banks), in relation to the scope of the Regulation;

– Small and medium-sized enterprises, in relation to the centralised procedure and the special financial/administrative incentives.

Beyond the proposal, the subsequent establishment of technical requirements (e.g. through the amendment of Annex I to Directive 2001/83/EC and through guidelines) for tissue engineered products will also be important to ensure that the overall regulatory framework on advanced therapies is balanced, tailored, and can keep the pace with scientific progress.

11. ANNEXES

11.1. IPTS Reports

http://www.jrc.es or available on request by email to:

Anne-katrin.bock@cec.eu.int or

Nicolas.rossignol@cec.eu.int

11.2. Consultation: summary list of key events, workshops and meetings

2001

– The Scientific Committee on Medicinal Products and Medical Devices (SCMPMD) adopts an opinion on "the state of the art concerning tissue engineering".

2002

– Adoption of the Commission proposal on the quality and safety of human tissues and cells (future Directive 2004/23/EC)[59].

– July: First round of public consultation on the need for a regulatory framework on TEPs.

2003

[59] COM(2002)319

– 11 July, 7 August, 9 September: expert meetings with representatives from the Danish Medicines Agency, the Afssaps (Agence française de sécurité sanitaire des produits de santé), the Scientific Committee on Medicinal Products and Medical Devices (SCMPMD) and the EMEA.

– 23 September: formal consultation of 25 Member States regulatory authorities

– October: First IPTS Report: "Human tissue-engineered products - Today's markets and future prospects"

2004

– 03 February: meeting with Eucomed/Europabio/EFPIA-EBE

– 19 February: expert meeting with DE, FR, NL, SE and UK representatives

– March-April: second round of public consultation, on the basis of a non paper.

– 31 March: adoption of Directive 2004/23/EC on the quality and safety of human tissues and cells.

– 16 April: Stakeholders conference gathering all interested parties (patients, hospitals, research, doctors, industry, ethics groups…)

– 29 April: formal consultation with Member States regulatory authorities

– 23 June: meeting with Eucomed/Europabio

– 19 October: consultation of the MDEG (Medical Devices Expert Group)

2005

– 26 January: meeting with Eucomed/Europabio/EFPIA-EBE

– May-June: last round of public consultation on the basis of a draft Regulation on advanced therapies and an accompanying consultation document

– 20 May: meeting with Eucomed/Europabio/EFPIA-EBE

– 25 May: expert meeting with DE, FR, NL, SE and UK representatives

– 1 June: formal consultation of 25 Member States regulatory authorities (Pharmaceutical Committee)

– 7 June: Stakeholders workshop gathering all interested parties (patients, hospitals, research, doctors, industry, ethics groups…)

– 20 June: End of the 2005 public consultation

2006 : 7 April: end of transposition period for Directive 2004/23/EC.

11.3. Summary of the 2002 public consultation

11.3.1. Background

In November 2000, the European Parliament and the Council adopted a Directive concerning medical devices incorporating derivatives of human blood and plasma[60]. This Directive modified Directive 93/42/EEC on medical devices. At that time, the Council and the Commission agreed that devices incorporating other derivatives of human tissues should be subject to a specific Directive.

The field of tissue engineering has evolved significantly in the meantime and it now seems appropriate to establish a regulatory framework in this area.

Tissue engineering is a new and rapidly developing technology, which aims at producing viable substitutes to restore, maintain or improve the function of human tissues or organs. It differs from standard therapies because the engineered product is integrated within the patient, affording a specific and potentially permanent cure of the disease, injury or impairment. Tissue engineering is very much an interdisciplinary field combining the application of principles of biosciences and engineering.

In July 2002, the Commission launched a public consultation to assess the "Need for a legislative framework for human tissue engineering and tissue-engineered products", so as to complement current rules on medicinal products[61], medical devices as well as donation and distribution of human tissues and cells[62].

11.3.2. Contributors

The Commission received **fifty-one contributions**. Many of the responses, in particular those provided by institutional bodies or industrial associations, were the result of a wider consultation.

The contributors can be subdivided into three main groups:

(1) Government/public institution officials

(2) Industry

(3) Researchers/experts

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60 Directive 2000/70/EC of the European Parliament and of the Council of 16 November 2000 amending Council Directive 93/42/EEC as regards medical devices incorporating stable derivates of human blood or human plasma

61 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.

62 Proposal for a Directive of the European Parliament and the Council setting standards of quality and safety for the collection, testing, processing, storage and distribution of human blood and blood components and amending Council Directive 89/381/EEC (COM(2000)816 final). Proposal for a Directive of the European Parliament and the Council setting standards of quality and safety for the donation, procurement, testing, processing, storage and distribution of human tissues and cells (COM (2002) 319 final).

The Commission received twelve responses from governmental/institutional officials, including nine Member States, one European institution, one intergovernmental organisation and one international regulatory agency.

Industry, including individual companies and industry associations, sent eighteen contributions. Ten of these contributions were provided by SMEs. Three respondents were larger companies active in the pharmaceutical area. Other contributions came from three European industry associations, one European association of medical doctors and one national industry association.

The Commission also received twenty-one contributions from researchers/experts. These came from twelve research institutions, six lawyers and three individual professionals (doctors, pharmacists etc.).

All contributions provided valuable background information for the Commission's further actions in this field.

11.3.3. Key findings

- **Need for a new legal framework**: industry and experts appeared largely in favour of a new legal framework for tissue-engineered products. There was no clear consensus among government and public institution officials: while a majority advocated a new regulatory framework, some proposed to use the existing legislation on medicinal products.

- **Definition and scope**: all respondents stressed the difficulty to define the scope of application of any new legislation. It was generally felt that, whatever the definition, there would always be grey zones and borderline products. Some contributors suggested the possibility to revise the scope of application of the Directives on medicinal products and/or medical devices in order to reduce the risk of borderline products.

- **Xenogeneic cells and tissues**: government and public institution officials were equally divided as to whether xenogeneic cells and tissues should be covered in any new legislation. Individual companies were favourable to the inclusion of xenogeneic products in the new legal framework, while industry associations wished to address xenogeneic cells and tissues only if they are used as ancillary elements in the manufacture of human tissue engineered products. Other experts were also divided over this question.

- **Outline for a possible Community framework**: binding specifications, standards and guidance documents were generally seen as useful instruments. These would not be mutually exclusive.

- **Procedural aspects**: a majority of respondents seemed to favour centralised approval procedure, albeit for different reasons. Several government and public institution officials highlighted the scarcity of scientific expertise in their country to evaluate tissue engineered products. Industry and experts, for their part, considered that a system based on mutual recognition would not be the best option. Amongst those who favoured a centralised approach, a majority supported a role for the EMEA in the

scientific approval process. However, some respondents were reluctant to involve the EMEA if this leads to lengthy examinations and important costs for business operators.

11.4. Summary of the 2004 public consultation

This document summarises the contributions made by stakeholders to DG Enterprise's web-based public consultation (closed on 30 April 2004). It also refers to comments provided in the framework of the stakeholders' conference held on 16 April 2004.

Stakeholders were invited to express their position in light of a consultation document published by DG Enterprise on 6 April 2004. This summary provides an overview of comments received by the closing date on the key issues identified in the consultation document.

11.4.1. Introduction

DG Enterprise received a total of **35 written contributions**, including comments from individual companies (8), research and academic centres (7), European and national industry associations (5), policy-makers and governmental experts (4), tissue and blood banks (3), consultants and lawyers (3), medical and hospital associations (2), third country experts (1), insurance organisation (1) and chamber of labour (1).

A vast majority of respondents supported the European Commission's initiative to propose legislation with respect to human tissue engineered products. Comments were generally in favour of a Regulation, rather than a Directive.

11.4.2. Scope and definitions

11.4.2.1.Scope

– Research and development trials: several respondents stressed that the exclusion of research and development trials from the scope of the proposal would de facto exclude clinical trials. They pointed out that clinical trials for human tissue engineered products should be addressed in the framework of this proposal.

– Lex specialis: the lex specialis principle, as described in the consultation paper, was generally supported by stakeholders. It is considered as a useful instrument to avoid overlap with existing legislation and minimise the risk of grey areas for borderline products.

– Clearing house function: the principle of a clearing house function was welcomed in many of the stakeholders' comments. Some expressed concern that the EMEA would have a dual role as assessment body and clearing house, but it was generally recognised that it would be difficult to appoint another competent body for this function. It was suggested that the body in charge of the clearing house function should be distinct from the EMEA's scientific committees for tissue engineered products and medicinal products. Stakeholders stressed that the terms of reference of this body should be well defined. Some of them requested that a decision to determine which legislation applies to a given product should be taken before clinical trials begin.

– Xenogeneic products: a vast majority of respondents agreed that xenogeneic living cells and tissues should be excluded from the scope of the proposal at this stage. However, it was often highlighted that it is impossible in practice to ensure that xenogeneic cells are not *present* in the final product. For instance, the use of xenogeneic scaffolds may result in the presence of inactive xenogeneic material in the final product. Some respondents suggested that legislation should ensure that any xenogeneic materials present in the final product are not viable.

– Cells of embryonic origin: a contribution suggested that human tissue engineered products derived from cells of embryonic origin should be excluded from the scope of the proposal.

11.4.2.2. Definitions

– Borderline products: many contributors insisted on the necessity to propose a definition which is as precise as possible, in order to avoid overlap and borderline issues. Different suggestions were made in this respect and are summarised below.

– Inclusion of derivatives of cells and tissues: a number of stakeholders stressed that derivatives of cells and tissues should be included in the definition of human tissue engineered products. Their objective is to address materials and products that do not currently fall under existing legislation on medicinal products or medical devices.

– Composite products: industry considered that, when a human tissue engineered product is used in conjunction with a medical device or a medicinal product, the composite product should be evaluated under a single, integrated authorisation procedure. The medicinal product or medical device part of the composite product would be assessed according to the same criteria as individual products, but verification of compliance would be done in the framework of the overall assessment of the tissue engineered product (i.e. no separate authorisation or CE marking required).

– "Structurally and functionally analogous": some respondents suggested that "structurally *and/or* functionally" analogous would be more appropriate. Indeed, the human tissue engineered product may not be a mere replacement of diseased tissues, but could be a different tissue fulfilling the same function.

– "Substantially manipulated": use of the term "substantially manipulated" in the definition of "engineered" triggered a number of comments by stakeholders. Some suggested that the word "substantially" should be deleted. Others considered that this term leaves too much room for interpretation. In this respect, it was suggested that a list of products could be drawn up, which would contain examples of minimally/substantially manipulated products. Attention was drawn to the fact that the US has established a list of 316 minimally manipulated products.

– "Placing on the market": some respondents considered the proposed definition of "placing on the market" as improper because it does not cover products manufactured and used in the same facility (in-house use, for instance in hospitals). They stressed that there is no reason why such products should not be subject to the same rules as tissue engineered products manufactured by industrial operators. A large majority of

stakeholders were of the opinion that hospitals, tissue banks and other local actors should be subject to the same rules as enterprises.

11.4.3. Authorisation procedure

The suggested two-tier approach was discussed in almost all contributions.

– Autologous vs. allogeneic: the procedural distinction between allogeneic and autologous products was generally considered as a possible starting point, but many contributions stressed that it should be complemented with other relevant criteria. Thus, some respondents proposed to consider parameters relating to the composition of the cell population in the tissue, the physiological function of the tissue or the risk induced by the product in relation to its functionality. Other criteria were proposed, such as single donor (national authorisation) vs. pooled donor (central authorisation) or donor/receiver identified (national authorisation) vs. universal donation (central authorisation). Some stakeholders, recognising that no single criterion offers practical solutions, suggested taking different parameters into account and to draw up lists of products to be approved at national level or at central level.

– Choice of procedure: some stakeholders stressed that both allogeneic and autologous products may carry the same level of risk. It was therefore proposed that the applicant may always choose between the centralised procedure and the decentralised procedure, regardless of the allogeneic or autologous character of the product.

– Centralised vs. decentralised procedure: some respondents insisted on the scarce availability of scientific expertise in the area of tissue engineering and stressed the need to create and maintain confidence in tissue engineered products. For these reasons, they advocated a fully centralised procedure that would pool the expertise available in Europe and build confidence in tissue engineered products. If a fully centralised procedure proves impossible to establish, it was also proposed to create a limited number of "centres of excellence" in Europe. These "centres of excellence" would have the capacity to deliver marketing authorisations, which would be valid throughout the Community.

11.4.4. Authorisation requirements

11.4.4.1.Clinical testing and clinical testing authorisation

– Clinical testing authorisation: very few comments were made on the principle of clinical testing authorisation, which seems to be widely accepted.

– Difference with medicinal products: stakeholders stressed that clinical tests for human tissue engineered products will be different from those carried out for medicinal products. It will therefore be essential for applicants to know at an early stage – i.e. before clinical tests begin – whether their product is a human tissue engineered product or a medicinal product. Directive 2001/20/EC was generally considered as a good basis for clinical trial requirements, but it needs to be adapted to reflect the specificity of human tissue engineered products.

– Testing requirements and risk-benefit analysis: many contributions underscored that non-clinical and clinical testing requirements should depend on the risk-benefit

analysis of the product. For instance, pre-clinical studies on animals may not be conclusive and randomised or blind tests may even be impossible. This means that, for each product, specific requirements may need to be established.

– Manufacturing licence and clinical trials: the consultation paper suggested that, "at the minimum, the manufacturing licences should be required for site manufacturing clinical trial material". Two respondents considered that the clinical trial stage was too early to request a manufacturing licence. It was argued that clinical trials would start even before the production plant is established.

– Import of material for clinical testing: proposals were made to apply the same rules as for material of EU origin and to grant only one authorisation for the Community as a whole.

11.4.4.2. Manufacturing authorisation

– Use of industry's expertise: industry representatives requested to be involved in the establishment of the requirements for manufacturing and marketing authorisations. Evaluations should be based on the risk-benefit analysis of the product.

– Authorised centres: different respondents considered that the implantation of human tissue engineered products should not be restricted to centres authorised in the Member States, for instance hospitals. The proposal should not impose any specific authorisations allowing practitioners to use human tissue engineered products.

– GMPs: Many stakeholders stressed that GMPs developed for medicinal products are not directly applicable to human tissue engineered products and will need to be redesigned. Recommendations were made to adapt these GMPs by taking into account the "Good Tissue Practice" in place in the United States, as well as ISO 9001 and ISO 13485.

11.4.4.3. Marketing authorisation

– Timeframe for scientific evaluation: a majority of stakeholders who expressed their views advocated a fast and simple evaluation. It was argued that the dossier would be less complex than for medicinal products. The timeframe for evaluation should therefore be less than 210 days. Different recommendations were made, ranging between 90 and 120 days.

– Fee reductions and other incentives: considering that the companies involved in tissue engineering are SMEs, many respondents requested a reduction of evaluation fees for such companies. Specific incentives, such as those offered for orphan drugs, were also requested on several occasions.

– Conditional approval: industry stressed that the possibility of conditional approval and fast-track approval needs to be envisaged.

– Variations: some respondents recommended establishing criteria to determine when a product should be considered as a variation of an authorised product. In addition, different suggestions were made, ranging from the obligation to approve variations to

the obligation to notify them. It was proposed that guidelines be developed for variations; these guidelines would be identical for all products.

– Data protection: the suggestion to use the same data protection rules as for medicinal products (biosimilar approach) was generally supported.

– Imports: industry indicated that the same requirements of quality, safety and efficacy should be imposed on imports and effective control mechanisms should be established.

– Donor information: a few stakeholders requested that the donor be informed of the usage made of the tissue which they provide as source material.

11.4.4.4. Authorisation of establishments

– A few respondents indicated that the implantation of tissues should not be restricted to centres authorised by the Member States.

11.4.5. Post-authorisation issues

– Safeguard clause: several respondents insisted on the necessity to establish strict requirements for the use of the safeguard clause, in order to avoid obstacles to the free movement of tissue engineered products.

– Vigilance: stakeholders recommended a vigilance system similar to that in place for medicinal products or medical devices. However, it is essential to ensure that this system remains cost effective, in particular for SMEs. Both allogeneic and autologous products could be listed in a central database.

– Traceability: several respondents mentioned that human tissue engineered products may require post-approval monitoring. A specific reporting mechanism should be established, taking into account the requirements for patient data protection.

– Grandfathering clause: the principle of a "grandfathering clause" for products already on the market/in use in Member States was generally accepted. However, some respondents considered that its application should be restricted, for instance by maintaining this principle only during the first five years after entry into force or by restricting the possibility to keep a product on the market without authorisation only in countries where this product has been marketed before the entry into force of the Regulation.

11.4.6. Ethical issues

– Free donation: the principles of free donation established in the European Convention of Human Rights should be respected. They forbid any direct payment of the donor even if the companies processing the tissues make profits.

– Patient information: in case of allogeneic donation, it is considered important that the donor is informed as far as possible of the potential use of his cells, including when they are processed by private companies.

– Ownership of the cells and tissues after donation: as legislation differs from one Member State to another, it is recommended that the Regulation should provide clarity on this issue.

– Traceability vs. anonymity and data protection: it is recognised that there is a need for full traceability of a product from the medical history of the donor, through to the complete processing and to the receiver years after implantation. Nevertheless, the Regulation should ensure that data protection, and particularly the anonymity of the donor and the receiver, is always guaranteed.

– Clinical tests: the ethical principle included in Directive 2001/20/EC on good clinical practice in the conduct of clinical trials on medicinal products for human use should be applied, although it is recognised that the Directive may not be fully applicable to other domains.

11.5. Summary of the 2005 public consultation

This document summarises the contributions made by stakeholders to DG Enterprise and Industry's web-based public consultation on advanced therapies, conducted in May-June 2005. It also refers to comments provided in the framework of several stakeholders meetings held in the meantime:

– 20 May: meeting with industry (Eucomed/Europabio/EFPIA-EBE)

– 25 May: expert meeting with DE, FR, NL, SE and UK representatives

– 1 June: formal consultation of 25 Member States regulatory authorities (Pharmaceutical Committee)

– 7 June: Stakeholders workshop gathering all interested parties (patients, hospitals, research, doctors, industry, ethics groups…)

Stakeholders were invited to express their position on the basis of a draft Regulation on advanced therapies, together with an accompanying consultation paper outlining the key elements of the proposal[63].

The Commission response to the issues raised and justification for the final Commission proposal are laid down in the Impact Assessment and in the Explanatory Memorandum of the Regulation on advanced therapy medicinal products.

11.5.1. Contributors

The Commission received **174 contributions**. Many of them, in particular the ones from regulators, the research community or the industry, are the results of wider consultation. A full listing of all parties providing comments is given at the end of this document.

The participants can be divided into 8 categories:

– Patients associations (1 contribution);

[63] For more details, see : http://pharmacos.eudra.org/F2/advtherapies/index.htm

– Healthcare professionals (11 contributions) including hospitals, tissue banks and doctors;

– Regulators (17 contributions) including EU and non-EU regulatory agencies, national ministries, international institutions and notifies bodies;

– Research Community (10 contributions), including associations and individuals;

– Industry (18 contributions) including associations, individual companies and consulting firms;

– Ethics-related organisations (6 contributions);

– Individuals (110 contributions);

– Others (1 contribution).

All contributions received provided valuable information for the Commission's further action in this field.

11.5.2. Summary of contributions

11.5.2.1. General comments

A vast majority of respondents welcomed the Commission's consultation paper, the opportunity to submit contributions, and explicitly supported the outlined objectives. As in the previous consultation rounds (2002 and 2004), the need for a harmonised legislation with respect to tissue engineered products was strongly emphasised. There was also a large consensus in favour of a Regulation, rather than a Directive, mainly in order to have a practicable system in place as soon as possible.

Broadly speaking, most of the contributors agreed with the **key principles and concepts** underlying the Commission's draft. In particular, the proposal to bring together gene therapy, somatic cell therapy and tissue engineering under the concept of 'advanced therapies' and within a single integrated framework building on existing legislation was generally supported. No philosophical objection against the link to existing legislation on medicinal products was raised. However, several contributors from various categories highlighted the importance of **adapting the framework**, in particular the technical requirements, to the specificities of the products concerned. Indeed, as recognised in the Consultation paper, advanced therapy products are neither medical devices nor 'conventional' medicines.

The suggested 3-tier regulatory strategy (1: overarching principles through co-decision; 2: technical requirements through 'comitology'; 3: detailed requirements through guidelines) was felt to be a sensible approach. The ability to amend technical requirements in a flexible manner so as to keep the pace with science and technology was strongly underlined.

The most controversial comments were related to the **Definition and Scope** sections of the proposal.

11.5.2.2. Definitions

A number of contributors challenged the proposed definition of human tissue engineered products. First, some argued that these products may not fit in the current definition of medicinal products (as laid down in Directive 2001/83/EC, as amended), which hence might have to be amended in order not to leave products unregulated.

Secondly, certain respondents, notably from the 'Industry', 'Healthcare professionals' and 'Regulators' categories, considered that the definition of 'engineered' human cells or tissues may leave too much room for interpretation, and may not define the boundary between tissues/minimally manipulated tissues and tissue engineered products in a sufficiently accurate manner. As in the 2004 consultation round, some respondents suggested deleting the word "substantially" (as in *"their normal biological characteristics, physiological functions or structural properties are substantially altered"*). Others considered that the adjective 'substantial' should not refer to the properties of the cells (as proposed in the draft), but to the type of manipulation that the cells are subject to. The concept of 'substantial manipulation' could then be applied in a similar way as in the US for 'more-than-minimal manipulation'. Several contributors provided useful examples and lists of manipulations that they would consider as entailing no 'substantial alteration'. Use of the Committee for Advanced Therapies to provide guidance on borderline cases (similarly to the Tissue Reference Group in the US) was also suggested.

Some respondents, in particular form the 'Healthcare professionals' category, emphasised the potential overlap between the current definition of somatic cell therapy medicinal products and the proposed definition of human tissue engineered products. Several technical proposals to clarify this borderline issue were provided. A few contributors also proposed to take this Regulation as an opportunity to revise also the definition of somatic cell therapy.

As regards combined advanced therapy medicinal products, certain stakeholders from the industry suggested to cover all cell/tissue based products incorporating medical devices, and not only those where the 'cellular' part of the product *"is liable to act upon the human body with action that cannot be considered as ancillary to that of the referred device"* (as suggested in the draft Regulation). It was stressed that these products –with the exception of blood derivatives- would otherwise not be covered by any Community legislation, as Directive 93/42/EEC excludes products incorporating or derived from tissues or cells of human origin.

11.5.2.3. Scope

On the Scope, three main points were raised:

Embryonic stem cells

A large number of respondents (mostly individuals and ethics-related organisations) called for a total ban on the use of embryonic stem cells (ES cells) for the manufacture of advanced therapies. The Regulation should be unambiguous that Member States are not forced to accept products which contradict their ethical position.

The Commission takes due note of this concern on such an important issue. However, it should be borne in mind that this matter was extensively debated during the adoption of the European Directive on the quality and safety of human tissues and cells[64]. In this context, the European Parliament, representing citizens, and the Council of the European Union, representing Member States, have recognised that there is, to date, no consensus in Europe upon which harmonised decisions could be taken on the use or prohibition of embryonic stem cells. Thus, decisions on such use or prohibition should, and will remain, a national responsibility. Nevertheless, it was also agreed that, if 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[65].

To avoid any misunderstanding, it should be clear that the proposed Regulation should by no means interfere with decisions made by Member States on the use or prohibition of any specific type of cells.

'One-off products' exclusion; industrial vs. non-industrial

Stakeholders expressed divergent opinions on the exclusion of advanced therapy medicinal products "which are made on a one-off basis, according to a specific and non-industrial manufacturing process, in order to comply with a medical prescription for an individual patient" (as proposed in the draft Regulation). On the one hand, contributors from the industry generally supported this exclusion, and highlighted the importance of ensuring a level playing field for all economic operators involved. On the other hand, other stakeholders from the 'Healthcare professionals' and 'Research' category stressed that the exclusion was too narrow, that the concept of 'industrial manufacturing process' may be too vague and that hospitals and university/research environments should not be imposed unnecessary regulatory overburdens such as marketing authorisation requirements. Several contributors suggested additional criteria to clarify the scope, e.g. in-house vs. non in-house use, mass production, or total exclusion of all autologous products.

Xenogeneic products

Contrary to the trend observed in the 2004 consultation round, a majority of those stakeholders who expressed their views on the subject challenged the exclusion of xenogeneic tissue engineered products, on the following grounds:

– Cell therapy medicinal products based on animal cells are already covered, since 2003, by the legislation on medicinal products[66];

– Medical devices incorporating (non viable) animal cells are already covered, since 1993, by the legislation on medical devices[67];

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64 Directive 2004/23/EC, OJ L102, 7.4.2004, p.48.

65 Recital (12) and Article 4(3) of Directive 2004/23/EC.

66 Part IV, Section 2 of Annex I to Directive 2001/83/EC, as amended by Directive 2003/63/EC, OJ L159, 27.6.2003, p.46

67 Directive 93/42/EEC, OJ L169, 12.7.1993, p.1

– Xenogeneic tissue engineered products are already in clinical development in Europe, and more are expected in a near future. To exclude them may hamper such developments;

– It may be difficult to argue that xenogeneic tissue engineered products are totally excluded from the Regulation, while even more controversial products (*e.g.* based on embryonic stem cells) are not;

– If excluded, xenogeneic tissue engineered products would not be regulated under Community legislation. The issue of unharmonisation and market segmentation would most likely remain.

For these reasons, it was suggested to include xenogeneic tissue engineered products in the scope of the proposal.

11.5.2.4. Committee for Advanced Therapies (CAT)

The concept of a specific Committee within the European Medicines Agency (EMEA) with appropriate expertise for the evaluation of advanced therapies was welcomed and explicitly supported by the vast majority of stakeholders.

A number of suggestions were made to amend the composition of the Committee and the relative representation of the various kinds of expertise and interested parties. In particular, some contributors challenged the need for representation of *all* Member States. The risk of an oversized Committee was highlighted. Respondents from the 'Regulators' category often stressed that the CAT should remain a scientific committee, whose composition should be determined solely by the expertise needed. A few stakeholders also raised the potential issue of confidentiality and conflicts of interest between regulators and applicants, in a scientific area where regulatory competence is scarce.

The respective roles of the CAT and the Committee for the Evaluation of Medicinal Products for Human Use (CHMP) appeared unclear to a number of stakeholders, from all categories. Some suggested that the CAT should be totally independent from the CHMP. Conversely, others stressed the importance of having one overarching body (the CHMP) responsible for the overall evaluation of the risk/benefit ratio of all medicinal products processed through the EMEA, notably for consistency reasons. In their view, the CAT should be considered as advisory to the CHMP.

11.5.2.5. Marketing Authorisation Procedure

The proposal for a fully centralised marketing authorisation procedure was supported by a large majority of respondents. It was considered as a good way to establish legal certainty and harmonisation, which are indeed key objectives of the initiative.

Nevertheless, a number of stakeholders also stressed the need to fully take in consideration the regulatory burden that such a procedure would entail, especially on small and medium-sized enterprises and certain tissue banks. It was argued that some of the concerned operators may only plan to sell products on a local or national market, and may not have the regulatory resources to cope with a centralised evaluation procedure. Special financial and administrative provisions for SMEs (fee reductions and deferrals,

translations, establishment of the SME Office etc.), together with special fee reductions for scientific advice on advanced therapies, were particularly welcomed in this respect. Suggestions on the overall timing of the procedure (210 days maximum + clock stops) and the need to put 'fast-track' approvals in place were also provided.

The issue of combined products evaluation raised contradictory comments. On the one hand, some stakeholders supported the principle of a 'one-stop shop' system, with one single evaluation of the whole product performed by the EMEA and the CAT. This approach was deemed necessary to avoid creating additional layers of bureaucracy, and was further supported by the presence of experts in medical devices at the CAT. On the other hand, others argued that the assessment mechanism should mirror the one currently in place for medical devices incorporating ancillary medicinal substances (such as blood derivatives), *i.e.* evaluation of the medical device part by a notified body and evaluation of the medicinal part by a national competent authority. It was felt that this alternative would take full advantage of the knowledge and competence that notified bodies may have already built in this field.

11.5.2.6. Marketing Authorisation Requirements

The principle of applying Directive 2004/23/EC to the donation, procurement and testing of cells manufactured in advanced therapies did not raise major issues. However, a number of contributors emphasised the need to clearly draw the line between this Directive and the proposed Regulation. This point was often related to the abovementioned issue of Definitions & Scope.

The provisions on good clinical practice (GCP) and good manufacturing practice (GMP), in particular the proposal to draw up detailed guidelines in line with those principles and specific to advanced therapy medicinal products, were welcomed by most respondents. As indeed recognised in the Consultation paper, stakeholders stressed that clinical requirements for advanced therapies will most likely be significantly different from those required for 'conventional' medicines. Emphasis was also put on the need to consult as early as possible all interested parties when drafting those guidelines.

In addition, some industry stakeholders provided detailed suggestions to amend Directive 2001/20/EC on GCP, in order to better accommodate tissue engineered products within this framework.

The proposal to amend Annex I to Directive 2001/83/EC in order to establish technical requirements for tissue engineered products was broadly supported, as 'standard' pharmaceutical requirements were obviously not considered appropriate. Industry, in particular, stressed the importance of close consultation when drafting those specific requirements, which may influence the practicability of the whole framework to a large extent. Some stakeholders also proposed to put more emphasis, already in the marketing authorisation application on risk-management and how the applicant would ensure monitoring of the safety and efficacy of the product in the long run.

11.5.2.7. Summary of Product Characteristics, Labelling, Packaging

Very few technical comments were provided on this section. One stakeholder stressed the value, in an emerging area were science is not mature and research very exploratory,

of ensuring that information to doctors, patients and the public in general is given in a clear, pedagogic and non-alarmist way.

11.5.2.8.Traceability

The principles of product and patient traceability were supported by a vast majority of stakeholders, so as to monitor products' safety in a long-term perspective. Compatibility with the provisions on traceability which are laid down in Directive 2004/23/EC was also supported.

However, several concerns were expressed as to how to implement those principles. The issues raised related to the protection of patients data, anonymity, and the practical aspects of collaboration between manufacturers and the hospital/private practice where the product is finally implanted. Several stakeholders proposed a clearer assignment of responsibilities to the various parties involved in the traceability chain. Others suggested that traceability systems should be handled with public money and managed at European level, possibly by the EMEA.

11.5.2.9.Final provisions: reporting and transitional period

Very few comments were provided on the reporting clause. One stakeholder suggested that the timing for reporting (within 5 years of the entry into force of the Regulation) might be too short, and that a longer period might be envisaged.

The principle of a transitional period was welcomed by most stakeholders. A few contributors suggested extending the period from three to five or seven years. One stakeholder proposed to apply the transitional period also to products which were *not* legally authorised at the time of entry into force of the Regulation. Others proposed to limit the evaluation of legally authorised products to manufacturing, vigilance and risk management requirements.

11.5.3. Annex: list of respondents to the public consultation:

Patients Associations:

– EURORDIS (European Organisation for Rare Diseases)

Healthcare professionals:

– Bernard Loty (Agence de la Biomédecine)

– Centro Nazionale Trapianti (National Transplant Centre, Italy)

– CPME (Comité Permanent des Médecins Européens)

– Deutsche Krankenhausgesellschaft (German Hospital Federation)

– DSO-G (German OrganTransplantation Foundation)

– EATB (European Association of Tissue Banks)

– HOPE (European Hospital and Healthcare Federation)

– Royal College of Physicians (UK)

– Spanish Association of Tissue Banking

– TBF (Banque de Tissus et Cellules privée)

– UK Tissue Services section of the National Blood Service and supported by EATB

Regulators

– Agemed (Spanish Agency)

– Alan Fauconnier, Belgian Health Ministry

– Council of Europe

– Dutch Ministry of Health, Welfare and Sport

– EMEA (European Medicines Agency)

– French Permanent Representation

– Genetic Science Safety and Regulation Team, Department of Health, UK, having consulted the UK Gene Therapy Advisory Committee

– INFARMED (Medicines Agency, Portugal)

– Irish Department of Health and Children, in consultation with the Irish Medicines Board

– Margarida Menezes, INFARMED (Medicines Agency, Portugal)

– MHRA (UK, in agreement with UK Government)

– MPA (Medical Products Agency, Sweden)

– PEI (Paul-Ehrlich Institut)

– Spanish Ministerio De Sanidad Y Consumo, Organizacion de Trasplantes

– Ständige Vertretung der Bundesrepublik Deutschland bei der Europäischen Union

– SwissMedic (Switzerland)

– TÜV Product Service GmbH

Research Community

– ESB (European Society for Biomaterials)

– ESGT (European Gene Therapy Society)

– INEB (Institute for Biomedical Engineering, University of Porto, Portugal)

– ISCT(International Society for Cellular Therapy) - Europe and JACIE (Joint Accreditation Committee for ISCT and EBMT(European Group for Blood and Marrow Transplantation

– Italian Working Group on Human Tissue Engineering

– P.V. Hatton, University of Sheffield, UK

– Francesco Frassoni, Ospedale San Martino, Genova, Italy

– Tim Hardingham, UK Centre for Tissue Engineering

– TEB (Tissue Engineering Platforms)

– Ulrich M. Gassner (University of Augsburg, Germany)

Industry

– AdvaMed (Advanced Medical Technology Association)

– Assobiotec

– BIA (UK BioIndustry Association)

– BPI (German Pharmaceutical Industry Association)

– CellTran Ltd

– Clinical Cell Culture

– EBE (submitted as 'informal comments')

– EFPIA (European Federation of Pharmaceutical Industry Association)

– Eucomed (Medical Devices association)

– EuropaBio

– Intercytex

– Isolagen

– Medidas Medical Technologies

– Miltenyi Biotec GmbH

– Smith and Nephew

– TiGenix

– VFA (German Association of Research-based Pharmaceutical Companies)

– Voisin Consulting

Ethics-related organisations

– CARE (Christian Action Research and Education)

– COMECE (Commission of the Bishops' Conferences of the EC)

– CORE (Comment on Reproductive Ethics)

– EKD (Protestant Evangelische Kirche in Deutschland)

– European Kolping Society

– UK Center for Bioethics and Public Policy

Individuals

- Achille Vernizzi
- Agnes du Temple
- Alain de Broca
- Alfonso González Fernández
- Ana Maria Aguiar
- Ann Heneghan
- Antonio Romano
- Axelle & Laurent Rousse
- Bernard David
- Bernhard Wilden
- Brian Collins
- Brian McKevitt
- C. Peyroche d'Arnaud
- Carine Brochier
- Catarina Rodrigues
- Chantal Lefebvre
- Christophe Buffin de Chosal.
- Civardi Claudio
- Cristina Piédrola Nadal
- D. Vincent Twomey
- Daniela Canfarotta
- David Manly
- Dick Humphreys
- Dominique Charlet
- Dominique de Hemptinne
- Dominique Magnette
- Edmund Adamus
- Elisabeth & Alain Riedel
- Emanuele Ortoleva
- Francesco Paolo & Pia Vatti
- François Brochier
- François Davost
- František Tondra
- Frederic Montavont
- Gabriella Mangiarotti Frugiuele
- Gianmaria Leotta
- Giovanna Rossi
- Giuseppina Lauritano
- Gonzalo Niederleytner
- Ildiko Mikulas
- Isabelle vS Grohol
- Iza Petryna-Kalinowska
- Jacqueline Dalrymple
- Jacques de Raigniac
- Jacques Salmon
- Jaime Moreno Ballesteros
- Jean Renaud
- Jean-Marc Baijot
- Jean-René Binet
- Jec Nizery
- Joan Murray
- John Franklin
- John Marechal
- Jorge Lazarocarr
- Judith Stockton
- Julia Heffernan.
- Kathy Sinnott
- Katrin Hatzinger
- Laura Geronazzo
- Lelia O'Flaherty
- Liam De Paor
- Lucien Van Eetvelde
- Luigi Regoliosi
- M.B Ní Fhuireastail
- Marco & Paola Strazzabosco
- Maria Ostaszewska
- María Rodríguez-Losada Aguado
- Marie Christine Urbistondo-Picavea
- Marie de blic
- Marie-Christine Ceruti-Cendrier
- Marie-Claude Hayoit

– Marina Robben
– Mario Barzaghi
– Marta Pochini
– Martin Brochier
– Mary & Kevin Mc Brien
– Mary tim Crowley
– Mary Barrett
– Michelle Coyle
– Miguel Ángel Sepúlveda Cariñanos
– Milo Connolly
– Miquel Mundet
– Mr & Mrs Delogne
– Muiris De Cuirteis
– Myke & Miriam Rosenthal-English
– Nathalie De Smet
– Oisin Martin
– Oliver Broderick
– Olivier Demeure
– Olivier Miret
– Pablo Mª Calzado Fernández
– Pascale Poussie
– Patrick d'Ursel
– Pedro-José Herráiz
– Philippe Caspar
– Philippe de Diesbach
– Philippe & Marie Pierre Milan
– Pierce Durand
– Pierre-Alexandre de Maere d'Aertrycke
– Pilar Pérez
– Piredda Michela
– Risteárd de Bhulbh
– Séamas de Barra
– Seamus Cunnane
– Sophie Balastre
– Tamara Sánchez Membibre
– Tony & Maire Carmody
– Tony Mullett
– Violaine & Olivier van Stratum
– Winifred Collins

Others

– Wellcome Trust