

Human tissue-engineered products: Potential socio-economic impacts of a new European regulatory framework for authorisation, supervision and vigilance

A synthesis report prepared by

**Anne-Katrin Bock and Emilio Rodriguez-Cerezo
(JRC-IPTS)**

**Bärbel Hüsing, Bernhard Bührlen, Michael Nusser
Fraunhofer Institute for Systems and Innovation Research
Karlsruhe, Germany**

European Commission

Joint Research Centre (DG JRC)

Institute for Prospective Technological Studies

<http://www.jrc.es>

Legal notice

Neither the European Commission nor any person acting on behalf of the Commission is responsible for the use which might be made of the following information.

Report EUR 21838 EN

© European Communities, 2005

Reproduction is authorised provided the source is acknowledged.

Preface

In 2001, the European Commission's Scientific Committee on Medicinal Products and Medical Devices came to the conclusion that human tissue-engineered products are not appropriately covered by any European regulatory framework. While the technology promises huge benefits and novel treatments for diseases there are specific risks connected to these kinds of products. A European level regulation is considered essential to guarantee safety and quality of tissue-engineered products applied and traded within Europe or being imported from overseas.

In 2003 JRC-IPTS carried out a study, upon request of DG Enterprise, giving an overview on European tissue engineering research and the developing commercial sector¹. In this study, the lack of a European-wide legal framework for human tissue-engineered products was identified as one of the challenges the tissue engineering sector is facing. Following public consultations in 2002 and 2004, the European Commission prepared a draft regulation intended to fill that gap. The aim is to harmonise legislation in the EU and to enable a common European market while safeguarding patient protection. The draft regulation was released for an additional public consultation in May 2005².

The European Commission introduced the Impact Assessment for major regulatory initiatives along the lines of the Better Regulation Action Plan³ with the aim to improve the quality and coherence of the policy development process. The regulatory initiative on tissue engineering belongs to this category.

JRC-IPTS was requested by DG Enterprise in December 2003 to assess the economic, social and environmental impacts of several regulatory options for tissue-engineered products as an input to the formal Impact Assessment. This report is the outcome of this project, carried out in collaboration with the European Science and Technology Observatory ESTO, in particular the Fraunhofer Institute for Systems and Innovation Research, Germany, between February and October 2004. The project was carried out on the basis of an outline for a regulation on tissue-engineered products available in February 2004. This synthesis report, summarising the project's results, was updated in May/June 2005 taking into account recent developments.

¹ Bock, A. K.; Ibarreta, D.; Rodriguez-Cerezo, E. (2003): Human Tissue Engineered Products - Today's Markets and Future Prospects. Synthesis Report. Report EUR 21 000 EN

² See <http://pharmacos.eudra.org/F2/advtherapies/index.htm>

³ Communication from the Commission "Action Plan: Simplifying and improving the regulatory environment"; COM(2002)278 final and "Better Regulation for Growth and Jobs in the European Union", COM(2005)97

Content list

Executive summary	7
1 Introduction	13
1.1 Definition of human tissue-engineered products	13
1.2 Scope and sources of information	14
2 Current situation of tissue engineering in the EU	17
2.1 Tissue engineering companies	17
2.2 Products on the market.....	19
2.3 Current markets for hTEPs	22
2.4 Tissue engineering in hospitals and tissue banks.....	22
2.5 Tissue engineering in the US and Japan	26
3 Current regulatory situation for placing hTEPs on the market	27
4 Outline of the proposed regulatory options for hTEPs	29
4.1 Overall regulatory approach.....	29
4.2 Regulatory options	29
5 Potential economic impacts of the proposed regulatory options for hTEPs compared to the status quo.....	33
5.1 Economic impacts: Tissue engineering companies.....	33
5.1.1 Classification of hTEPs.....	33
5.1.2 Compliance with regulatory requirements	34
5.1.3 Post-approval phase	36
5.1.4 Impact of cost changes depending on player profile.....	37
5.2 Impacts on upstream players.....	39
5.3 Impacts on downstream players	39
5.4 Impacts on the opportunity to access new international markets.....	40
5.5 Impacts on time to market.....	41
5.6 Impacts on innovation and R&D investment	41
5.7 Impacts on competition	42
5.8 Economic impacts: Hospitals and tissue banks.....	43
5.9 Economic impacts: Public budget costs for regulatory surveillance of hTEPs	44
5.10 Impacts of cost changes depending on member states.....	46
5.11 Employment, training and education	47
5.11.1 Employment	47
5.11.2 Education and training needs	48
6 Potential social impacts.....	49
6.1 Safety	49
6.2 Availability.....	49
6.3 Ethical aspects.....	50
7 Potential environmental impacts	53
8 Conclusions	55
9 References	59

List of Tables

Table 2.1:	Categorisation of SME European tissue engineering companies according to employee numbers (N= 44).....	19
Table 2.2:	Employees and turnover of tissue engineering companies by size.....	19
Table 2.3:	Number of hTEPs on the market per company, differentiated for hTEP type and company size	20
Table 2.4:	Companies and the region of market (1999-2003)	20
Table 2.5	Products and the region of market	21
Table 2.6:	Authorised tissue and cell establishment with activities in tissue engineering in France.....	23
Table 2.7:	Clinical applications of hTEPs in the UK.....	24
Table 2.8:	UK Tissue Banks with tissue engineering research activities.....	25
Table 2.9:	Tissue banks in Germany which hold a manufacturing authorisation for human tissues	26
Table 3.1:	Regulation for autologous and allogeneic hTEPs in EU member states, March 2004	27
Table 4.1:	Main differences between the centralised and decentralised authorisation procedure for hTEPs	31
Table 5.1	Changes in cost drivers for placing hTEPs on the market – the classification process.....	34
Table 5.2	Changes in cost drivers for placing hTEPs on the market – compliance with regulatory requirements	35
Table 5.3	Changes in cost drivers for placing hTEPs on the market – post-approval phase.....	37
Table 5.4:	Characteristics of player's profile determining the cost impact of the proposed regulatory options for hTEPs	38
Table 5.5:	Costs for public budgets related to different hTEP authorisation procedure options.....	45

List of Figures

Figure 2.1	Network of key factors influencing innovation in the tissue engineering sector.....	17
Figure 2.2	Tissue engineering companies in Europe.....	18

Executive summary

Regenerative medicine is an emerging field of medical practice applying recent advances in biotechnology to enhance healing by using the body's own mechanisms. Within this field, tissue engineering aims to regenerate biological tissues by using human cells aided by supporting structures and/or biomolecules such as growth factors. Human tissue-engineered products (hTEPs) are expected to have a considerable impact on medical practice and to enhance patients' quality of life by improving existing treatments and offering new treatments for currently incurable conditions. These products largely fall outside the scope of current European legislation. Approaches taken by the member states vary and the European market is fragmented.

To address this, a European level regulation is now being prepared. Its goal is to ensure hTEPs are of high quality, safe and effective and by overcoming national differences to lay the foundations for a single Europe-wide market for these products. The framework complements already existing regulation on medical devices, medicinal products, and human tissues and cells.

The purpose of the study described in this report is to identify and assess the potential economic, social and environmental impacts of several European regulatory options for hTEPs in comparison to the status quo. The work was requested by the European Commission's Directorate General Enterprise as part of the Impact Assessment process of the proposed regulation. The study is largely based on data on the commercial hTEP sector published by JRC-IPTS and the European Science and Technology Observatory (ESTO) in 2003⁴. Additional surveys and interviews with experts and stakeholders took place between February and October 2004.

The core regulatory options include a marketing authorisation⁵, which would be granted either through an exclusively centralised hTEP authorisation procedure, or through a two-tier hTEP authorisation, centralised and national, depending on the type of product. In the latter case, allogeneic products (i.e. those where the tissue donor differs from the recipient) would need a marketing authorisation delivered at Community level. For autologous products (i.e. those for which the original tissue was drawn from the recipient of the product), manufacturers could choose between national and centralised marketing authorisation procedures. In both options, the marketing authorisation would be valid in all EU member states.

Marketing authorisation will impose certain manufacturing requirements. All products will need to comply with high standards of safety, quality and efficacy, although the details of these have yet to be defined. All hTEPs will also need a manufacturing authorisation, granted by the national competent authorities. Post-authorisation vigilance and long term traceability of patients receiving hTEPs will also be required. For hTEPs used in research and clinical trials no marketing authorisation will be required. Xenogeneic TEPs for human use, i.e. TEPs including cells and tissues of animal origin, are also not covered.

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.

⁵ Marketing authorisation refers to "placing a hTEP on the market", which is a legal term and means the making available of a hTEP with a view to distribution and/or use in the Community. It is not necessarily linked to commercialisation.

Human tissue-engineered products in Europe today

The commercial tissue engineering sector in Europe is characterised by small research-based technology-intensive biotechnology companies. About 113 tissue engineering companies were identified in 2003⁴, all but five in the countries that were member states prior to 1 May 2004 (EU-15). Many are SMEs (small and medium-sized enterprises), with less than 50 full-time-equivalent employees (FTE). About 35, mostly autologous hTEPs were identified as being on the market in 2003. These products were mainly skin replacements and knee cartilage products, with just a few bone products. The majority of hTEPs due to come onto the market over the next 5 years are also expected to be autologous.

The markets for hTEPs appear localised and fragmented. Larger companies, but also SMEs sell their products in more than one country, and allogeneic products seem generally to reach a broader market. However, there is as yet no instance of a product that is available in all EU member states.

The lack of a common European regulatory framework means the situation of hTEPs varies greatly from country to country, ranging from no regulation at all to classification as medicinal products. Requirements for safety, quality and efficacy of hTEPs vary accordingly. Opaque and lengthy procedures, compounded by a lack of hTEP-specific expertise in some authorities, can make it difficult for hTEP manufacturers to bring their products to market. Moreover, manufacturers are currently forced to repeat the whole procedure for each additional country in which they wish to sell their product.

In addition to companies, also tissue banks and hospital laboratories produce hTEPs. However, there are only limited data available for Germany, the UK, and France on the scope and extent of their tissue engineering activities. It seems that currently hospitals carry out research or produce fairly simple, autologous hTEPs for in-house treatments. Tissue banks consider tissue engineering as a future strategic option, but do not yet produce any hTEPs. Activities presently seem to be limited to a few institutions per country.

Economic impacts

The proposed regulatory options will reduce the risks and uncertainties manufacturers face by providing a transparent European framework. However, it will require more stringent standards on safety, quality and efficacy, as well as post-authorisation vigilance. This could increase the overall cost of obtaining market approval (although the accessible market will be considerably bigger). The extent to which it does so will depend on the different conditions in the member states and the position of the individual manufacturer. Experts estimate that about 20% of companies might need substantial adaptation to the new requirements.

It is likely to take longer to bring new products on to the market if requirements on the quantity and quality of data are made more stringent. This is a particularly crucial issue for SMEs. However, when requirements are met, authorised hTEPs will have immediate access to all national markets in the EU: a clear benefit for firms with an international outlook. A single market for hTEPs in Europe could intensify competition as firms pursue higher sales with which to offset their higher compliance costs. Such a market would also be more attractive to companies from outside the EU, adding further competitive pressure. Access to markets, however, also depends on other factors, such as awareness among doctors and patients, and also reimbursement mechanisms. By

subjecting hTEPs to stringent scientific assessment the regulation could increase patients trust and so lead to more rapid growth of the market as a whole.

Adapting to and compliance with the regulation could tie up resources that might otherwise be available for investment in R&D. This is felt to be particularly likely in the case of SMEs. As well as delaying the launch of hTEPs and limiting the range a given company develops and produces, this could tip the scales in favour of larger firms better able to target pan-European markets. This could then lead to market consolidation in the form of takeovers or product licensing. In this scenario, larger players are likely to increase their market share. SMEs might then try to target products on niche markets which are less attractive for larger players. Cooperation between firms, and between firms and hospitals in order to run clinical trials could become more common in this new competitive environment. Similarly to the biopharmaceuticals sector, a vertical structure might develop in which large companies outsource innovative research to SMEs, for instance. In the longer term, a transparent regulation and larger market is likely to make the tissue engineering sector more attractive to investors. This might improve the position of SMEs by making it easier for them to obtain finance.

Hospitals and tissue banks either restrict themselves to research activities, or production for in-house treatments or, in the case of tissue banks do not yet produce any hTEPs and consider tissue engineering rather as a future strategic option. The proposed regulatory options do not require marketing authorisations for hTEPs in clinical or preclinical research, thus research-driven hospitals are not expected to face major impacts. The other players, often public, non-profit institutions, currently focus their activity on autologous hTEPs and target a local level, in the future potentially regional or national levels. Thus potential benefits of the regulatory options such as access to other European markets and planning security, which could offset increased costs, are less relevant compared to internationally oriented companies. It can be expected that the current trend of concentration due to adaptation to national and European standards (e.g. Directive 2004/23/EC) will continue and similar developments such as vertical specialisation and a diversification of business models as in the case of companies will occur.

Upstream players such as tissue banks providing cells and tissues to hTEP manufacturers and hospitals carrying out clinical trials are not expected to face requirements that go beyond already existing European regulation. Others, such as providers of equipment or GMP⁶ grade ancillary reagents could see increased sales in the short term as hTEP manufacturers adapt. Downstream players such as doctors, patients and insurers might face higher product prices as companies seek to recoup their increased compliance costs. However, increased market transparency should encourage better informed product choices, possibly leading to more effective treatments and lower costs.

The burden of implementing and maintaining the proposed regulatory options will be borne by the public. The cost of running the regulatory regime will depend on how the tissue engineering sector develops. The option of a two-tier marketing authorisation approach is likely to be more expensive than the centralised approach, given the legal obligation to set up and maintain parallel infrastructure at national level, even in countries without a developed tissue engineering sector and only few or no applications to be expected. The way the operating costs are spread among the different authorities

⁶ Good Manufacturing Practice

would then depend on the future share of allogeneic products and the degree of preference of manufacturers of autologous products for centralised authorisation.

The impact of the tissue engineering sector on employment in the EU is currently slight. Rough estimates suggest that direct employment by the sector could be at present of the order of about 10,000 FTE. Tissue engineering is a technology-intensive sector requiring highly qualified staff to work in research and development, production, the regulatory authorities, and hospitals. Businesses and regulatory bodies could well face staff shortages in the short term due to competition for staff from other sectors such as the pharmaceuticals industry. Few national authorities as yet have experience with hTEPs and demand for suitably qualified staff will be high. This might become an issue in the case of a two-tier marketing approach.

Social impacts

Strict and harmonised standards for safety, quality and efficacy should improve the safety of patients using hTEPs by considerably reducing the likelihood of adverse events resulting from hTEP treatment. The anticipated improvements in health status and quality of life for patients and the public in general are long-term effects that will depend on how the tissue engineering field as such develops.

The advent of a single European market for hTEPs is likely to increase the availability of hTEPs by allowing products to be sold in more countries at a time. This is more likely in the case of allogeneic products and large companies' products. Companies from outside the EU might be attracted by the large single market. Depending on the approach taken for product variants, marketing of improved products might be delayed. Small firms in particular might be unable to go through a full authorisation for each variant: especially when the product life cycle is only a few years.

In practice, patients' access to this kind of treatment depends on more than just product availability. Reimbursement policies are particularly significant. Currently, hTEPs are much more expensive than conventional treatment options and cost-effectiveness data are scarce. Product prices may rise initially as a result of higher regulatory compliance costs, but increased competition and economies of scale could eventually drive hTEP prices down. At present there is no general coverage of hTEP treatments in the public health system or private health insurance in any EU member state. The proposed regulatory options will not have a direct impact on reimbursement policies but might improve the negotiation position.

Environmental impacts

The environmental risks of producing and using hTEPs are generally considered to be low: production volumes are small; the substances involved are biodegradable; human cells do not survive long outside controlled laboratory conditions; and production conditions are strictly controlled. Nevertheless, knowledge of the potential environmental hazards of hTEPs is limited and the issue of environmental risk assessment might need to be addressed. Moreover, if future hTEPs include genetically modified cells, legislation on genetically modified organisms would be applicable.

Conclusion

The proposed regulatory options will provide clear rules and a level playing field for manufacturers of hTEPs. Detailed requirements and guidance have not yet been defined but will influence the regulation's implementation and its impact.

In the case of a two-tier marketing authorisation approach, genuine harmonisation of requirements throughout Europe and recognition of authorisations granted at national level are crucial so as to avoid imposing an unnecessary administrative and regulatory burden that might impede the further development of hTEPs or have a disproportionate impact on small operators more likely to make use of the national authorisation procedures.

In the case of a centralised marketing authorisation, direct access to the Community market would be facilitated, but the regulatory burden would need to be adapted to the special nature of operators in the tissue engineering field, in particular SMEs. The development of risk-dependent requirements without compromising safety, quality and efficacy of hTEPs will be important for small operators, which are the main producers of rather 'simple', probably autologous 'low-risk' hTEPs. As the sector is still young and developing, it has the opportunity to adapt. In addition to monitoring the implementation and operation of the regulation, specific support measures might be considered to ensure product development and market authorisation is not excessively burdensome for small manufacturers, including hospitals and tissue banks.

Furthermore, the regulation could help build trust in this new technology, thereby encouraging its acceptance in medical practice and reimbursement policies.

1 Introduction

With the advancement of tissue engineering a novel concept of medical treatment can be envisaged. It aims at regenerating the diseased tissues (and organs as a future perspective) *in vitro* or through a combination of *in vitro* and *in vivo* processes and implanting the product at the diseased site to achieve full functionality. Improved healing processes and a higher quality of life are expected results, probably leading to lower costs of treatment in the long term.

Human tissue-engineered products (hTEPs) first reached the market in the mid 90's. They are products consisting of human cells, usually grown on some kind of scaffold and possibly in the presence of biomolecules such as growth factors. In 2001 the European Commission's DG SANCO Scientific Committee on Medicinal Products and Medical Devices (SCMPMD) concluded that these products, based on their specific characteristics and risks are not appropriately covered by any European regulatory framework (European Commission 2001). Directive 93/42/EEC⁷ on medical devices explicitly excludes human cells or tissues or products containing or derived from tissues or cells of human origin. On the other hand, the requirements for medicinal products laid down in Directive 2001/83/EC⁸ on medicinal products are not fully suitable for hTEPs. Due to the lack of a comprehensive and uniform regulatory framework, member states developed different approaches to deal with hTEPs, resulting in fragmentation of the European market. A new regulation is now under preparation with the aim to ensure the safety, quality and efficacy of hTEPs being put on the market, safeguarding the patients' health, and guaranteeing the free movement of hTEPs within the Community.

With the aim to improve the quality and coherence of the policy development process and as an action of the Better Regulation Action Plan (European Commission 2002 and 2005) the European Commission introduced the Impact Assessment for major regulatory initiatives, to which category the proposal on tissue engineering belongs. The basic requirements are laid down in the Communication from the Commission on Impact Assessment (European Commission 2002a). Against this background, JRC-IPTS has been requested by DG Enterprise in December 2003 to carry out an analysis of potential economic, social and environmental impacts of proposed regulatory options for hTEPs in comparison to the status quo. The analysis was executed by JRC-IPTS and the European Science and Technology Observatory Network ESTO, in particular the Fraunhofer Institute for Systems and Innovation Research, Germany, between February and October 2004. The study used as a basis the information gathered in an earlier JRC-IPTS study, "Human tissue-engineered products – Today's markets and future prospects", published in December 2003 (Bock et al., 2003). During the course of the impact assessment, the regulatory approach was further discussed and developed. This study is based on the outline that was available in February 2004 (see Chapter 4 for further description).

1.1 Definition of human tissue-engineered products

For the identification of companies and products the definition used by the SCMPMD was applied (see also Bock et al., 2003):

⁷ OJ L 169 , 12/07/1993 P. 0001 - 0043

⁸ OJ L 311 , 28/11/2001 P. 0067 - 0128

“Tissue engineering is the regeneration of biological tissue through the use of cells, with the aid of supporting structures and/or biomolecules” (European Commission, 2001).

For the written surveys for tissue engineering companies and regulatory authorities as well as for interviews a preliminary definition developed by DG Enterprise in the preparation process of the regulation was used (February 2004):

A human tissue-engineered product (hTEP) means any autologous or allogeneic product which:

- *contains, consists of, or results in engineered human cells or tissues; and*
- *has properties for, or is presented as having properties for, the regeneration, repair or replacement of tissue, where the new tissue or cells, in whole or in part, are structurally and functionally analogous to the original tissue that is being regenerated, repaired or replaced.*

Engineered means any process whereby human cells or tissues have been substantially manipulated, so that their normal/specific physiological functions have been attained.

Human tissue-engineered products are derived from living cells or tissues, with the final product containing viable or non-viable cells. They may, for their function, also contain cellular products, bio-molecules and biomaterials (including chemical substances, scaffolds and matrices).

1.2 Scope and sources of information

The study focuses on the commercial human tissue engineering sector. Additionally, tissue banks and hospitals are active in tissue engineering. They have been covered to a lesser extent only for Germany, the United Kingdom and France.

The analysis focuses on potential economic, social and environmental impacts, considering direct and indirect, positive and negative, short-, medium- and long-term impacts. The complete innovation system for developing, producing, authorising, placing on the market and using hTEPs was considered. Geographically, the study includes the European Union and the new member states as well as candidate countries. However, commercial tissue engineering activity in the new member states as well as candidate countries is currently of minor importance, thus the analysis focuses on EU-15. International competition with third countries such as the USA and Asian countries was also considered.

Information was retrieved from relevant scientific publications, reports, and studies, identified via database, internet and manual searches. Stakeholders' position papers and reactions to the public consultation carried out in June 2002 by DG Enterprise were also considered.

Questionnaire-guided interviews (1 hour to 1.5 hours duration) were carried out 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.

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 hTEPs, 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 (Bock et al., 2003), 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 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).

2 Current situation of tissue engineering in the EU

Tissue engineering is a developing sector with a strongly interdisciplinary research and development basis. Technology and knowledge transfer from research to commercial application and clinical practice is an important factor. The majority of companies active in tissue engineering are young, small, research-based and technology-oriented biotechnology companies, but also larger companies are active in this field as well as tissue banks and hospitals. Private venture capital and public funding are important for further development of applications. A favourable regulatory framework, a high demand as well as a positive perception of hTEPs by doctors, patients and health insurance companies plays a crucial role. Figure 2.1 provides an overview on the network of key factors influencing the development of the tissue engineering sector.

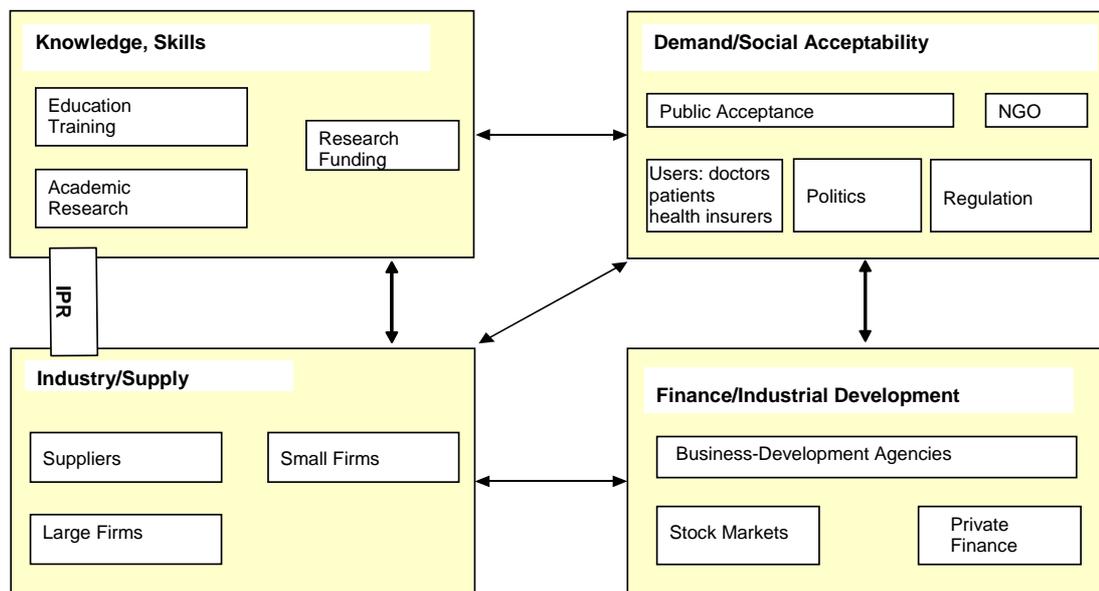


Figure 2.1 Network of key factors influencing innovation in the tissue engineering sector

IPR = Intellectual Property Rights, NGOs = Non-Governmental Organisations; Source: Fraunhofer ISI

2.1 Tissue engineering companies

In Europe, about 113 companies have been identified which are active in the field of tissue engineering (Bock et al., 2003). These companies can be divided into core tissue engineering companies⁹ (54 companies; 48%), “broader definition” tissue engineering companies¹⁰ (48 companies; 42%) and companies that are active in developing tissue-engineered products for *in vitro* use only, i.e. not for therapeutic purpose (11 companies; 10%).

⁹ The activity of core tissue engineering companies fully complies with the tissue engineering definition selected for this study.

¹⁰ “Broader definition” tissue engineering companies carry out activities which are directly relevant for tissue engineering, but do not comply fully with the definition, for example the activity concentrates on the construction of bioreactors for tissue engineering. Additionally medical device and pharmaceutical companies which are involved in joint R&D activities in tissue engineering, but for which this presents only a minor activity in the company, are included in this category.

The distribution of these companies within Europe is shown in Figure 2.2. Germany (39 companies) and the UK (18) belong to the countries with the most tissue engineering companies. They are followed by France (10), Sweden (10), Switzerland (8) and the Netherlands (6). Only few companies have been identified in Italy (2) and Spain (3), and none in other Mediterranean countries such as Greece or Portugal. The only new member state with tissue engineering companies identified is the Czech Republic with 3 core tissue engineering companies.

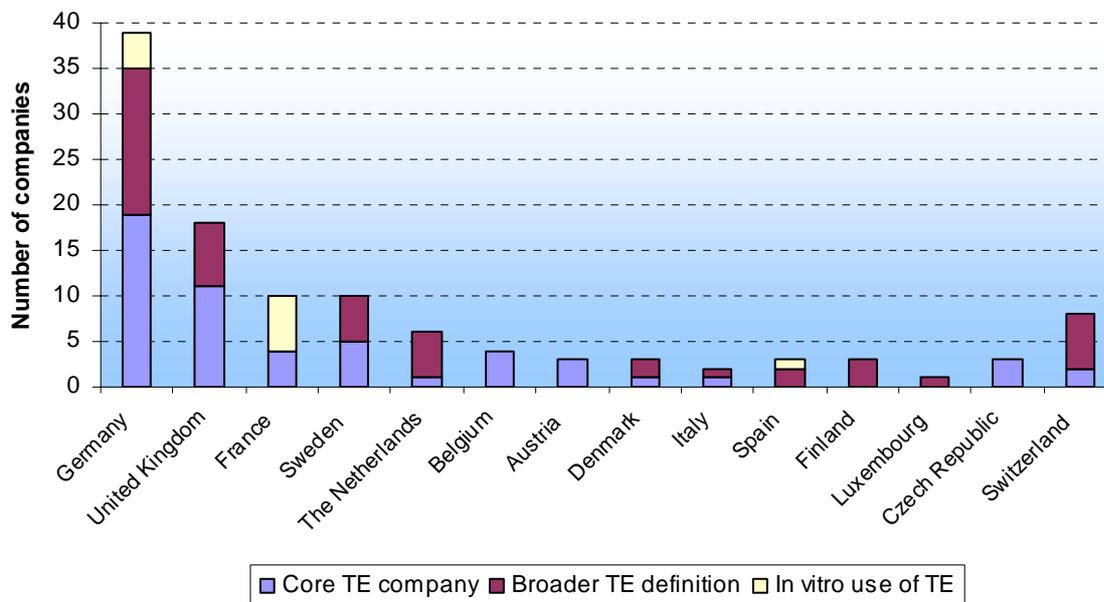


Figure 2.2 Tissue engineering companies in Europe

Source: Fraunhofer ISI

Of the 113 companies identified 91 are small and medium sized companies with less than 500 employees, mostly belonging to the biotechnology sector (80 of 113 companies). 24 companies belong to the medical device sector and 9 are pharmaceutical companies. For 44 of the 91 SMEs more information on the number of employees was available (Table 2.1). About 75% of the 44 SMEs have less than 50 full time equivalent employees (FTE). This figure corresponds to the results of the survey, where responding SMEs had a mean of 25 FTE. Only one core tissue engineering company was identified in Europe with more than 100 employees.

In small and medium sized tissue engineering companies more than half of the employees work with hTEPs and the companies generate a major part of their turnover from hTEPs. On the contrast, for large companies tissue engineering represents only a part of their business (Table 2.2; the figures cannot be directly compared because of the different case numbers).

Table 2.1: Categorisation of SME European tissue engineering companies according to employee numbers (N= 44)

Number of SME	Employees/company (full time equivalents)				Total
	≤ 20	21 - 50	51 - 100	> 100	
all TE SME	25	8	7	4	44
Core TE SME	13	4	5	1	23
Share of SME					
all TE SME	57 %	18 %	16 %	9 %	100 %
Core TE SME	57 %	17 %	22 %	4 %	100 %

Source: Fraunhofer ISI

A direct comparison of shares of hTEPs turnover in total turnover is only possible for 6 companies (5 SMEs and one large company) which reported both values in the survey. The SMEs generate their total turnover with hTEPs, whereas hTEPs represent only a small share of the turnover of the large company. The absolute turnover of the large company with hTEPs is greater than the turnover of the 5 SMEs together (12 M€ vs. 11 M€).

Table 2.2: Employees and turnover of tissue engineering companies by size

Category of company		Total number of employees	Number of employees in hTEPs	Total turnover (Million Euro)	Turnover hTEPs (Million Euro)
SME	Mean	24.7	13.3	2.15	1.87
	N	15	13	12	6
Large company	Mean	22,000	130	3,594	12
	N	3	1	3	1

Source: Fraunhofer ISI company survey 2004

2.2 Products on the market

In 2003 about 35 hTEPs marketed in the EU were identified, mainly skin replacements (18 products) and cartilage products (15) and only 2 bone products (Bock et al., 2003). 90% of these products were autologous products. This figure corresponds to the results of the written survey carried out in 2004. From 20 companies that responded to the survey, 14 companies indicated having commercialised 27 products between 1999 and 2003, 19 autologous (70%) and 8 allogeneic products. The company survey seems to cover the present market situation quite well, but is probably underestimating the number of autologous products. Table 2.3 shows the distribution of products per company. 24 of the 27 products (= 89%) are commercialised by SMEs, reflecting the importance of SMEs in the tissue engineering sector.

Table 2.3: Number of hTEPs on the market per company, differentiated for hTEP type and company size

Type of hTEP	Number of products placed per company (written survey 2004)								Bock et al. 2003
	0	1	2	3	4	5	7	total	total
autologous and allogeneic								27	35
- SME	5	6	2	1	1		1	24	
- Large company	1	1	1					3	
autologous								19	
- SME	5	7	3			1		18	
- Large company	2	1						1	
allogeneic								8	
- SME	13		3					6	
- Large company	2		1					2	

Source: Fraunhofer ISI company survey 2004

From the 14 companies that have products on the market, 11 are SMEs and 3 are large companies (Table 2.4). All of them have products on their home market. There is no clear correlation between the size of the company and the region of market; there are nearly as many SMEs marketing their products just on the home market as also beyond the EU. However, none of the large companies restricts its activity only to the home market.

Table 2.4: Companies and the region of market (1999-2003)

Region of market (1999-2003)	Number of companies	% of companies	SME	Large company
- only home market	5	36%	5	0
- home or other EU country	3	21%	2	1
- also beyond EU ¹¹	6	43%	4	2
Total	14	100%	11	3

Source: Fraunhofer ISI company survey 2004

Table 2.5 shows that the commercialised products are distributed over different markets. There is no clear correlation between the number of products per company and the regions it is targeting. Most companies with a small hTEP portfolio market their products on the home market, but there are as well companies with few products that market them also in other countries. From the 27 commercialised products identified in the company survey, 6 products are marketed only on the home market of the respective company, 9 are marketed in other EU countries as well and 12 are marketed also in third countries. Regarding only autologous products the distribution between the regional

¹¹ Home country and other region (n=1), Home country and EU and other region (n=1), Home country and USA and Asia (n=1), Home country, EU, Asia and other region (n=1), Home country, EU, USA, Asia and other region (n=2).

categories is uniform. However, no allogeneic product is only marketed on the home market of the respective company. It seems that companies with allogeneic products are always export-oriented.

Table 2.5 Products and the region of market

Region of market	Number of products placed per company						Total number of companies (per row)
	1	2	3	4	5	7	
autologous and allogenic							
- only home market	4	1					5
- home or other EU country	2					1	3
- also beyond EU	1	2	1	1			5
autologous							
- only home market	4	1					5
- home or other EU country	1				1		2
- also beyond EU	2	2					4
allogenic							
- only home market							
- home or other EU country		1					1
- also beyond EU		3					3

Source: Fraunhofer ISI company survey 2004

The survey to the national authorities (data from 16 countries have been included, from which 7 indicated having received dossiers for authorisation) revealed that from the 52 dossiers received from 1999 to 2003 about 42 were for autologous products and 10 for allogeneic products. 70% of the dossiers were submitted by domestic companies, 15% from companies from another EU country and 15% from companies from third countries. Regarding only autologous products, the majority of the dossiers (32 from 42) came from domestic companies, whereas only 6 came from another EU member state and 4 from third countries. This supports the observed tendency to market autologous products on national markets already observed with the company data.

Regarding possible future developments, the respondents to the company survey indicated plans to extend their activities in the coming 5 years. 17 companies plan to market in total 44 new products between 2004 and 2008, 30 of those being autologous. Thus the majority of new hTEPs in the near future will be autologous. Provided the 27 products commercialised so far stay in the market and all planned 44 products will actually be put on the market, the number of available products will increase 2 to 3 fold to 71 products. This is consistent with the expectations of the national authorities which expect a strong increase (30% of the respondents) or an increase (50% of the respondents) in the number of dossiers being submitted. Companies envisage an increase in the number of products in all market regions, although there are indications that efforts to access international markets will increase. There is no especially great increase foreseen by companies for allogeneic products, both product categories increase similarly.

2.3 Current markets for hTEPs

Current sales of hTEPs are estimated at about 60 million Euro per year world-wide (Bock et al., 2003). They are thus much lower than earlier market estimates available from several sources (e.g. market volumes of 25 billion Euro in 2001 up to 376 billion Euro in 1999 were estimated; Bassett 2001, Vacanti & Langer, 1999; see also Bock et al., 2003). A more recent analysis from Frost & Sullivan nevertheless expects revenues for the US tissue engineering market to increase to 1.3 billion \$ in 2007, including bone products with a share of 50%, skin-engineering and wound repair products with 35% and cartilage repair products with 15% (Osborne 2004). However, estimations have to be taken with care as it is often not clear what definition of tissue engineering they are based on. Furthermore, indications might be included for which products are still in the R&D phase. Moreover, it is often not clear if it has been assumed that every patient will be treated with a tissue-engineered product, which is unrealistic.

There are several factors that are responsible for the discrepancy between market estimations and actual sales figures. Currently available hTEPs cover only very specific indications, for which they compete with traditional treatments. They have the potential to increase the quality of life of patients but have no unique life saving function. Additionally, the traditional treatments are well established and usually less costly. Data on cost-effectiveness of hTEPs compared to conventional treatments are widely missing. Reimbursement of hTEPs is at present only possible on a case-by-case basis. Experts' opinions are divided over the question whether the use of allogeneic instead of autologous products could lead to significant cost reductions. Allogeneic products should allow for a continuous, automated graft production. However, actual prices show no significant differences between allogeneic and autologous products. There is also specific knowledge required from medical staff for handling and implantation of hTEPs, probably only available in specialised centres. At present also investment in the tissue engineering sector is limited because of the long term and uncertain development perspectives.

2.4 Tissue engineering in hospitals and tissue banks

Tissue engineering activity in hospitals and tissue banks in Germany, the UK and France currently seems to be limited to a few players per country. The scope of activities is restricted to mainly autologous and rather simple hTEPs, targeted at the in-house or local level. Activities often are at an early stage, and the role of hospitals and tissue banks in tissue engineering is still evolving. Most of the hospitals and tissue banks are public, non-profit organisations.

Three different types of players have been identified:

- Research-driven hospitals are integrated in or affiliated with national academic Centres of Excellence in tissue engineering or core tissue engineering companies. They carry out preclinical research with plans to proceed until early clinical trial stages. Mainly autologous but also allogeneic products are under development. Limited production is carried out or planned for clinical trials using GMP production facilities. For placing on the market of hTEPs, collaboration with companies or out-licensing is envisaged; applications for marketing authorisation is not part of the strategy. Typical examples are the UK Centre for Tissue Engineering in Liverpool and the Tissue Engineering Laboratory of the University Hospital Charité in Berlin, Germany.

- Treatment-driven hospitals often are specialised hospitals focusing on optimising treatment of patients. Research activities do not include the development of new hTEPs but rather optimisation and comparisons with other treatment options. The products are either procured from companies or are manufactured in-house. Activities focus on autologous hTEPs. Manufacturing is currently for in-house use but might expand in the future. However, commercialisation of hTEPs is not envisaged. Typical examples are Robert Jones & Agnes Hunt Orthopaedic Hospital with OsCell manufacturing facility in Oswestry, UK, the Hospices Civils de Lyon, France, and the University Hospital Freiburg, Germany.
- Strategy-driven tissue banks consider tissue engineering as a strategic option for the future. Currently there seems to be no tissue bank producing hTEPs. Research is focusing on the use of allogeneic tissue-derived and decellularised matrices to be seeded with autologous cells. Research is partly carried out in cooperation with leading tissue engineering research groups. Typical examples are the UK National Blood Service --Tissue Services, the Etablissement Français du Sang, Centre Atlantique, Site Tours, and the German Non-profit Society for Tissue Transplantation.

Situation in France

For carrying out tissue engineering in France, an authorisation as a tissue and cell establishment is needed. Additionally a product or procedure-specific authorisation is required for marketing hTEPs.

Table 2.6: Authorised tissue and cell establishment with activities in tissue engineering in France

Establishment; location	Tissue engineering research activity
Hospices Civils de Lyon - banque de tissus de l'Hôpital Edouard Herriot ; Lyon	Keratinocytes, chondrocytes
Centre de Transfusion sanguine des Armées "Jean Juilliard" ; Clamart	Mesenchymal stem cells for orthopedic use
Etablissement Français du Sang ; Tours	Mesenchymal and dendritic cells for clinical trials
Etablissement Français du Sang ; Besançon	Cornea for clinical trials
Génopoiétic; Meribel	Chondrocytes
Société TBF; Bron	Chondrocytes
Laboratoires Génévrier; Antibes	Keratinocytes
OST-Développement; Clermont-Ferrand	Bone

Source: ISI Fraunhofer

Currently there are 44 authorised tissue and cell establishments, most of them belonging to the French Blood Service (Etablissement Français du Sang EFS; 24 institutions) and to hospitals (14 institutions). Out of these 44 institutions 8 are active in tissue engineering, including 4 private companies (Génopoiétic, Société TBF, Laboratoires Génévrier, OST-Développement) (Table 2.6). No product authorisation has been granted so far, but applications for autologous chondrocyte products are being prepared.

Situation in the UK

In the UK there are several academic tissue engineering centres, often linked to hospitals, active in tissue engineering, as well as tissue engineering units in public hospitals, and tissue banks. Activities in academic centres are mainly in the preclinical phase with plans to proceed to clinical trials in the near future. Few small clinical trials have been carried out so far. Routine treatment with cartilage products is carried out in two hospitals (Table 2.7). These hospitals follow different strategies for hTEP production: one cooperates with a tissue engineering company and the other has manufacturing facilities in-house.

Table 2.7: Clinical applications of hTEPs in the UK

Institution name	Type and number of hTEPs	Remarks
Routine treatment		
Robert Jones and Agnes Hunt Hospital, Oswestry National Health Service (NHS) hospital, specialised in orthopaedics	Autologous chondrocyte implantation (ACI; Brittberg technique plus 1 variant) 260 patients treated from 1997-2004; in 2005 manufacturing of 100 ACIs/year	Hospital-owned, purpose-built hTEP manufacturing facility (OsCell; OsCell is the only NHS facility which has its own laboratory for growing Chondrocytes for Autologous Chondrocyte Implantation) Extension of capacity and delivery to other clinics than RJAHH in the UK planned
Royal National Orthopaedic Hospital, Stanmore NHS hospital, specialised in orthopaedics	Autologous chondrocyte implantation appr. 500 patients treated from 1998-2004	Since 2001 manufacturing contract with Verigen (10 years, minimum of 50 patients to be treated annually)
Research activities/clinical trials		
University of Bristol, Academic Rheumatology group (Prof. Hollander), Bristol Interdisciplinary Academic Rheumatology and tissue engineering research group	Tissue engineered cartilage Number, type: no information available	Ultraclean room facilities built for engineered cartilage implant delivery to patients
University of Sheffield Centre for Biomaterials and Tissue Engineering Interdisciplinary academic research centre for tissue engineering	Cultured autologous keratinocytes on a special acrylic acid coating (Clinical trial)	Product development and manufacturing by spin-off company CellTran Ltd CellTran has an accredited clean room facility since 2003
Blond McIndoe Centre, Queen Victoria Hospital, East Grinstead Research centre in plastic and reconstructive surgery	Cultured corneal epithelial cells (autologous or allogeneic); 20 patients, clinical trial (phase I and II) Autologous chondrocytes for knee cartilage repair (20 patients) Cultured autologous keratinocytes (2 patients with burns, 3 patients treated with Integra seeded with autologous cells, 1 patient reconstructive surgery)	In 2004 new clean room facility installed, in compliance with Directive 2004/23/EC and GMP standards Doubles cell culturing capacity, larger clinical trials planned

Source: Fraunhofer ISI

The majority of tissue banks in the UK are members of the British Association for Tissue Banking. In 2002 the association had 40 members. A voluntary accreditation scheme is in practice by the Medicines and Healthcare Products Regulatory Agency based on the voluntary Code for Practice for Tissue Banks (UK Department of Health 2001). Four of those are active in preclinical tissue engineering research (Table 2.8). National Blood Service - Tissue Services is currently expanding its facilities in Liverpool including facilities for the production of hTEPs for several thousand patients per year. It seems to be the most advanced tissue bank in the three countries studied. As a first product tissue-engineered skin is considered.

Table 2.8: UK Tissue Banks with tissue engineering research activities

Tissue Bank	Tissue engineering research activities
East Grinstead Eye Bank	Corneal epithelial cells to reconstruct the surface of the eye.
National Blood Service - Tissue Services	1) The development and validation of novel sterilisation and disinfection protocols for tissue matrices. 2) the development and optimisation of protocols for the preparation of matrices for tissue engineering. 3) The development of tissue engineered heart valves.
Royal Brompton and Harefield Heart valve Bank, London	Tissue engineering of heart valves; tissue engineered patches being produced for congenital defects
University of York, Medical Cryobiology Unit	Tissue engineering, especially of blood vessels and skin

Source: Information taken from BATB 2003; Fraunhofer ISI

Situation in Germany

In Germany academic centres, often with integrated hospitals, and treatment-oriented hospitals are active in tissue engineering. According to the German Ministry of Health and Social Security no hTEP manufacturing authorisation has been granted to a hospital so far, a legal condition for producing hTEPs. This indicates that hTEPs are not produced on a routine basis. Interviewees from hospitals confirmed that hTEPs for clinical treatment are rather procured from tissue engineering companies. There is the possibility that small amounts of hTEPs are produced and applied under an exceptional rule of the German Medicines Act. If tissue and cell procurement, processing and clinical use are carried out by the same doctor, no manufacturing authorisation is needed.

The situation for tissue banks is very diverse because of the lack of a comprehensive uniform legislation due to historical reasons. Apart from many small tissue banks, mostly local bone banks, there exist three large tissue banks which process tissues and have manufacturing and product authorisations for certain human tissues. They seem not to be active in tissue engineering. This is also true for the Non-profit Society for Tissue Transplantation (DSO-G), which was founded in 1997 and is currently building up a network of tissue processing facilities. Manufacturing authorisations have been applied for. Tissue engineering is considered as a possible future option; no tissue engineering research is currently carried out.

Table 2.9: Tissue banks in Germany which hold a manufacturing authorisation for human tissues

Tissue bank, location	Characterisation
Tissue Bank, Institute for Transfusion Medicine, University Hospital Charité, Berlin	Formerly National Tissue Bank of the German Democratic Republic, now non-profit university tissue bank In 1999, delivery of 948 tissue transplants, mainly bone (66 %), amniotic membranes (25 %), demineralised bone matrix (5 %), tendons, ligaments (3 %), others (1 %)
German Institute for Cell and Tissue Replacement, Berlin	Private, non-profit tissue bank Provides broad spectrum of human tissues
Tutogen Medical GmbH, Neunkirchen	Private company. Develops, manufactures, and markets bio-implants and medical devices for tissue and bone repair. Tutogen's main products are preserved bone allografts from donated human tissue and also bone xenografts. The company also offers the possibility for tissue banks and clinics to have tissue that was removed from patients processed by Tutogen. The company, headquartered in the USA, has production facilities in Neunkirchen, Germany, and in the USA

Source: Information from interviews, <http://www.charite.de/itm/Inhalt/5Gewebe.html>, <http://www.tutogen.com/company.htm>; Fraunhofer ISI

2.5 Tissue engineering in the US and Japan

The commercial tissue engineering sectors in Europe and in the US have similar characteristics (for details see Bock et al., 2003). Although the environment seems to be more favourable in the US, as already clinical trials can be reimbursed, and after product approval the largest health market world-wide can be accessed, the sector is facing similar problems as in Europe. By end of 2002 about 20 products had entered in clinical trials in the US. Only four have been approved by the US Food and Drug Administration so far. Six applications were abandoned or failed and 10 applications were still in clinical trials. The sector still has to produce a profitable product (Lysaght & Hazlehurst 2004).

The scientific and technological level is equally high in the US and Europe (Bock et al. 2003). There is more research carried out in the US concerning borderline, controversial approaches, such as the use of xenogeneic cells and tissues and embryonic stem cells. 80% of the newly emerging companies in the field between 2000 and 2002 were stem cell based, whereas about 70% of the companies exiting the market in that time period focused on structural applications such as skin or cartilage. The survey carried out by Lysaght & Hazelhurst (2004) comprised 89 companies, 23 of those being European companies.

In Japan public investment in tissue engineering has increased considerably and it is currently the leading country in Asia in this sector. A number of world class research facilities have been created. It is possible that based on that investment Japan will emerge as a leading force in the globalisation of tissue engineering (Williams 2003).

3 Current regulatory situation for placing hTEPs on the market

Currently hTEPs are difficult to classify according to existing European regulatory frameworks. This results in different strategies employed by member states to deal with hTEP authorisation (Table 3.1).

Table 3.1: Regulation for autologous and allogeneic hTEPs in EU member states, March 2004

	Country	Austria	Belgium	Bulgaria	Cyprus	Finland	France	Germany	Ireland	Latvia	Netherlands	Poland	Slovakia	Spain	Sweden	UK	Malta	Italy
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		●●				●●						●	●●				●

Coloured points mark regulations which are relevant for ● autologous and ● allogeneic hTEPs.

* Where the authorities stated that even other regulatory acts were relevant, these were specified as follows: In Austria, hTEPs are also authorised through the hospital where the receiving patient is treated. In Belgium, the procurement of raw human material and final delivery is reserved to licensed tissue establishments. In Finland, some hTEPs are on the market without any regulation. Germany applies an import authorisation for products from third countries, and in Slovakia autologous hTEPs are licensed by a product authorisation of the carrier material.

Source: Fraunhofer ISI authority survey March 2004, interviews

Table 3.1 shows that there is a wide variety of approaches for authorising hTEPs in Europe. In some countries hTEPs are not classified and thus not regulated at all, so hTEP manufacturers do not have to meet specific requirements for putting their

products on the market, apart from obtaining import licences if necessary (e.g. Ireland and the Netherlands). In some countries hTEPs are classified as medicinal products, e.g. Austria, Germany, Finland and Belgium, and manufacturers have to comply with the respective requirements. In Spain, UK and Sweden hTEPs are classified on a case-by-case basis as medical devices or as medicinal products. Additionally, some countries shaped their approach along the lines of dealing with other biologics, with tissue banks playing a prominent role (e.g. France, Spain, and Belgium). Accordingly, hTEPs can only be placed on the market through accredited tissue banks.

The diversity regarding authorisation of hTEPs results in a broad variety between member states concerning required levels of quality, safety and efficacy for hTEPs. Additionally, in some member states hTEPs might be treated differently depending on the status of the respective manufacturer (company, tissue establishment, research facility), leading to different levels of quality, safety and efficacy of hTEPs on that level as well. There are also practical problems for companies resulting from the special status hTEPs currently have, such as the identification of the competent authority, unsuitable regulatory requirements, judgement on a case-by-case basis and ultimately the fragmentation of the European market.

4 Outline of the proposed regulatory options for hTEPs

4.1 Overall regulatory approach

The definition of hTEPs is structure/function-oriented. In order to address borderline cases with other products, in particular somatic cell therapy products and some gene therapy products, and existing legislation on medical devices (Directive 93/42/EEC), medicinal products (Directive 2001/83/EC) and human tissues/cells (Directive 2004/23/EC¹²), two options are envisaged from a legal point of view:

- The development of a separate, distinct and stand-alone regulatory framework for hTEPs, independent of already existing regulatory frameworks. In this case, applicable regulatory principles, including those which already exist in the legislation on medicinal products or medical devices, would have to be (re)established in the hTEP regulation. It might also be necessary to adapt Directive 2001/83/EC on medicinal products and include somatic cell therapy products under the new hTEP regulation (DG Enterprise 2004).
- The development of an integrated regulatory framework covering not only hTEPs, but also other “advanced therapies” like gene therapy and somatic cell therapy. In that case a new, specific regulation on advanced therapies would lay down the tailored rules for evaluation and authorisation of these products, but would otherwise build upon already existing legislation, in particular Regulation (EC) 726/2004¹³ defining Community procedures for the authorisation and supervision of medicinal products for human and veterinary use and establishing a European Medicines Agency, Directive 93/42/EEC on medical devices, and Directive 2004/23/EC on human tissues and cells (DG Enterprise 2005).

In both options, the interface between the regulatory framework on hTEPs and existing legislations needs to be adequately defined.

4.2 Regulatory options

As a basis for this impact assessment the outline of the proposed regulatory options for hTEPs available in February 2004 was used. The main characteristics are:

- Autologous and allogeneic hTEPs are covered as defined.
- All products, irrespective of the character of the manufacturer, need a marketing authorisation as well as a manufacturing authorisation. A marketing authorisation is not needed for hTEPs intended solely for research and development purposes, including clinical trials.
- High standards concerning safety, quality and efficacy are required for hTEPs to be placed on the market. Requirements on quality, safety and efficacy will be defined at a later stage and guidelines will be developed by EMEA.
- A marketing authorisation is required for the placing on the market of hTEPs. Two alternative options are envisaged:

¹² OJ L 102, 7.4.2004, p.48-58

¹³ OJ L 136, 30.4.2004, p. 1-33

- A fully centralised marketing authorisation approach for all products. The scientific evaluation of the application is carried out by EMEA, and the final marketing authorisation is granted by the European Commission.
- A two-tier marketing authorisation approach. Allogeneic products need to be authorised at Community level (EMEA and Commission), while manufacturers of autologous products can choose between the centralised procedure and the national level approach.

In both options, the marketing authorisation granted would nevertheless be valid in all EU member states. In the case of the two-tier authorisation approach, this would imply recognition by the member states of the marketing authorisations granted by national authorities.

- In the case of a two-tier authorisation approach, a common guidance for authorisation of allogeneic and autologous hTEPs would be developed and agreed at European level. EMEA would supervise national authorisation procedures. In the case of a fully centralised authorisation procedure, this would not be necessary.
- For combination products, including in addition to human cells and tissues medicinal products and/or medical devices, the medicinal product or the medical device will have to comply with the legal requirements of Directive 2001/83/EC or Directive 93/42/EEC, respectively. In these cases a single integrated authorisation might be envisaged.
- Manufacturing authorisation will require production according to good manufacturing practice (GMP). Specific GMP guidelines will be developed.
- A marketing authorisation requires a risk analysis and a risk management programme. The scientific evaluation follows the principles laid down for medicinal products, where necessary adapted to specificities of hTEPs. At EMEA a scientific body for this task will be established. EMEA will develop guidelines for the scientific assessment.
- Implantation of hTEPs will only be allowed in hospital environments.
- The scientific assessment has a timeframe of maximum 210 days (stop-clock periods). An accelerated procedure is foreseen with a maximum of 150 days.
- The marketing authorisation will be valid for 5 years and would become indefinitely valid in case of renewal. A conditional authorisation is foreseen, with certain requirements to fulfil.
- Variations need to be notified and approved. Guidelines will be developed by EMEA.
- Data protection will follow the '8+2+1' rule, as defined for medicinal products.
- Applicants might request scientific advice from EMEA (or a national competent authority in the case of the two-tier approach). EMEA will develop guidelines for procedures for scientific advice.
- Applications to EMEA will be required in English. In the case of the two-tier approach, applications to national authorities will be in the member states' language(s).
- Post-market surveillance and vigilance will be required including a long-term traceability of patients to be ensured by hospitals and manufacturers. The pharmacovigilance database will incorporate hTEPs.
- There will be a transitional period for those products already on the market when the new regulation will enter into force.

More detailed information on the requirements included in the proposed regulatory options is presented in Tables 5.1, 5.2 and 5.3. The main differences between the centralised and decentralised procedure are listed in Table 4.1.

Table 4.1: Main differences between the centralised and decentralised authorisation procedure for hTEPs

	Centralised Procedure	Decentralised Procedure
Competent authority for marketing authorisation	EMA + European Commission	National authority/ies (under EMA guidance)
Location of competent authority	London, UK + Brussels, Belgium	Member state
Competent authority for manufacturing authorisation	National authority/ies (under EMA guidance)	National authority/ies (under EMA guidance)
Language	English	Member state's language(s)
Fees	EMA fees	National authority/ies fees

Source: Fraunhofer ISI

5 Potential economic impacts of the proposed regulatory options for hTEPs compared to the status quo

In the following, potential impacts of the proposed regulatory options for tissue engineering are described in comparison with the status-quo situation. The implementation of a European regulation on hTEPs will provide clear guidance for the sector and assure high standards of safety, quality and efficacy. On the other hand the complexity of the regulatory framework in the medical field in Europe will increase with possible overlaps and cases of unclear classification.

Inherent to the proposed regulatory options are several conflicting goals and issues that require consideration. Applicants as well as authorities need consistent and binding rules and sufficiently high standards regarding safety, quality and efficacy of hTEPs need to be enforced. On the other hand, favourable and flexible conditions are needed to be able to place innovative hTEPs on the market ("future-proof regulation"), also with regard to the main players being SMEs. Harmonised procedures and standards throughout the EU need to be ensured in a cost-effective manner without compromising simplicity, accessibility and effectiveness of the new legislation. Also aspects of public and ethical concern inherent to hTEPs need to be respected (e. g. conditions of use of human tissues for commercial purposes, use of human embryonic stem cells etc.).

5.1 Economic impacts: Tissue engineering companies

Data from the companies concerning costs for placing hTEPs on the market in Europe and for the post-approval phase could not be obtained. However, due to the heterogeneity of the regulatory approaches in the member states, it can be expected that those data would have been of only limited value. Thus, the following will include mainly qualitative descriptions.

Three groups of cost drivers have been identified for placing hTEPs on the market: costs related to the classification process of hTEPs, costs related to the compliance with regulatory requirements and costs related to the post-approval phase.

5.1.1 Classification of hTEPs

Currently, it is often difficult for companies to identify competent authorities and the responsible contact person due to uncertainties concerning the classification of hTEPs. Companies also reported lengthy and time-consuming processes to obtain a classification, aggravated by a lack of hTEP-specific expertise in some authorities. The approach taken by the authority is sometimes dependent on the specific contact person in the authority and might change with the contact persons. In every individual country where the hTEP is planned to be marketed the whole process needs to be repeated. Table 5.1 shows an overview of the status quo situation and expected changes due to the proposed regulatory options. Overall a clear improvement of the situation can be expected with corresponding cost reductions for applicants.

Table 5.1 Changes in cost drivers for placing hTEPs on the market – the classification process

Step for placing hTEPs on the market	Status quo situation	Proposed regulatory options for hTEPs	Direction of change under the proposed regulatory options as compared to status quo
Classification of hTEPs	Broad variation and inconsistency among and within member states. Range: no classification at all, classification on a case-by-case basis, classification as a medicinal product	Unambiguous classification of hTEPs, based on definition and specificity of the proposed regulatory options (' <i>lex specialis</i> ')	Improvement
Regulatory framework to apply	Variation, depending on classification	Proposed regulatory options for hTEPs	Improvement
Identification of competent authority	May be difficult, due to difficulties with classification of hTEPs	EMA/European Commission or national authorities	Improvement
Identification of responsible staff within authority	May be difficult, due to differences of hTEPs from medicinal products and medical devices	Will be assigned	Improvement
Procedure to follow	Depends on classification; may nevertheless be unclear, intransparent and decided on an "ad hoc basis"	Will be defined	Improvement
Duration of procedure	May vary. Large variations in duration reported, from "very quick" to 1.5 to 2 years	210 days with stop-clock periods	Defined duration improvement; overall duration may be still too long, especially for "simple" hTEPs
Endpoint of regulatory procedure	Depends on classification and country, may not be transparent for applicant	Marketing authorisation for the product, manufacturing authorisation	Improvement
Geographical validity of the authorisation	National	All EU member states. This implies the recognition by member states in the case of a two-tier marketing authorisation approach	Improvement (provided the recognition functions efficiently, in the case of a two-tier authorisation approach)
Temporal validity of the authorisation	May be restricted in time (e. g. 1 year for import licenses, annual renewal required)	Five years, indefinitely after first renewal	Improvement

Source: Fraunhofer ISI

5.1.2 Compliance with regulatory requirements

Companies reported non-transparent procedures and in some cases even the need for local consultants familiar with national requirements to proceed with an authorisation procedure. Requirements vary widely in the EU, dependent on classification, country-specific focus (safety issues, donor selection, GMP), type of product and type of applicant (company, university etc.). In some countries (Belgium, France, Spain,

Lombardy – Italy) hTEPs can only be imported through national tissue establishments, which costs approximately 20% of the margin per tissue-engineered product as a fee.

Regarding the proposed regulatory options, potentially high compliance costs are connected to clinical trials. The increase in costs depends on the current situation in the member state (wide variability in Europe, requirements range from no trials required, literature data are sufficient to extensive product-specific trials required). Compliance costs depend as well on the specific guidance to be developed by EMEA. There might be additional tests necessary for hTEPs, on the other hand unnecessary tests stemming from the medicinal products regulatory framework might be abandoned. According to experts, further research is necessary to improve the scientific knowledge base for deciding which evidence is needed for proving quality, safety and efficacy of hTEPs. Additional costs might arise due to necessary changes in the manufacturing process for adaptation to required GMP standards (at present only in some countries mandatory) and long-term traceability (no special attention has been paid to this issue yet; only general pharmacovigilance systems in place). Further details are given in Table 5.2.

Table 5.2 Changes in cost drivers for placing hTEPs on the market – compliance with regulatory requirements

Step for placing hTEPs on the market	Status quo situation	Proposed regulatory options for hTEPs	Direction of change under the proposed regulatory options as compared to status quo
Level of stringency for autologous and allogeneic products	May vary among countries, not defined	Same level of stringency for autologous and allogeneic hTEPs	May be tightening
Requirements to comply with in order to obtain market approval	Vary. May depend on several factors: classification, country, type of product, type of hTEP manufacturer, consideration of hTEP specificities	Not yet defined in detail, will depend heavily on guidance to be developed	Partly improvement, partly tightening Requirement to develop scientific basis further to decide which evidence is required to prove quality, safety, efficacy of hTEPs
Applicability of requirements to hTEPs	Lack of hTEP-specific guidance, applicants are sometimes requested to comply with requirements unsuitable for hTEPs	Not yet defined, but intention to consider hTEP specificities	Improvement
Manufacturing authorisation according to GMP standards	Mandatory only in few countries, voluntary compliance by some hTEP manufacturers	Manufacturing of hTEPs in compliance with principles of GMP standards for Medicinal Products in inspected and authorised manufacturing sites	Partly improvement, for the most part tightening
Data from clinical trials	Requirements may vary. Depend on classification of product, country, product, traditional use of similar products.	Will be required, not yet defined in detail, depends heavily on guidance to be developed	Partly improvement, for the most part tightening

Potential economic impacts of the proposed regulatory options for hTEPs

Step for placing hTEPs on the market	Status quo situation	Proposed regulatory options for hTEPs	Direction of change under the proposed regulatory options as compared to status quo
Expertise in authorities	Lack of hTEP-specific expertise in authorities	Specific Scientific Committee at EMEA, guidance, scientific advice, training and supervision of national authorities by EMEA in case of two-tier approach	Improvement However, there is substantial scepticism whether goals can be achieved in case of two-tier approach.
Opportunity to build up experience	Country-specific approach required, only limited "learning from previous experience" possible	Harmonisation throughout the EU	Improvement However, there is substantial scepticism whether true harmonisation can be achieved in case of two-tier approach.
Opportunity to obtain scientific advice prior to application	May be country- and authority-specific	Available	Improvement
Fees	Are country- and authority-specific, to be paid in each country, in some countries applicants are obliged to have contracts with tissue banks in order to obtain import licences; substantial fees must be paid to these tissue banks	Are country- and authority-specific, fees for centralised procedure (EMEA) higher than for national procedure, to be paid only once, not in every member state, no need for contracts with tissue banks any more(?)	Partly improvement, partly tightening
"8+2+1" clause	Not implemented	Implemented	Improvement for innovative companies, tightening for "generics" producers

Source: Fraunhofer ISI

5.1.3 Post-approval phase

At present, costs in the post-approval phase arise from regulatory requirements such as post-authorisation surveillance, risk management, yearly renewal of import licences, and regular inspections. Additionally, companies face costs for marketing, including training of medical doctors, identification of gate keepers, and reimbursement negotiations. The proposed regulatory options are likely to demand tighter post-authorisation surveillance and long-term traceability. Further details are listed in Table 5.3.

It can be expected that due to the proposed regulatory options cost reductions concerning classification of hTEPs can be realised as well as an increase in planning security for companies. In the beginning learning costs will arise, because companies have to become familiar with the new regulation, the new authorities and probably few had contacts with EMEA before. The costs for compliance with the new regulation are expected to increase as companies will face harmonised but comparatively strict requirements. However, the level of increase will vary throughout the member states as well as the extent individual applicants will be affected, depending on the particular status quo situation. The increase depends also on the specific requirements that will be

defined at a later stage (kind of tests that need to be carried out to prove quality, safety and efficacy of hTEPs, strict risk-dependence of requirements). Costs for the post-approval phase will likely increase as there will be stricter requirements for post-authorisation surveillance and long-term traceability than in the current status quo situation.

Table 5.3 Changes in cost drivers for placing hTEPs on the market – post-approval phase

Step for placing hTEPs on the market	Status quo situation	Proposed regulatory options for hTEPs	Direction of change under the proposed regulatory options for hTEPs as compared to status quo
Requirements for post-authorisation surveillance/ vigilance	Usual pharmacovigilance requirements apply, long-term traceability usually not required	Usual pharmacovigilance requirements apply, long-term traceability (30 years) required, also after market exit of hTEP manufacturer	Tightening
Risk management in case of adverse events	No information available	Systems for risk management required	Partly tightening
Authorisation of variations in the authorised product or process	No information available	Guidance to be developed by EMEA	Partly no change, partly tightening
Costs for regular inspections	Country- and authority-specific	Country- and authority-specific	Partly no change, partly tightening
Implantation of hTEPs	Depends on classification of hTEP, no detailed information available	Implantation of hTEPs should only be possible on prescription in authorised centres (hospital environment).	Tightening
Reimbursement	Country-specific	Beyond the scope of proposed regulatory options	Not affected, slight improvement in the long term possible

Source: Fraunhofer ISI

Overall an increase in costs for market authorisation can be expected due to tightening standards requiring quality, safety and efficacy of hTEPs. The largest increase in costs can be expected in the short term, due to the need to adapt to the new requirements. Gains, through improved efficiency, better access to the European market, economies of scale in hTEP production and a rise in awareness, acceptance and trust on the patient and doctor side, will rather be realised in the medium to long term.

5.1.4 Impact of cost changes depending on player profile

The level of costs as well as the ability to cope with additional costs depends on the applicant's profile. Table 5.4 lists the characteristics of a company which influence the expected cost impact. Larger companies are more likely to be less affected by the proposed regulatory options for hTEP, but also small companies can be able to cope well with the new situation. According to experts' estimations, about 50% of the current players will be able to cope well, additional 30% might need some adaptation and

around 20% would need substantial adaptation which might go beyond their capabilities. There are no comprehensive data available on the tissue engineering players to support these estimations with a profound assessment.

Table 5.4: Characteristics of player's profile determining the cost impact of the proposed regulatory options for hTEPs

Level of costs versus gains/required efforts to comply with proposed regulatory options	
relatively low	relatively high
Good knowledge of regulation in the health sector	Science-based, research-oriented, lack of understanding for regulation in the health sector
Own experience with authorisation procedures, preferably of biologics and medicinal products	No experience with authorisation procedures for biologics and medicinal products; experience with authorisations of medical devices only
Experience with and good contacts to competent authorities (EMA, national authorities)	No experience with competent authorities, experiences only with notified bodies for medical devices
High level of safety and quality already implemented (e. g. GMP, quality management systems)	Low level of safety and quality implemented (e. g. no GMP facilities, no quality management system), or in process of transition (e. g. in the process of implementing the requirements for Directive 2004/23/EC)
Production of hTEPs in larger quantities	Production of hTEPs in very small quantities (laboratory scale)
Location in a country where relatively high standards are already required/implemented	Location in a country where no or only relatively low standards are required/implemented
Sufficient resources (e. g. large company)	Limited resources (e. g. start-up company, VC financed company)
High (organisational and financial) flexibility to adapt to changing conditions	Limited (organisational and financial) flexibility to adapt to changing conditions (e. g. hospitals, tissue banks)
Internationally oriented marketing strategy	Nationally oriented marketing strategy
'Low-risk' (autologous) hTEP	High-risk (allogeneic) hTEP

Source: Fraunhofer ISI

One of the proposed regulatory options envisages a two-tier marketing authorisation approach. In this case, allogeneic products would be authorised via a centralised procedure involving EMA. For autologous products, the dossier could also be submitted to a national competent authority. This approach takes into account the current situation with autologous products more likely to be produced by small companies, hospitals or tissue banks, for which the administrative burden and the costs of a central procedure would be significant (there have not yet been set any fee levels for hTEP authorisation, but for example fees for authorisations of medicinal products lie in the range of 230,000 Euro at EMA compared to several ten thousand Euro in EU member states). Thus applicants with allogeneic products might face higher fees and thus higher overall costs than applicants with autologous products.

However, the lower fee of a national authorisation procedure might be one advantage for small operators, but might not sufficiently reduce the burden. The same level of

quality, safety and efficacy is required for autologous and allogeneic products. Fees represent only a minor cost compared to e.g. conducting clinical trials, implementation and maintenance of GMP facilities, and of long-term traceability. For striking the balance between safeguarding the quality, safety and efficacy of hTEPs and affordable authorisation procedures for small operators additional options could be taken into account. The risk connected to a hTEP should determine the level of necessary scrutiny and 'low-risk' products could need to comply with less requirements. This would translate into a less burdensome procedure for operators who produce rather 'simple', probably autologous, 'low-risk' products. Additionally, reduction of administrative burden by less paperwork, simplified forms, easy access to support and advice, lower fees, and fast track procedures could be considered. Considerations might also include specific provisions for hTEPs which have orphan drug characteristics¹⁴.

5.2 Impacts on upstream players

Two recent directives currently require significant adaptations from the providers of cells and tissues and from clinics carrying out clinical trials, also for hTEPs. These are Directive 2004/23/EC¹⁵ on setting standards of quality and safety for the donation, procurement, testing, processing, preservation, storage and distribution of human tissues and cells (to be transposed by member states before 07.04.2006) and Directive 2001/20/EC¹⁶ on the approximation of the laws, regulations and administrative provisions of the member states relating to the implementation of good clinical practice in the conduct of clinical trials on medicinal products for human use (to be transposed by member states since 01.05.2004). It is expected that there will be no additional requirements on the basis of the proposed regulatory options for hTEPs. However, the details of the interface between the above mentioned regulatory frameworks and the proposed regulatory options have not been set yet and care should be taken not to put additional administrative burdens on the operators.

Other upstream players, such as providers of equipment or consumables have to adapt to provide their customers with materials or services in compliance with the new requirements according to the proposed regulatory options. Under the proposed regulatory options for hTEPs ancillary reagents might be subject to tighter controls (e.g. production under GMP standards). As these reagents have not been well controlled in the past and are often only available from small companies there might be a shortage of these reagents in the interim phase, when the providers have to adapt to the new requirements and the supply might be limited. In this situation big buyers purchasing larger quantities compared to small operators might be given an advantage. On the other hand providers might face improved sales opportunities in the short term due to increased demand e.g. also for GMP conform equipment or implementation of quality management systems.

5.3 Impacts on downstream players

Downstream players, such as medical staff, patients and health insurers might face increased product and treatment prices for hTEP, if hTEP manufacturers refinance increased compliance costs via higher product prices. On the other hand, prices might

¹⁴ See Regulation (EC) N° 141/2000, OJ L 18, 22.1.2000, p.1-5

¹⁵ OJ L 102, 7.4.2004, p. 48 - 58

¹⁶ OJ L 121 1.5.2001, p 34-44

decrease due to more competition, a more transparent market, and cost reductions due to economies of scale. Currently there is little information available on potential differences in quality, safety and efficacy of hTEPs for similar indications. Thus products might be selected on the basis of incomplete or biased information or a comparative assessment is carried out by the users. The scientific assessment to be carried out in the authorisation process will transfer related costs from the downstream users to the authorities and might enable a better choice.

5.4 Impacts on the opportunity to access new international markets

Based on the survey data, it can be assumed that few very small hTEP manufacturers are oriented only towards the national market and do not envisage any extensions. The majority of companies already market their products on an international scale (EU, US, world) or is planning to do so. Decisive factors for this are the maturity of the company, the company's size (all large tissue engineering companies have their products on international markets; for SMEs no clear correlation between size and market exists, in general they are more likely to approach international markets in form of partnerships with often larger companies) and the type of hTEP in the portfolio (allogeneic hTEPs are currently commercialised internationally, while autologous products are marketed nationally and internationally). No correlation could be seen between the number of hTEPs in the portfolio and the regional scope of marketing.

From the company's perspective there are three clusters of factors currently determining the entry into new markets: attractive regulatory framework and good access to the regulatory authorities; attractive market size and growth including good reimbursement conditions, as well as high demand and good access to hospitals and medical doctors already familiar with hTEPs; and, a bit less relevant, a close contact with cooperation partners and availability of in-house financial, marketing and distribution resources. These factors also influence the availability for hTEPs to patients, and especially the 'demand and reimbursement' factors are expected to gain more importance in case full harmonisation of regulation and requirements on a European level can be achieved.

The regulatory framework is only one of the important factors influencing the development of the tissue engineering sector. Demand and company-internal factors are as important for realisation of market extension and success. Reimbursement, lying in the full competence of the member states, is also a crucial factor. Currently, achieving reimbursement for hTEP treatment is difficult, as negotiations with health insurance companies often take a long time, which is difficult to survive for small operators. Some hTEPs still are regarded as experimental due to the early stage of development and on these grounds reimbursement is declined. However, reimbursement is a prerequisite for the full exploitation of market potentials. Experts' opinions are divided on whether the proposed regulatory options will promote general reimbursement in the member states. An unambiguous classification and an authorisation according to harmonised high standards regarding quality, safety and efficacy might lead to better acceptance, in analogy to medicinal products, of which the majority - once authorised - is reimbursed. On the other hand, against the background of difficult financial situations of health care systems in many member states, the medical need and relative benefits of hTEPs compared to alternative treatment options are important. Additional clinical data might be required and this might pose a difficulty for smaller hTEP manufacturers.

The establishment of a common EU market will most probably have positive effects in the short term, due to reduction in risks related to the access of new markets and in

reduction of time and resources needed. In the longer term, positive effects are expected due to increased trust, higher demand and thus higher sales also due to the enlarged market. The sector might become more interesting to investors due to positive sales expectancies and increased reliability. A harmonised high standard regulation could also positively influence the access to third country markets, if international convergence and mutual recognition of regulatory frameworks is actively strived for. The EU could become an attractive market also for non-EU companies. This would additionally increase competition in the field, which might have negative effects on companies which are less developed in terms of innovation capabilities. However, companies from third countries will be faced with national market characteristics. Issues such as awareness and necessary training of medical staff or reimbursement will leave EU companies with a certain advantage in their home markets.

Considering company structures, large companies might be currently better prepared to access international markets with hTEPs. The complexity and novelty of hTEPs requires a more resource-intensive marketing and distribution approach, for which smaller companies might need a competent partner.

5.5 Impacts on time to market

The time to market for a product is crucial, all the more for SMEs, which have to generate sales as soon as possible to reduce their cash burn rates. The proposed regulatory options will make it less time-consuming to identify the competent authorities for authorisation of hTEPs and to enter additional European markets. The compliance with the regulatory requirements might on the one hand need less time as there will be clear requirements spelt out, counselling and a defined duration of the authorisation process. On the other hand, depending on the extent and quality of data required for proof of quality, safety and efficacy, clinical trials might become more extensive, and they are one of the main time drivers in the health sector.

It can be expected that there will be an increase in the time required for the first entry into the market due to requirements such as clinical trials. However, a reduction in time to other national markets in the EU might be experienced, based on true harmonisation of requirements and authorisation procedures (and, in the case of a two-tier authorisation approach, recognition of authorisations granted at national level). This would result in an advantage for companies which are internationally oriented and in a disadvantage for companies which focus on only one national market.

However, market access is closely related to the reimbursement issues. Compared to the US, at present EU companies in theory have some time advantage because in some countries a manufacturing authorisation for autologous products is sufficient for putting the product on the market. Nevertheless, regarding the lack of reimbursement this advantage could hardly be realised commercially.

5.6 Impacts on innovation and R&D investment

Tissue engineering is a highly innovative and research-intensive sector. It is a challenge for the proposed regulatory options to provide a stable and reliable framework for tissue engineering development without creating barriers for innovation, and to be flexible enough to cover future generations of hTEP. A variety of factors determine the success in practice and cannot be assessed today: expertise in regulatory authorities to enable a

flexible reaction to novel products, a true harmonisation of scientific product assessment in the case of the two-tier approach, timely adaptation of guidance and standards to scientific progress, and consideration of hTEP specificities to cover necessary characteristics while avoiding unnecessary requirements.

Innovation depends - among others - on the level and structure of R&D investment. According to experts' opinion the following impacts on the level of R&D investment can be expected:

- Investment in the medium to long term will increase due to more confidence of investors in the sector. The increased transparency of the proposed regulatory options, potentially higher sales, a more efficient innovation process make a higher return on investments possible.
- Free access to the EU market could increase sales and reduce costs for companies due to economies of scale. An increase in R&D investment could be the result.
- The planned data protection ('8+2+1' rule) might result in an improved situation compared to the status quo (difficulty of patenting tissue engineering processes, possibilities of generics coming on the market). This might positively influence investment behaviour.

In the short term, investments might be shifted from R&D to adapting the company to new regulatory requirements (e.g. GMP facilities, clinical trials), especially in the case of SMEs. Some companies might even close down if they are unable to adapt to the proposed regulatory options. Their innovative capacity might be lost or might be taken over by other players, perhaps from third countries. On the other hand the proposed regulatory options could lead to the situation that new tissue engineering companies are able to enter the market and others could be able to enlarge their tissue engineering business due to reduced risks. Small companies, due to increased compliance costs for hTEP authorisation might reduce their portfolio and focus on fewer, very promising products.

5.7 Impacts on competition

It is expected that the proposed regulatory options will lead to a level playing field for all actors throughout Europe. This might result in an intensification of competition as more companies, also from third countries, will try to take advantage of the internal market, with a view to recover higher compliance costs. This applies especially to large companies with sufficient internal resources for an international distribution strategy. The development depends strongly on the reimbursement situation. According to experts' opinion, in the medium to long term a market structure similar to the biopharmaceutical sector might develop, with highly innovative research being performed by SMEs. For optimisation of the product portfolio large companies will increasingly focus on allogeneic (and some autologous) products targeting larger markets in the EU and in third countries such as the US. Their product pipeline could be enlarged 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 products and focus on a few products, probably targeted at niche markets, which are unattractive for larger companies. In analogy to the orphan drug regulation, the support of products for rare diseases could provide a possibility to create interesting market niches for SMEs.

Cooperation might become more significant for the sector, with SMEs cooperating with larger companies for marketing and distribution of their products or to finance their

R&D activities. In the long run these processes will be rather driven by global economic pressures.

Companies not being competitive, i.e. producing sub-standard products regarding quality, safety and efficacy, and/or targeting only a very small home market, and/or sharing the market niche with conventional treatments or other hTEPs might not be able to survive. New entrants or surviving companies will be SMEs with high quality products which are able to react quickly to market changes. The interviewed tissue engineering companies were confident to be well prepared for a more competitive market.

5.8 Economic impacts: Hospitals and tissue banks

Of the three different categories of hospitals and tissue banks identified only the treatment-driven hospitals and the strategy-driven tissue banks are expected to be impacted by the proposed regulatory options to a larger extent. In general, the majority of interviewees, especially the leading edge players, are confident to be able to comply with future legal manufacturing standards, since efforts have already been made to comply with current national or international standards and regulatory requirements, for example the new Directive 2004/23/EC on human cells and tissues.

Leading research-driven hospitals do not expect major negative impacts from the proposed regulatory options as long as research activities are only affected regarding the manufacturing of hTEPs for clinical trials. GMP manufacturing facilities are already available or planned. Marketing authorisations would be approached in collaboration with strategic partners (spin-off companies, out-licensing). Other players in this category seem to be less informed on regulatory requirements regarding introduction of novel treatments and perceive regulations often as unnecessary and negative for innovative research.

Leading treatment-driven hospitals with dedicated manufacturing facilities for hTEP are similar to tissue engineering companies regarding technical equipment, quality assurance, qualification of staff and manufacturing capacity. In contrast to the manufacturing authorisation the marketing authorisation is perceived as more challenging and in principle as inappropriate. Due to misinterpretation of the legal term the marketing authorisation is perceived as linked to commercialisation. Most of the hospitals are however public institutions which do not commercialise hTEPs and often operate on a non-profit, cost recovery basis. In general, a national authorisation process is preferred, but at present there seem to be no devised strategies for future positioning of the institution in a harmonised regulatory environment. Few, larger facilities could develop into elements of nation-wide manufacturing and distribution infrastructures with regional manufacturing centres. Smaller treatment-driven hospitals perceive the establishment of own manufacturing facilities as too demanding considering the current technical possibilities.

Larger strategy-driven tissue banks comply already today with high technical standards, smaller entities are unlikely to enter into tissue engineering activities. Also these organisations could be part of a future nation-wide tissue engineering infrastructure. A marketing authorisation is considered as problematic because of the notion of commercialisation for those not familiar with the legal terms. For tissue banks relying on altruistic tissue donation there is the concern that this misunderstanding could interfere with the non-profit image of their activities and influence negatively the

willingness of donating organs or tissues. Generally, a national authorisation process for marketing application would be preferred.

Hospitals and tissue banks active in tissue engineering often are public, non-profit institutions with a local or future national scope of activities. Hence, the advantage of being able to access other European markets, higher planning security and increased trust of investors in the field have a much lower relevance compared to companies. However, more stringent regulatory requirements will increase costs also for these players. At present it seems that strategies of how to react to the changing regulatory situation have not been developed by many players.

Some larger hTEP manufacturing facilities in hospitals and tissue banks can be regarded as competitors to tissue engineering companies. Nevertheless, the outcome of this competition is open due the often public, non-profit character of hospitals and tissue banks. The fixed production costs are considered to be similar for both types of actors. 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 and thus improving the companies' market position. Private tissue banks, in contrast to public, non-profit organisations, behave quite similar to tissue engineering SMEs.

5.9 Economic impacts: Public budget costs for regulatory surveillance of hTEPs

Public budgets will be affected by the proposed regulatory options through the change in costs for regulatory surveillance of hTEPs. There are three cost categories to consider: Installation of an institutional infrastructure being in charge of hTEP authorisation, maintenance of this infrastructure, and the operational expenditures. For the current situation the relevant cost types in these categories cannot be specified for the EU because of the heterogeneous systems in place in the different member states. Table 5.5 lists the types of costs for public budgets for two different options for hTEP authorisation.

The first option assumes that for both product types, autologous and allogeneic, the central authorisation procedure via EMEA needs to be followed. In this case EMEA would be responsible for marketing authorisations for hTEPs, development of guidance for marketing and manufacturing authorisations, and advice, guidance and monitoring of national authorities regarding manufacturing authorisations. The tasks of the national authorities would be manufacturing authorisations and inspections of manufacturing sites, under guidance and surveillance of EMEA.

The second option considered is a two-tier approach. The centralised authorisation is mandatory for allogeneic products, while manufacturers of autologous products can choose between the centralised or national procedure. In this case EMEA would have the same tasks as in Option 1 and additionally would have to provide guidance, advice and monitoring of national authorities regarding marketing authorisations. The national authorities would additionally have to cover marketing authorisations for autologous products under guidance and monitoring of EMEA. All member states, independent of the development of a national tissue engineering sector and respective applications,

would have to build up the necessary infrastructure and expertise for the evaluation of autologous products. The two-tier approach would hence result in additional tasks for both, EMEA and the national authorities.

Table 5.5: Costs for public budgets related to different hTEP authorisation procedure options

Authorisation procedure	Central procedure only		Central and national procedure	
	EMEA	National	EMEA	National
Competent authority				
Cost types	Tasks	1*,(2*),4*	2	1,(2),3*,4
Implementation of infrastructure, e. g.				
Building, offices	1,4	2	1,3,4	1,2
Technical equipment	1,4	2	1,3,4	1,2
Hiring scientific and administrative staff	1,4	2	1,3,4	1,2
Implementation of committee and working groups	1,4	2	1,3,4	1,2
Identification of experts, setting up pools of experts	1,4	2	1,3,4	1,2
Development, implementation working programme	1,4	2	1,3,4	1,2
Development, implementation operating procedures	1,4	2	1,3,4	1,2
IT infrastructure, setting up databases	1,4	?	1,3,4	1,2
Development basic guidance for hTEP authorisation	1,2		1,2	
Dissemination of guidance to applicants e. g. through publication, education, training	1	2	1	1,2
Dissemination of guidance to authorities e. g. through publication, education, training	4		3,4	
Participant in education and training		2		1,2
Maintenance of infrastructure, e. g.				
Salaries and other staff-related expenditures	1,4	2	1,3,4	1,2
Fees and expenditure reimbursement for committees, external experts, inspectors	1,4	2	1,3,4	1,2
Maintenance of building and equipment	1,4	2	1,3,4	1,2
Maintenance IT infrastructure, updating databases	1,4	?	1,3,4	1,2
Development and updating of guidance	1,2		1,2	
Continuous education and training of authorities	4	2	3,4	1,2
Operational expenditure directly related to authorisations				
Advice to authorities	4		3,4	
Scientific advice to applicants	1	2	1	1,2
Evaluations, scientific assessment of dossiers for marketing authorisation	1		1,3	1
Assessment of applications for manufacturing authorisation	4	2	4	2
Inspection of manufacturing sites	4	2	4	2
Meetings, travel expenses	1,4	2	1,3,4	1,2
Studies and consultants	1,4	2	1,3,4	1,2
Translation, Publications	1,4	2	1,3,4	1,2

* 1: marketing authorisation, 2: manufacturing authorisation, 3: Advice, guidance and surveillance of member states regarding marketing authorisation, 4: Advice, guidance and surveillance of member states regarding manufacturing authorisation

Source: Fraunhofer ISI

It can be expected that relatively large initial efforts would be required to establish the needed infrastructures. Once that has been accomplished, costs for maintenance of infrastructure will arise continuously. The operational expenditures, directly related to authorisations, will come up as soon as submitted applications need to be assessed.

They depend on the number of applications, and might increase with a positively evolving tissue engineering sector. In the medium to long term increases in efficiency can be expected due to experience gained. The need for continuous education and training of staff as well as the need for surveillance of national authorities might decrease over time.

As can be clearly deduced from Table 5.5, although only in a qualitative way, the two-tier approach will create higher overall costs for public budgets than the centralised approach:

- The two-tier approach creates additional tasks for EMEA and the national authorities and thus increased fixed costs for implementation and maintenance of the required infrastructure.
- Harmonised levels of standards and expertise throughout Europe need to be developed and maintained, resulting in higher needs for education and training, as well as advice, guidance and surveillance provided by EMEA.

Distribution of operational costs between EMEA and national authorities will depend on the future share of allogeneic and autologous products in all applications for authorisation and on the preference of manufacturers of autologous products to use the central approach. EMEA as well as national authorities are financed partly by fees and partly by provisions from the EU or the member state, respectively. The financial provisions for the planned hTEP authorisation procedures have not yet been defined in detail, although it is likely that they will be similar to the provisions in the medicinal products sector. The combined direct costs for the two-tier approach for EMEA and member states will be higher. Additionally, the burdens for member states' national budgets will be higher considering the two-tier approach.

Apart from the difference in costs (which need to be quantified to be useful as a decision basis) there are other factors that should be considered. Apart from the advantage of creating lower costs, a centralised procedure might facilitate true European harmonisation concerning authorisation of hTEPs as well as an easier adaptation to future development and requirements in the sector. The two-tier approach might be more accessible for small operators, it might facilitate tapping tissue engineering expertise in the member states and an earlier identification of emerging ethical issues. The naturally tighter links to the respective national health care systems might be important with a view to deliver and reimburse hTEP treatments.

5.10 Impacts of cost changes depending on member states

Currently hTEPs are preferably marketed in the home country of the respective company, in countries with a pragmatic or clear approach to hTEP authorisation and an attractive demand side and good reimbursement conditions. Countries which combine several of these preferred characteristics are Germany, UK, Italy, Belgium, Austria, Finland and Sweden. With the harmonised regulation and access to the internal European market the demand and reimbursement issue will gain more importance.

The impact of the proposed regulatory options on manufacturers and national authorities (in the case of the two-tier approach) depends very much on the status quo situation in the member states, such as high level of expertise (France, Germany, UK, Sweden, Netherlands, Denmark), high level of safety/quality standards (Germany, UK, Sweden; Spain, Ireland and Denmark improving position), number of hTEP manufacturers (Germany, UK, Sweden, Belgium, the Netherlands, Austria and France), and available

support measures to facilitate adaptation to the new regulation (as e.g. in Spain, UK, the Netherlands, Austria).

5.11 Employment, training and education

5.11.1 Employment

Currently, the level of employment in the tissue engineering sector can only be estimated. A survey conducted by the Brown University, USA, covered 66 US companies and 23 European companies. According to this survey, in 2002, 2,611 full-time equivalent employees (FTE) were engaged in tissue engineering research and development (Lysaght & Hazlehurst 2004). For the EU tissue engineering sector in 2003, between 2,238 and 5,230 FTE were estimated, based on 113 identified tissue engineering companies and extrapolation of staff numbers for about 44 of these companies (see Table 2.1). Tissue banks and hospitals, which are also active in tissue engineering, have not been included. Additionally, the research and clinical research sector, suppliers, medical staff as well as authorities and consultants should be added to the estimations.

An analysis of the German biotechnology sector revealed that about 20% of the direct employment effects (about 69,500 FTE) could be attributed to companies, 50% to workforce in academic and non-academic research institutions and about 30% in companies of the supply sector (Menrad et al. 2003). Applying these results to the tissue engineering sector, the direct employment effect in Europe would be in the order of magnitude of at least 10,000 FTE. Overall the contribution of the tissue engineering sector to employment in Europe is negligible, as the sector still is developing and rather small.

Tissue engineering is a high technology sector which needs highly qualified staff in research and development, production, regulatory authorities, and hospitals. Regarding direct short-term impacts, staff of hTEP manufacturers as well as consultancies needs information and training on the new requirements according to the proposed regulatory options. Working experience with GMP production is necessary, and experts might not be readily available as also for example the pharmaceutical industry is competing for them. According to experts' opinion, about 20% to 50% of the companies might need to make efforts in this area. Expected consolidation of the sector with a few rather small companies closing down will not influence the employment statistics significantly.

Also staff in the supply sector for tissue engineering, e.g. tissue banks, suppliers of equipment and reagents, needs training and appropriate qualifications to comply with the new requirements. Staff in tissue engineering research will probably not be directly affected by the proposed regulatory options; however, compliance with certain regulatory standards already in the research phase may be required. Research topics might change due to regulatory issues (e.g. more focus on risk assessment, quality assessment) and potential growth of the sector and its production (e.g. focus on large scale production issues).

Regarding authorities and considering the two-tier approach, qualified personnel is required in EMEA as well as in each member state. At EMEA a new scientific committee is planned. In case of the two-tier approach the development of guidance for authorisations and support to national authorities by EMEA will be needed. Considering the results of the survey, 9 out of 16 countries that answered did not yet receive any

tissue engineering dossier. Thus the experience with these products is very low and the need for new, specifically qualified staff high. There are no figures available on the number of staff needed in the national authorities and EMEA.

5.11.2 Education and training needs

Two crucial aspects of the implementation of the proposed regulatory options refer to the development and implementation of guidance taking specificities of hTEPs into account and to the enforcement of safety, quality and efficacy checks throughout Europe in a harmonised way. This requires highly qualified staff at the regulatory institutions with specific high level expertise concerning hTEPs. In case of the two-tier approach, to obtain that expertise in each member state during the coming years is a matter of concern for authorities. Special attention should be paid to establish a scientific committee at EMEA with the appropriate expertise. The introduction of transparent procedures to avoid conflict of interests and the avoidance of any bias that could favour certain players over others is important.

Guidance should be developed in a timely way, in a transparent process and with the best available expertise. In case of the two-tier approach, national authorities might need training in the implementation of the regulation, its interpretation and the use of the guidance. This is a prerequisite for achieving a harmonised approach to hTEP authorisation throughout the member states. Also companies will need to adapt to the new regulation. Support via early information and timely availability of guidance through EMEA will advance that process.

Training is also of great significance for medical staff, as the quality, safety and efficacy of tissue engineering treatment depends to a large extent on the handling and implantation in the hospital. The proposed regulatory options require a hospital environment for treatment; requirements for qualification of medical staff lie in the competencies of the member states. Currently, specific training is provided by the companies. For a potential improvement of the clinical success of hTEP treatments it might be desirable to define quality standards for education and training of medical staff and to perform quality assessment of these courses. Medical doctors associations could play a role here.

There is also a need to inform health insurance companies as well as investors about the changes to expect from the implementation of the proposed regulatory options.

6 Potential social impacts

The social impacts that are covered in this chapter include potential impacts on the protection of patient's health and the availability of hTEPs for patients. Impacts on the health status and quality of life of patients and the public in general are long-term impacts that depend on the development of tissue engineering as such and have not been assessed in this study. Ethical aspects are outlined, a more thorough assessment was carried out by the European Group on Ethics in Science and New Technologies (EGE).

6.1 Safety

Specific risks are connected to the sourcing of cells and tissues, their handling during production of hTEPs, the preservation or storage of the product, the implantation process and the long-term implantation in the patient. Due to the diverse regulatory situation in Europe and different or non-existent standards for safety, quality and efficacy of hTEPs, a lack of agreed scientific criteria for safety, efficacy and quality as well as post-authorisation surveillance, there is a risk that potential safety gaps might result in accidents or adverse events with possible severe consequences for the patient. This could also result in a negative public perception and little trust in hTEPs. However, none of the interview partners from national authorities or companies was aware of any such event in Europe, most probably due to the current prevalence of 'low-risk' products and relatively high standards applied by manufacturers although not required by law.

The proposed regulatory options are generally seen as a prerequisite to ensure high safety standards and thus is expected to reduce the risk for adverse events considerably. Market transparency will be increased with the result that substandard hTEP manufacturers would be pushed out of the market, contributing to increase the trust in the products and thus increase demand and investment in the longer term.

6.2 Availability

The availability of hTEPs in the EU is difficult to assess. There are about 35 products on the market (see Chapter 2.2), including skin replacements, cartilage products and few bone products. It can be assumed that most products are marketed at least on the home market of the respective company. No product is available in all EU member states. Other actors in the field such as tissue banks and hospitals contribute with additional products, currently on a local level. However, the number of this kind of actors seem to be limited at present.

Several factors influence availability of hTEPs in Europe in a positive or negative way and this results in a mixed overall picture. The realisation of a common market for hTEPs will most probably lead to increased availability of hTEPs because the products will be placed on more national markets. This is more likely to happen for allogeneic products and/or products from large companies. Also companies from third countries might be attracted by a large common market. Increased trust and larger demand due to harmonised and strict product standards will influence availability positively. The prolongation of time to first market under the proposed regulatory options might lead to a delayed availability of new hTEPs, although the possible quicker access to additional EU markets after obtaining the authorisation might counterbalance that effect.

Product improvements and variations might result in the need for a renewed authorisation, either the complete or a reduced process. Guidelines detailing the approach to product variations have not yet been developed. It might not be affordable for small operators to go through a full authorisation for each variation, considering that the product life cycle is only a few years. In the short to medium term the need to adapt to several new regulatory frameworks (Directive 2001/20/EC, Directive 2004/23/EC, new regulatory approach for hTEPs) might lead to a reduction in production and development of hTEPs (e.g. lack of GMP manufacturing capacities, lack of ancillary reagents of GMP quality, shift of company resources from R&D to compliance with regulatory requirements).

Some companies will be forced out of the market due to incompliance with the regulatory standards. This might lead to a decreased availability of hTEPs. However, this is a desired effect and supports safeguarding patients' safety. However, also resource-poor companies might face difficulties to be competitive, e.g. considering a shortage in GMP ancillary reagents, or an aggressive pricing policy by large companies. Due to higher compliance costs, companies will probably concentrate on fewer products. Especially products for a very focused market with potentially lower sales could require additional support in analogy to the orphan drug approach.

Availability of hTEP treatment for patients also depends on other factors, such as

- awareness of health care providers and patients of tissue engineering and hTEPs
- education and training of medical staff to ensure clinical success
- market transparency and ability to select the best suited product
- post-authorisation vigilance and traceability which respects the right for privacy, confidentiality and anonymity of patients.
- product cost and product prices, and reimbursement by health insurance companies.

At present no EU member state has a general coverage of hTEP treatments by statutory or private health insurances. The proposed regulatory options will not have any direct impact on reimbursement policies, but might provide a better negotiation position. Due to substantial R&D efforts and a technically challenging production process hTEPs are inherently costly. The requirement to comply with high standards for quality, safety and efficacy according to the proposed regulatory options might result in further increased product and treatment prices. On the other hand, intensified competition because of better market access, and economies of scale effects could help to reduce hTEP prices. However, considering the currently available products, they are in most cases significantly more expensive than conventional alternatives. But cost-cost-comparisons provide only part of the picture, a superior cost-effectiveness is decisive, including relevant effects such as improved health outcomes, better quality of life, less side effects, and shorter hospital stays. There are currently only few data regarding cost-effectiveness of hTEPs (see Bock et al., 2003). Yet, considering limited resources of health care systems, there is a need for cost-effectiveness analyses of hTEP treatments. It might be recommendable to initiate and support conducting such studies, which results could also feed back to reorientation of R&D towards more clinically cost-effective and competitive applications.

6.3 Ethical aspects

The use of human cells and tissues for research and production of hTEPs are connected to several ethical issues. Cells and tissues can be sourced from deceased or living donors, (aborted) fetuses, cell lines and human embryos and with each source specific

issues arise. Especially the use of human embryos for derivation of embryonic stem cells, the conditions of use of human cells and tissues for research and the conditions for use of human cells and tissues for commercial purposes (altruistic cell and tissue donation versus commercialisation of hTEPs, issues of benefit sharing, and avoidance of commercialisation of the human body) are the subject of controversial discussions in Europe. Various aspects have been covered by the EGE in its opinions from the last years¹⁷.

The use of animals as cell and tissue sources for treatment of humans is currently viewed critically because of pathogens posing safety risks not only for the treated individual but also for the public in general. There might be the need to balance individual benefits of the treatment against public risks. The use of animal tissues raises questions on possible impacts on the recipients' identity and personality as well the relationship between humans and animals. Animal welfare is another important issue to consider. Recommendations on how to deal with xenogeneic implants have been adopted recently by the Council of Europe (Council of Europe 2003).

The provision of equal access to hTEP treatments is an issue, considering limited resources of health care systems. In the future, hTEPs might be developed that not only restore tissue functions but are able to improve certain body functions, thus enhancing performance of human beings. Traceability of hTEP products and patients might pose problems concerning data protection, privacy, confidentiality and anonymity of patients.

¹⁷ Opinion no. 8 (1996): Ethical aspects of patenting inventions involving elements of human origin; opinion no. 11 (1998): Ethical aspects of human tissue banking; opinion no. 12 (1998): Ethical aspects of research involving the use of human embryo in the context of the 5th framework programme; opinion no. 15 (2000): Ethical aspects of human stem cell research and use; opinion no. 16 (2002): Ethical aspects of patenting inventions involving human stem cells; opinion no. 19 (2004): Ethical aspects of umbilical cord blood banking; see http://europa.eu.int/comm/european_group_ethics/index_en.htm

7 Potential environmental impacts

There are two ways hTEPs potentially could have an impact on the environment: through the production process or through the use. Emissions of potentially hazardous substances into the environment could occur due to normal production, due to accidents or due to disposal of production waste. Different substances are used throughout the production of hTEPs:

- Human cells, scaffolds and biomolecules. In general 'low-risk' human cells are used in hTEPs. Genetically modified organisms (GMOs) are only used in research and are not present in commercialised products; this, however, might change in the future.
- Ancillary reagents: growth media, growth factors, hormones or antibiotics might be applied. Also substances resulting from the conversion, degradation, contamination or other reactions might be produced.
- Contamination with higher risk organisms than the human cells used might occur during the production process.

However, environmental risks are considered to be relatively low, because of the low production volume, the use of readily biodegradable substances, the very limited survival of human cells outside controlled laboratory conditions, and strict production conditions. Furthermore, there exists already a regulatory framework to prevent, minimise and treat emissions (national laws for approval and inspection of production facilities; Directive 96/61/EC¹⁸ on integrated pollution prevention control; Directive 75/442/EEC¹⁹ on waste; Council directive 91/689/EEC²⁰ on hazardous waste; Directive 90/219/EEC²¹ as amended by Directive 98/81/EC²² on the contained use of genetically modified micro-organisms).

In recent years awareness was raised to potential environmental impacts of medicinal products and their metabolites due to excretion with urine and faeces and the incomplete treatment of these substances in waste water treatment. Thus pharmaceutically active compounds have been found in significant concentrations in surface waters located downstream of municipal sewage treatment plants and in drinking water.

The knowledge base concerning environmental impacts of pharmaceutical substances is narrow. Based on the precautionary principle, the emission of these substances should be prevented and an environmental risk assessment carried out prior to market authorisation (Directive 2001/83/EC on the Community code relating to medicinal products for human use).

Currently there are no data on potential hazards of hTEP to the environment. Due to low production volumes and the rather structural than metabolically mode of action of hTEPs it can be assumed that risks will be low. However, these assumptions need to be assessed thoroughly and the inclusion of environmental risk assessment in the proposed regulatory options should be considered on that basis.

¹⁸ Official Journal L 257 , 10/10/1996 P. 0026 - 0040

¹⁹ Official Journal L 194 , 25/07/1975

²⁰ Official Journal L 377 , 31/12/1991 P. 0020 - 0027

²¹ Official Journal L 117 , 08/05/1990 P. 0001 - 0014

²² Official Journal L 330 , 05/12/1998 P. 0013 - 0031

Potential environmental impacts

In the future it might be possible that hTEPs include genetically modified cells. In case this product is implanted in a patient, the implant is considered a GMO which is released into the environment and thus falls under Directive 2001/18/EC²³. The patient himself, as long as the germ line cells are not modified, is not considered a GMO. For experimental releases as well as putting on the market, GMOs are subjected to an environmental risk assessment according to Directive 2001/18/EC.

²³ OJ L 106 , 17/04/2001 P. 0001 - 0039

8 Conclusions

Currently, the tissue engineering sector is dominated by small, research-oriented and technology-based biotechnology companies. Additionally a limited number of hospitals and tissue banks is active in tissue engineering. The sector is still in an early development phase; however, expectations towards a fundamental change of medical practice made possible by hTEPs are high. The current diverse regulatory situation for hTEPs in Europe is not considered favourable for tissue engineering development, but the lack of a harmonised system is only one of a number of challenges for the sector. The proposed regulatory options for hTEPs will most probably have an overall positive effect, laying the foundation for further advance of tissue engineering. However, much depends on the detailed arrangements of the regulation, e.g. requirements for clinical trials, and on a true European harmonisation of authorisation requirements.

Economic impacts

In the short term, commercial hTEP manufacturers will face an increase in costs due to higher standards for safety, quality and efficacy to comply with as well as tighter requirements for the post-approval phase. According to experts, further research is necessary to improve the scientific knowledge base for deciding which evidence is needed for proving quality, safety and efficacy of hTEPs. The development of criteria for a scientific risk assessment to identify 'low-risk' hTEPs with the aim to reduce requirements for testing accordingly is also considered necessary.

In the medium to long term, positive impacts are expected due to gains in efficiency, access to a large market with potentially increased production and resulting economies of scale as well as increased awareness and trust in hTEPs from the user side. The time to the first marketing of the product in one EU member state might increase because of a more demanding authorisation process but this will be balanced by a quicker access to other markets in the EU. This favours in principle companies with an international orientation. However, other factors, in particular reimbursement of hTEP treatments, influence market access as well. Crucial is also a true harmonisation of standards throughout all member states, to avoid the introduction of additional requirements for certain products by member states or the invocation of the safeguard clause. This would especially affect SMEs. In this respect, a centralised approach appears more appropriate to ensure such harmonisation.

The proposed regulatory options aim at providing a level playing field for all actors in a common market. Competition will intensify due to easier access to once protected markets also from third countries. It is expected that large companies will increasingly focus on allogeneic products, better suited to cover large markets. They might increase their market share, as they are generally more internationally orientated than SMEs and have more resources at their disposal. Increased competition and tighter requirements for marketing of hTEPs will also lead to some companies exiting the market. These will be characterised by sub-standard products and/or a focus on a rather small home market. According to experts' estimations, about 50% of the current players will be able to cope well, additional 30% might need some adaptation and around 20% would need substantial adaptation which might go beyond their capabilities.

Investment in R&D will probably decrease in the short term as resources will be shifted towards adapting the company to the new regulatory requirements, e.g. implementing quality control systems or GMP production facilities. In the medium to long term a clear regulation might lead to a more transparent tissue engineering sector. More trust and

awareness from users but also from investors could increase available resources through increased sales or investments. As compliance costs increase it might become economically unattractive to develop a large range of hTEPs. Instead companies might focus in their portfolio on fewer, profitable products.

Providers for the hTEP sector will face adaptation to new legislation as well. This is true for cell and tissue providers (especially according to Directive 2004/23/EC) and clinical researchers carrying out clinical trials (Directive 2001/20/EC). But also e.g. providers of ancillary reagents, often SMEs, need to adapt to GMP production, which might result in a short-term shortness of supply.

Downstream, users of hTEPs might face increased product prices as companies need to recover higher compliance costs. However, a more transparent market will enable better informed product choices, avoiding the use of sub-standard products. Product prices may also decrease due to intensified competition and reduced costs due to economies of scale.

Hospitals and tissue banks in Germany, France and UK currently have limited activities in tissue engineering, focusing on research or on the production and treatment with rather simple, autologous hTEPs on an in-house or local basis. Activities are still developing and the situation might change in the future. For some actors manufacturing hTEPs in-house seems for the time being too laborious, but once technical progress enables for example fully automatic production, more institutions might enter into hTEP production. Larger institutions such as tissue banks might develop nation-wide networks for manufacturing and distribution of hTEPs. It is expected that the proposed regulatory options will lead to similar developments as for companies, characterised by concentration, vertical specialisation and integration and a diversification of “business” strategies. Some of the benefits of the proposed regulatory options, such as access to other European markets and more planning security are less relevant for the mostly public, non-profit hospitals and tissue banks. This puts more emphasis on possibly increased costs due to more stringent requirements. Tissue banks play currently a limited role in tissue engineering in Germany, and the UK. The situation might be different in the central and eastern European countries, where tissue banking is part of the scientific and research activities and thus might be more prone to taking a leading role in tissue engineering in these countries than private companies.

The implementation of the proposed regulatory options will also put pressure on public budgets. In the short term, the building up of the necessary infrastructure will incur costs, in the medium to long term maintenance costs and operational costs will gain more importance and will arise continuously. The two-tier approach will be more costly than a centralised procedure for all products, as parallel infrastructure needs to be build up at EMEA and at national authorities and additional tasks need to be covered. The distribution of costs between EMEA and national authorities depends on the preference of manufacturers of autologous products for the decentralised or centralised procedure and on the future relative share of allogeneic products. The level of fees to be paid by applicants has not yet been decided.

Social impacts

With strict harmonised standards for safety, quality and efficacy the safety of patients using hTEPs in principle is improved. It can also be expected that the availability of products throughout Europe will increase, although the actual access for patients to this kind of treatment depends on many more factors, for example reimbursement. Due to

research-intensive development and a complex manufacturing process hTEPs are inherently costly products. Additionally, specific expertise is required for implantation. Currently, there is no clear evidence available on cost-effectiveness of hTEPs compared to alternative treatments. These clinical data probably will be necessary to achieve reimbursement, resulting in an additional burden for hTEP manufacturers. The availability of new or further developed hTEPs might be affected by the companies focusing on fewer more profitable products and depends on the detailed requirements for authorisations of variations.

The tissue engineering sector at the moment does not play a major role in Europe concerning employment levels. However, mostly highly educated and well trained staff is needed and 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. pharmaceutical industry) for the same workforce. There will arise a considerable training need for all actors facing the implementation of the proposed regulatory options.

Environmental impacts

At present, little is known about potential environmental impacts connected to hTEPs. While emissions from production processes are already rather well covered by existing legislation, there are no data concerning potential environmental impacts due to the use of hTEPs. However, due to the low production volume and their rather structural than metabolic function in the body it can be assumed that risks will be low. However, this assumption should be further assessed.

In the future, the use of genetically modified cells in hTEPs might subject hTEP production and use to requirements of Directives 90/219/EEC and 2001/18/EC on the contained use of genetically modified micro-organisms and on the deliberate release into the environment of genetically modified organisms, respectively, and the environmental risk assessment foreseen for GMOs.

Impacts on SMEs versus large companies

SMEs play a significant role in the tissue engineering sector. Currently 24 from 27 products having been indicated in the company survey are commercialised by SMEs. Additionally, there are hTEPs provided by small operators such as hospitals or tissue banks. Thus it is very important that the proposed regulatory options provide a framework suitable for SMEs while safeguarding high standards for safety, quality and efficacy.

In general, large tissue engineering companies can cope easier with new, stringent regulations. Tissue engineering presents only one part of their business, thus they might have already e.g. GMP facilities installed for other purposes as well. Moreover, they have more resources at their disposal for adaptation and compliance. Compared to SMEs, large companies will also be better able to take advantage of the common market as it is easier for them to invest in the necessary post-approval marketing and educational activities in the different markets. It is expected that large companies will increasingly focus on allogeneic products covering large markets. Through takeovers of SMEs and licensing of products they will enhance their portfolio and increase their market share.

SMEs might need strategic partnerships and cooperations for targeting international markets. Facing intensified competition they might focus on niche products in the

medium to long term, e.g. for rare diseases. In this context an approach similar to orphan drugs could render these niches more attractive for SMEs.

One of the differences between the centralised and the decentralised authorisation process is the fee to pay by the manufacturers, as requirements concerning safety, quality and efficacy have to be the same for autologous and allogeneic products. But fees are only a minor cost compared to other compliance costs. Thus it might be necessary to introduce additional support measures for small operators which are the main producers of simple, probably 'low-risk', autologous products: a science-based risk assessment to define 'low-risk' products and an accordingly lower level of requirements for those products, reduction of administrative burden, easy access to support and advice by authorities and lower fees. A short time to market is crucial especially for SMEs. The overall duration of the authorisation process might still be too long, in particular for simple hTEPs. Fast track procedures might be considered to accelerate assessment of 'low-risk' products or of products with high medical need. Conditional authorisation might be another option. The possibility to reimburse manufacturing costs already in the clinical trials stage, as it is done in the US, could be especially useful for resource-poor companies.

9 References

- Bassett, P. (2001) Progress and Promise in Tissue Engineering Research. Drug & Market Development Publications Online Feature Article;
<http://www.drugandmarket.com>
- BATB (2003): BATB British Association for Tissue Banking Official Handbook 2003. London: British Association for Tissue Banking (BATB), pp. 1-60
- Bock, A. K.; Ibarreta, D.; Rodriguez-Cerezo, E. (2003): Human Tissue Engineered Products - Today's Markets and Future Prospects. Synthesis Report. Report EUR 21 000 EN. Seville: Institute for Prospective Technological Studies, pp. 1-49
- Council of Europe (2003): Recommendation of the Committee of Ministers to member states on xenotransplantation, in: Eur J Health Law, Vol. 10, No. 3, pp. 305-315
- DG Enterprise (2004) Proposal for a harmonised regulatory framework on human tissue engineered products: DG Enterprise consultation paper, 6 April 2004
- DG Enterprise (2005) Proposal for a Community regulatory framework on advanced therapies: DG Enterprise consultation paper, 4 May 2005
- European Commission (2001): Opinion on the State of the Art Concerning Tissue Engineering. Adopted by the Scientific Committee on Medicinal Products and Medical Devices on 1st October 2001. Doc.SANCO/SCMPMD/2001/0006Final. Brussels: European Commission-Health & Consumer Protection Directorate General, pp. 1-15
- European Commission (2002) Communication from the Commission "Action Plan: Simplifying and improving the regulatory environment"; COM(2002)278final
- European Commission (2002a) Communication from the Commission on Impact Assessment; COM(2002)276final
- European Commission (2005) Communication from the Commission "Better Regulation for Growth and Jobs in the European Union"; COM(2005)97final
- Lysaght, M. J.; Hazlehurst, A. L. (2004): Tissue engineering: the end of the beginning, in: Tissue Engineering, Vol. 10, No. 1-2, pp. 309-320
- Menrad, K.; Blind, K.; Frietsch, R. et al. (2003): Beschäftigungspotenziale in der Biotechnologie. Karlsruhe: Fraunhofer IRB Verlag, p. 145
- Osborne, R. (2004): Tissue Repair, Regeneration Could "Revolutionize" Health, in: BioWorld Financial Watch, Vol. 12, No. 18, pp. 1-11
- UK Department of Health (2001) A Code of Practice for Tissue Banks. Available at <http://www.dh.gov.uk/assetRoot/04/03/42/63/04034263.pdf>
- Vacanti, J.P., Langer R. (1999) Tissue engineering: the design and fabrication of living replacement devices for surgical reconstruction and transplantation, in: The Lancet 354, No. Supplement 1, pp. S32-S34
-

References

Williams, D. F. (2003): The Japanese Approach to Tissue Engineering. The Report of the Royal Academy of Engineering Mission to Japan. London: The Royal Academy of Engineering, pp. 1-59