Tissue Engineered Products – need and requirements for an appropriate harmonised EU regulatory framework

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Table of contents

List of Abbreviations:

ACI	autologous chondrocyte implantation
AMG	Arzneimittelgesetz
AIMD	active implantable medical device Directive 90/385/EEC
Art	Article
BLA	Biologic License Application
BPI	Bundesverband der Pharmazeutischen Industrie
BWP	Biotechnology Working Party
CAT	Committee of Advanced Therapies
CBER	Center for Biologics Evaluation and Research
CE	Certificate of Europe
CHMP	Committee for Medicinal Products for Human Use
CP	Centralized Procedure
CVMP	Committee for Veterinary Medicinal Products
DG	Directorate General
DP	Decentralized Procedure
EC	European Community
EEC	European Economic Community
EMEA	European Medicines Agency
EU	European Union
FDA	Food and Drug Administration
GCP	Good Clinical Practice
HCT/Ps	Human Cells, Tissues, and Cellular and Tissue-Based Products
IDE	Investigational Device Exemption
IND	Investigational New Drug Application
IVDD	*in vitro* diagnostic medical device Directive 98/79/EC
MA	Marketing Authorisation
MDD	medical device Directive 93/42/EEC
MR	Mutual Recognition
MS	Member States
MHRA	Medicines and Healthcare Products Regulatory Agency
PEI	Paul-Ehrlich-Institut
PHS	Public Health Service
PMA	Premarket approval
SANCO	An acronym for "Direction générale de la **san**té et de la protection des **co**nsommateurs". European Commission Health and Consumer Protection Directorate-General (DG SANCO)
SCMPMD	Scientific Committee for Medicinal Products and Medical Devices
SME	Small and medium-sized enterprises
(h)TEP	(human) tissue engineered product
TPM	Third Party Manufacturer
UK	United Kingdom
US	United States of America

1. Introduction

Tissue engineering is a new interdisciplinary technology that combines the principles of life sciences and engineering. It aims at assembly of biological substitutes that will restore, maintain and improve tissue functions following damage either by disease or traumatic processes. This form of therapy differs from standard therapies in that the engineered tissue becomes integrated within the patient, affording a potentially permanent and specific cure of the disease state, thereby avoiding repeated surgeries for the exchange of worn out medical devices respectively lifelong treatment with an immunosuppressant after organ transplantation. Current applications of this "regenerative medicine" include treatment for skin, cartilage and bone diseases or injuries. Other more complex applications like the substitution of heart valves, blood vessels or nerve tissue are in development.

Expectations into the potential of this new technology have been enormous, on the side of scientists and technicians as well as on the side of financial analysts. Even conservative estimates of the tissue engineering market expected only for the US market 1.7 bio USD in 2007 (Bock et al., 2005). Yet, current sales of human tissue engineered products (hTEPs) are estimated at about 60 million EUR per year worldwide (Bock et al., 2003). The discrepancy between market estimations and current sales figures might be caused by a bundle of barriers for market entry:

- long development cycles due to the high complexity of TEPs
- prevalence of SMEs or hospitals and tissue establishments with limited resources
- lack of a comprehensive regulatory framework for TEPs
- trouble with reimbursement due to missing data on clinical efficacy
- lack of proved business models
- lacking experience of practitioners with innovative technology

The unfavourable environment seems to have greater impact on the European market for TEPs than on the US market. A study of the European Commission on hTEP markets and prospects identified the lack of a pan-European regulatory framework as one of the major impediments to the development of this technology in Europe (Bock et al., 2003). Although the scientific and technological levels seem to be comparable to the situation in the US economic operators tend to manage their business activities within national frontiers. The business activities of the majority of the market players – SMEs or hospitals – remain locally limited due to the autologous character of the products. But those companies that produce allogeneic TEPs in batches are interested to market them in as many countries as feasible. This business strategy will be heavily impaired by the fragmented regulatory requirements in the European Member States (MS). Companies in the US only need a single product assessment and a single product license for access to the entire US market.

In January 2002, the European Commission launched a 30 point action plan titled "Life sciences and biotechnology – a strategy for Europe" for the development of biotechnology in Europe (European Commission 2002, COM/2002/27). The European MS agreed to foster research in this area. Any upcoming growth in this area should be

accompanied by creation of a regulatory environment that guarantees the highest level of safety to patients throughout Europe. The Community regulatory requirements should be proportionate to the level of risk conferred by the product. Based on this action plan, the European Commission took over the task to establish a suitable regulatory framework for TEPs at European level.

In July 2002, the Commission launched a public consultation to assess the need for a separate legislative framework for hTEPs, the key principles for the regulatory regimen and the provisions for authorisation and market access. Till the adoption of the final proposal on a regulation for advanced therapy medicinal products in November 2005 a fundamental change of the initial approach occurred: The original idea of a separate regulatory framework for human TEPs besides the existing frameworks for medical devices and medicinal products has been completely revised in favour of an extension and adaptation of existing medicinal product legislation. TEPs have been established as third category of advanced therapy medicinal products. This innovative class of medicinal products will be regulated by an amendment to Regulation (EC) No 726/2004 and Directive 2001/83/EC.

Key objectives of this framework should be:

- to guarantee a high level of human health protection for all patients in Europe treated with advanced therapies (to comply with Article 152 of the Treaty establishing the European Community (EC Treaty).
- to harmonize market access throughout Europe creating homogeneous conditions for marketing authorisation, supervision and post-authorisation vigilance and, by this, ensures the free movement of advanced therapies within the Community (to comply with Article 14 of the EC Treaty).
- to strengthen competitiveness of European market players by providing a clear and comprehensive regulatory regime which does foster investments into this emerging field of technology and confers legal certainty to economic operators.
- to create a framework that provides enough flexibility to keep pace with the speed of innovation in this sector.

The following chapters will evaluate the role of tissue engineering as new form of medical treatment and the current regulatory environment for TEPs. By following up the genesis of the final proposal for a Regulation on Advanced Therapy Products the definition of TEPs and the scope of the proposed regulatory framework shall be clarified.

Details on quality, pharmacotoxicological and clinical requirements for TEPs have still to be published. It has been clarified that TEPs that are intended to be placed on the market and are industrially manufactured need a marketing authorisation that will be issued via the centralized procedure. Procedural details will have to be clarified. A new scientific body to assess the applications for TEP-marketing authorisations will have to be established.

The basic principles of the new framework have been broadly appreciated by the stakeholders. But there are several crucial issues that might jeopardize one key objective of the framework: to strengthen competitiveness of the European market players. In the

long term this might also impact accessibility of innovative products for European patients.

2. Tissue Engineering – a promising new discipline of biotechnology

The principle idea of tissue engineering involves "inducing the body to regenerate a part that is missing" (Commission, MEMO 05/429, 2005). For this purpose tissue engineering applies the principles of life sciences (cell and molecular biology, medicine, biochemistry, genetics) and of engineering (materials science and biomedical engineering) to the development of biological substitutes that can restore, maintain or improve tissue function. Before the emergence of this innovative technology the idea of regenerative medicine rested with the use of continuously improved medical devices and organ transplantation. But these repair methods are coupled with considerable shortcomings. Usage of medical devices will never be able to fully repair the natural function and might require repeated replacement of defective or worn out devices. Organ transplantation suffers from rare availability of suitable organs and the need for life-long immunosuppression. Tissue engineering aims on full, long-term regeneration of natural functions.

Typically, a TEP is composed of a cell component (living or not living) and a medical device like component (the matrix or the scaffold), which is of natural or synthetic origin. Often a biological or chemical substance is added to the matrix or the cell culture media to induce specific physiological processes like differentiation or proliferation of the cells.

The principle techniques of tissue engineering are:

- harvesting of living cells from an organism
- propagation of the cells in culture systems or bioreactors
- often seeding of the cells to a synthetic or natural scaffold and stimulation to form specific tissues
- injection of the cells or transplantation of the in-vitro pre-formed three-dimensional (3D) cell/biomaterial composites into the patient.

The presence of a medical-device like component in the TEP that is delivered to the patient is not absolutely required. Sometimes cells are seeded within a scaffold or matrix, which may degrade or dissolve as the new tissue is formed. In other cases, a synthetic scaffold can provide the basis for tissue regeneration in an *ex vivo* bioreactor. After formation of the tissue-like structures cells are harvested from this reactor for infusion into or transplantation to the patient. This is the principle of the evolving technology of perfusion culture systems that allow for cultivation of cells under defined cheer stress thereby enhancing the formation of natural like structural properties of the cultivated cells. Structural tissues can also be generated outside the body of the treated patient – e.g. artificial liver systems that use human or animal derived liver cells in appropriate bioreactors.

The final "Proposal for a Regulation of the European Parliament and of the Council on advanced therapy medicinal products and amending Directive 2001/83/EC and

Regulation (EC) No 726/2004) aims at covering all these categories of TEPs by a comprehensive description of the components of TEPs:

Art 2(1b) of the final proposal of the Commission:

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

This means that neither a medical device part (like a matrix or a scaffold) nor biological or chemical substances are indispensable components of TEPs.

The source material of a TEP, the living cell, should be ideally non-immunogenic, highly proliferative, easyly to harvest and have the ability to differentiate into a variety of cell types with specialized functions. Different cell types are in use or under development (Kim and Evans, 2004):

- mature differentiated cells
- adult stem cells or somatic stem cells
- embryonic stem cells

Currently marketed products for skin, cartilage and bone repair are mainly derived from mature cells isolated from those tissues that will undergo repair (e.g. chondrocytes, keratinocytes, fibroblasts). Due to their poor property for proliferation and differentiation the usage of mature (non-stem) cells is restricted.

Adult stem cells are resident stem cells located in specific tissue compartments and responsible for intrinsic continuous tissue regeneration (e.g. for skin and blood cell renewal). With the help of specific growth factors or bio-molecules they can be stimulated to differentiate into specific tissue types. Unlike embryonic stem cells they cannot be indefinitely grown in tissue culture. Current research activities often use mesenchymal stem cells derived from bone marrow which are delivered as a cell suspension for cardiac or meniscal repair. They lack immunogenic properties and are therefore suitable as allogeneic cell source.

Embryonic stem cells are isolated from a blastocyst before uterine implantation. They demonstrate pluripotency even after prolonged cell culture. They can be induced to differentiate into any cell type and they are able to colonize tissues of interest after transplantation. Yet, serious ethical concerns delimit research on this field of tissue engineering.

Depending on the source of the living cells the TEPs are differentiated into:

- *Autologous product:* a product derived from cells and tissues removed from one person and used in/on the same person. These products are characterized by a low association of immune complications. Due to the individual character there is no batch control for universal clinical use.

- *Allogeneic product:* a product derived from cells or tissues removed from one person and used in/on another person. The advantage of usage of such cells is

the possibility for standardization of the procedure, linked to establishment of a quality control system. Yet, allogeneic cells bear a higher potential of immune complications.

- *Xenogeneic product:* a product derived from cells or tissues removed from an organism of another species and used in/on a human patient. Main advantages of use of xenogeneic products are better availability, the possibility for standardization of the procedure, linked to establishment of a quality control system. The main obstacle is the high immunogeneic potential as well as high risk of transmission of viral infections.

Research activities on TEPs started several decades ago. In the early 1980, first successful creation of artificial skin was published (Burke et al., 1981). In 1994, first clinical results were published about the "Treatment of Deep Cartilage Defects in the Knee with Autologous Chondrocyte Transplantation" (Brittberg et al. 1994). In early 1995, Genzyme launched its first autologous cell therapy product for cartilage repair – Carticel® - initially as an unregulated device. Two years later, in August 1997, this product was the first of any tissue engineered products to be granted a marketing authorisation by the FDA. Still today the range of marketed tissue-engineered products is rather narrow: skin substitutes, knee cartilage and products for small bone lesions. Research activities are focused on the extension of already existing applications (like the development of complete epithelial layers, the extension of applications of tissue-engineered cartilage to joints other than the knees, or products for the treatment of larger bone lesions) as well as on the development of more complex structures like heart valves, blood vessels, bioartificial liver or regeneration of nerve tissue.

At present between 100 and 200 companies in the US and Europe are engaged in tissue engineering (Bock et al, 2005). The majority of the market players are SMEs that produce autologous tissue grafts. The current total sales achieved by marketing of TEPs worldwide amounts to 50 to 60 mio EUR (Bock et al., 2003). This is only a small proportion of the estimated market size of the application fields skin repair, cartilage and bone regeneration that sums up to 11,7 bio EUR (Bock et al., 2003). In these areas there is rough competition between TEPs and highly sophisticated medical devices. Looking at cost effectiveness there are only few data available. But there seems to be a trend favouring conventional therapies even when long term effects are considered.

Nevertheless, with further development of this sector there might arise products that show clear advantages to conventional products, especially regarding patient compliance. TEPs are designed for potential permanent cure of the disease, injury or repair and might spare repeated surgeries. Furthermore, progress in research might allow for treatment of diseases where no other treatment option exists.

3. Current regulatory environment

Since more than 10 years, tissue engineered products have been manufactured and marketed. Despite the considerable health risk that might be conferred by these products any European guidance documents or standards on TEPs are missing until now. Many TEPs contain a medical device component and living cells. Each of these components is addressed by specific regulatory frameworks but none of them explicitly allows for

application to TEPs. It is therefore in the disposition of each Member State how to regulate this product group.
As the US has the longest experience with this kind of products some countries like UK take pattern of the US system, others – like Germany – follow the regulatory regimen applied to medicinal products.

3.1 Coverage by existing regulations

TEPs are currently not specifically addressed by any legislative framework. They are neither covered by the current Medical Device regulatory framework nor the medicinal product legislation although both regimens have been continuously amended to take account of rapid progress and involvement of biotechnology into the medicinal sector.

3.1.1 *Medical device legislation excludes human tissues*

There are three principle Directives pertaining to medical devices:

- the medical device Directive 93/42/EEC (MDD)
- the active implantable medical device Directive 90/385/EEC (AIMD)
- the *in vitro* diagnostic medical device Directive 98/79/EC (IVDD)

AIMD and IVDD are special legislations for special applications and do not address putative applications of TEPs. The scope of the MDD more generally covers instruments, apparatus, appliances, materials or other articles, whether used alone or in combination for prevention, treatment, or alleviation of diseases or handicaps. This general scope could allow for subsuming TEPs. Yet, Directive 93/42/EEC explicitly does not apply to "transplants or tissues or cells of human origin nor to products incorporating or derived from tissues or cells of human origin", as outlined by Art 1(5 f) of the Directive. Also the recent amendment Directive 2000/70/EC which regulates inclusion of biological materials into medical devices explicitly does not target tissue transplants. Directive 2000/70/EC aims at "amending Directive 93/42/EEC so as to include in its scope only devices which incorporate, as an integral part, substances derived from human blood or plasma. However, medical devices incorporating other substances derived from human tissues remain excluded from the scope of the said Directive."

3.1.2 *New regulations for biological products but not for TEPs*

From the scientific point of view tissue engineering is an advancement to those methods of cell therapy that are based on infusion or application of individual cells, that have been manipulated in vitro but that are not organized in a tissue-like structure. These cell therapy products and – if cells have been genetically modified - gene therapy products have been included in the existing pharmaceutical legislation by integrating them into the regulatory framework of Directive 2001/83/EC. The appropriate amendment of Directive 2001/83/EEC was defined by Commission Directive 2003/63/EC of 25 June 2003. As laid down by No. 9 and 10 of the preamble gene therapy medicinal products

and cell therapy medicinal products represent a new category of biological medicinal products in the sense of Articles 1 and 2 of Directive 2001/83/EC.

Directive 2003/63/EC also laid down to replace the old Annex I of Directive 2001/83/EC by a new Annex I that not only details the new standardised marketing authorisation dossier requirements (briefly the CTD format) for medicinal products, but also defines specific requirements for particular medicinal products. For the latter ones the Commission decided on separation into two subsections: Part III of Annex I details specific requirements for biological medicinal products, radio-pharmaceuticals, homeopathic, herbal and orphan medicinal products, whereas Part IV is addressing technical requirements for advanced therapy medicinal products. This group comprises gene therapy medicinal products (human and xenogeneic) and somatic cell therapy medicinal products (human and xenogeneic).

The definition of somatic cell therapy medicinal products as laid down by section 2 of Part IV, Annex I of Directive 2001/83/EC is rather extensive and reveals a putative overlap of this product group with TEPs. The general description of somatic cell therapy products contains elements that could also characterize TEPs (for a precise legal definition of TEPs see section 4.1.2):

> "Somatic cell therapy medicinal products shall mean the use in humans of autologous (…), allogeneic (…) or xenogeneic (…) somatic living cells, the biological characteristics of which have been substantially altered as a result of their manipulation to obtain a therapeutic, diagnostic or preventive effect through metabolic, pharmacological and immunological means. This manipulation includes the expansion or activation of autologous cell populations *ex vivo* (e.g. adoptive immuno-therapy), the use of allogeneic and xenogeneic cells associated with medical devices used *ex vivo* or *in vivo* (e.g. micro-capsules, intrinsic matrix scaffolds, bio-degradable or not)."

Furthermore the list of examples of somatic cell therapy medicinal products contains "cells manipulated and combined with non-cellular components (e.g. biological or inert matrixes or medical devices) and exerting the principle intended action in the finished products".[1]

In view of this definition it seems to be consistent to establish a common framework for both product groups. Yet, extensive discussions were necessary to end up with this solution. It was not in the scope of the amendment of Directive 2001/83/EC to include tissue engineered products, all the more as there has been no exact definition of this product category at the time of the amendment (for evolvement of the definition of TEP see section 4.1.2).

[1] The Paul-Ehrlich-Institute (PEI) interprets the example as description of TEPs. Yet, the institute notes that the requirements laid down in Part IV of Annex I to Directive 2001/83/EC would have to be amended concerning scaffolds and the interaction between cells and scaffolds; http://pharmacos.eudra.org/F2/advtherapies/Stakehcom2005/Regulators/Paul%20Ehrlich%20Institut.pdf PEI 2005

3.1.3 *Partial inclusion of TEPs by Directive 2004/23/EC*

The Amsterdam Treaty[2] (Article 152) gave the EU the mandate to pass laws on the quality and safety of human tissues and cells, human organs and blood used in medical treatment. This legislative measure aimed on regulation of the strongly expanding field of therapeutic treatment based on the use of tissues and cells of human origin which are frequently acquired through cross-border exchange. A common set of high standards should ensure the same level of protection from transmissible diseases in every Member State.

In March 2004, the Council and Parliament adopted Directive 2004/23/EC setting binding requirements for the safety and quality of human tissues and cells from patient to donor as well as setting standards for tissue establishments in order to ensure a comparable level of safety throughout the EU. The Directive must be transposed by MS till April 2006. Directive 2004/23/EC also provided for the Commission to elaborate on the rules laid down, by setting technical standards for blood and tissue donation, procurement and storage. Implementation of this provision has been fulfilled with adoption of Directive 2006/17/EC in February 2006.

According to Art 2 of Directive 2004/23/EC this Directive "shall apply to the donation, procurement, testing, processing, preservation, storage and distribution of human tissues and cells intended for human applications and of manufactured products derived from human tissues and cells intended for human applications." Yet, applicability of this Directive to TEPs is confined by another provision of Art 2: "Where such manufactured products are covered by other directives, this Directive shall apply only to donation, procurement and testing." This means that the definition of the term "manufactured" will be the main criterion for inclusion of a cell or tissue based product into the scope of the Directive.

The term "manufactured product" is further explained in the preamble of Directive 2004/23/EC. Point 6 of the preamble determines that "tissues and cells intended to be used for industrially manufactured products, including medical devices, should be covered by this Directive only as far as donation, procurement and testing are concerned, where the processing, preservation, storage and distribution are regulated by other Community legislation." The term "industrial manufactured" is also used in Art 2(1) of Directive 2001/83/EC (as amended by Directive 2004/27/EC). This Directive is valid only for human medicinal products that are "either prepared industrially or manufactured by a method involving an industrial process". Unfortunately, a legal definition of the term "industrial" is not available.

The subsidiarity principle stipulated by Directive 2004/27/EC finds its counterpart in Art 3 of the final proposal. This provision takes reference to Directive 2004/27/EC as far as donation, procurement and testing of the source cells of advanced therapy medicinal products are concerned.

[2] The Amsterdam Treaty was signed on 2 October 1997 and entered into force on 1 May 1999. It amends the wording of Article 152 (ex Article 129) of the EC Treaty from 1957.

3.2 Risk-based approach in the US

Carticel® – an autologous cartilage repair service developed by Genzyme - was first launched in the US as an unregulated device in early 1995, largely due to the fact that the Food and Drug Administration did not have a protocol to evaluate human autologous tissue and cell therapy products[3]. Facing the potential risk of bacterial, fungal or viral infection or other communicable diseases from tissue transplants, the FDA were the first health authority to develop a protocol for such cellular products. The FDA asked Genzyme to file a biological license application for Carticel® which was issued 1997 (Lloyd-Evans, 2004). The Carticel case triggered the FDA to introduce the so-called "Proposed Approach" of 1997.[4] Level and type of regulation should be appropriate to the risk posed by the product characteristic. A platform of minimal requirements applies to all cells and tissues. Additional requirements are added where necessary for safety reasons and product effectiveness. The scope of the approach includes – besides cells, tissues and cellular and tissue-based products (HCT/Ps) combination products of tissue/device and tissue/drug. Vascularized organs, xenografts, blood products and minimally manipulated bone marrow are excluded.[5]

There are two main regulatory tiers:

- *Products which are regulated only under section 361 of the PHS Act*

  Tissues that undergo only minimal manipulation (like cell selection or separation, grinding or freezing), that are intended for a homologous application to achieve a structural (and not a metabolic) outcome and do not combine with non-tissue components, the FDA will not impose any product licensing or pre-market approval requirements (21CFR1271). Yet, they have to comply with regulations on good tissue practice and donor suitability.

- *Products which are regulated under section 361 and IND/BLA (biological products) or IDE/PMA (medical devices).*

  HCT/Ps which are more than minimally manipulated need a market approval according to their categorisation, most probably as medical device – then the Center for Devices and Radiological Health (CDHR) will take the lead in regulating the TEP - or as biological product – then it is regulated by the Center for Biologics Evaluation and Research (CBER) with appropriate input from other centers. 2002, a special Office of Cellular, Tissue and Gene Therapies has been installed within the CBER.

The classification of the engineered product - and the decision which agency will have prime responsibility for the regulatory process - is effectively predetermined by its primary mode of action. To ensure cross-Center consistency in product classification and product approval paradigms the inter-Center Tissue Reference Group (TRG) has been established in 1997. The TRG deals with all questions on jurisdiction and applicable regulation of human cells, tissues and cellular and tissue-based products (HCT/Ps) which are passed on by the Centers or the Office of Combination Products which has been established 2002. All recommendations of the TRG are published on a

[3] http://biomed.brown.edu/Courses/BI108/BI108_1999_Groups/Cartilage_Team/matt/Carticel1.html

[4] Federal Register, March 4 1997, 62, 9721; CBER Docket 97N0068, Center for Biologics Evaluation and Research, Rockville (1997)

[5] for an overview of the Regulatory situation in the US see: WTEC Panel Report on Tissue Engineering Research, January 2002

particular FDA website and allow to take reference to these recommendations for similar products.[6]

Since issuing of the proposed approach the FDA has amended the US Code of Federal Regulations by a broad range of documents thereby formalizing the regulation of human tissue and cell therapies through a rule-making process. Key documents concern:

- All establishments manufacturing HCT/Ps have to register and list their HCT/Ps with FDA (66FR 5447).
- Tissue establishments are also required to evaluate donors and to establish current good tissue practices for HCT/Ps (64FR 52696 and 66FR 1508).

3.3 Fragmented Regulatory Landscape in the EU

In most countries there is an established regulatory process for assessing cell and tissue banks based on the control system established for blood-processing and organ transplantation facilities. But this process secures only oversight to the first steps in the manufacturing of TEPs and does not regulate control of the finished product and conditions for market access. Most member states use existing regulations for medical devices or medicinal products to regulate TEPs on a case-by-case basis. Novartis reported that the regulatory environment for its commercially available tissue engineered skin product Apligraf® ranged from unregulated to transplant to medical devices to pharmaceutical legislation within Europe.[7]

The current practical approaches are characterized by the fact that in the EU the great majority of TEPs is still of autologous nature or is of allogeneic origin but manufactured for an individual patient and produced and transplanted within one hospital. Cross-border exchange of TEPs is still the exception.

Germany:
TEPs are currently covered by the German Medicines Act (AMG). According to Art 21(1) AMG only those medicinal products that have been granted MA may be placed on the market. The previous limitation to ready-prepared medicinal products has been replaced – to comply with Directive 2004/27/EC - by a new terminology that refers to the manner of manufacturing. Proprietary medicinal products are prepared industrially or manufactured by a method involving an industrial process. There is no official definition of the term "industrially prepared". Interpretations range from manufacturing in compliance with GMP requirements to application of standardized processes. In any case, the alignment of the definition of medicinal products to the manufacturing process means an expansion of the scope of the medicinal product legislation and has consequences for managing the market access of TEPs.

Art 21(2) No 1a AMG lays down exemptions from the obligation to apply for MA for those medicinal products which use human derived substances for their manufacturing and which are determined for autologous use or for an individual patient. This exemption does not apply to vaccines, gene therapy medicinal products and somatic cell therapy medicinal products. As outlined above (section 3.1.2) the definition of somatic

[6] Tissue Reference Group Annual Report: /www.fda.gov/cber/tissue/trgfyrpts.htm
[7] Report of the EuropaBio Industry Hearing, 2005; contribution of Detlef Niese, Novartis

cell therapy products as defined by Directive 2001/83/EC is rather extensive. Therefore serious concerns were raised regarding future regulatory requirements for the implantation of autologous chondrocytes (ACI)[8]. Up to the 14th Amendment of the AMG these cell preparations did not need a MA as they were not regarded as proprietary medicinal products but as a ready-prepared product prepared for an individual patient. The recent introduction of a new definition for medicinal products mainly takes reference to the type of manufacturing process. Any product which is industrially prepared becomes a medicinal product according to Art 2(1) AMG. This means that autologous chondrocytes prepared according standardized processes might be subject to the obligation to apply for MA. The draft version of the 14th Amendment of the AMG[9] could only be interpreted in this way (Gerstberger and Greifeneder, 2005). Associations of the pharmaceutical industry heavily criticized the impact of this change introduced by the draft version of the 14th Amendment of the AMG on tissue engineering companies and achieved a change of the draft proposal[10] (Sickmüller and Wilken, 2005). In order not to impediment the just evolving business of young SMEs that are mainly engaged in ACI and in order to leave room to a specific European regulation addressing TEPs those products that involve autologous somatic cell preparation and propagation intended for tissue formation and tissue regeneration have been excluded from the regulation of somatic cell therapeutics. This means current regulatory practice will be maintained. Companies or tissue establishments engaged in autologous cell manipulation only need a manufacturing license of the regional health authority. Yet, allogeneic TEPs are not exempted from the obligation to apply for MA.

United Kingdom:

There is no specific regulation on TEPs. A voluntary code of practice for the safety and quality of human tissue and cell-derived products was published in 2002. This has been replaced by the Human Tissue Act 2004. It regulates activities like removal, storage and use of human tissue for transplantation and research and establishes the Human Tissue Authority (HTA) to advise on and oversee compliance with the Act.

Assigning regulatory responsibility is based on the same principle as applied in the US. A matrix settled with cells or combined with stimulatory proteins will be assessed according to its main action: if the main action is primarily a support function then the product will be regulated mainly by the medical device section of the MHRA. If the scaffold only provides a carrier function for the active constituents, cells or biomolecules then the medicinal product section will take the lead in regulatory assessment (Bock et al., 2003; Lloyd-Evans, 2004).[11]

[8] also often named ACT for autologous chondrocyte transplantation

[9] available at the website of the German Parliament: http://www.bundestag.de/ausschuesse/archiv15/a13/a13a_anhoerungen/99_104_Sitzung/aBT-Drs/5316.pdf

[10] consequences for tissue engineering companies were heavily criticized in the position papers of the BAH and BPI reg. 14th Amendment of the AMG; position papers are available via internet: http://www.bundestag.de/ausschuesse/archiv15/a13/a13a_anhoerungen/99_104_sitzung/cStellungnahmen/Bundesverband_der_Arzneimittel-Hersteller.pdf and http://www.bundestag.de/ausschuesse/archiv15/a13/a13a_anhoerungen/99_104_sitzung/cStellungnahmen/Bundesverband_der_Pharmazeutischen_Industrie.pdf

[11] Scientific Report on Exploratory Workshop „Regulation and Governance of Human Tissue Engineered Products in Europe", held at the University of West of England, Bristol, U.KI., June 23-24 2004. EW 03-189. www.esf.org.generics/1925/03189Report.pdf

France:
TEPs are not addressed as a separate concept. The existing legislation for medical devices and medicinal products and the Tissue and Cells Directive 2004/23/EC is considered as sufficient basis for regulation of TEPs. Any manufacturing site that produces tissue engineered products has to apply for an accreditation as a tissue bank. For marketing TEPs a procedure specific authorisation is additionally required (Bock et al., 2003).

Other countries:
Spain and Sweden follow a similar strategy as UK. Ireland, the Netherlands and Poland do not at all have developed any regulatory regimen to manage TEPs. Austria and Belgium apply the medicinal products legislation with some special provisions added for TEPs like authorisation by the involved hospital in case of Austria or the compulsory inclusion of licensed tissue establishments in case of Belgium (Bock et al., 2005).

4. European approach for a common framework

The fragmentation of legal requirements in the Member States not only confers legal uncertainty to the economic operators and impedes free circulation of TEPs within the community but also may establish different levels of health protection in the MS and even hinder access of patients to innovative therapy in some countries.

The fragmentation presents furthermore a hurdle to the market entry of global players that have to recruit national experts to place a product on the market of any country. Facing this extra costs they will evaluate market entry into each European country thoroughly on a cost-profit base. [12/13]

As long as the legal situation for TEP products has not been harmonized in the EU and market entry requirements are at the disposal of each MS reimbursement of TEPs will also be at the discretion of each MS. At present there is no general coverage of hTEP treatments in the public health system or private health insurance in any MS (Bock et al., 2005).

This is true also for Germany. Autologous TEPs (e.g. for cartilage repair) can be marketed without clinical trial data, as they do not need MA. But insurance agencies ask for data on cost-effectiveness and long-term efficacy of the treatment. As these data could only be provided through specifically designed clinical studies which currently do not exist insurance companies refuse to take the cost for TEP therapy for out-patient treatment. In case of hospital treatment the cost for ACI would have to be included in the DRG system. Yet, hospitals till now have refused to include cost for cultivation of cartilage cells by respective companies. So, these companies have to negotiate costs with the patient himself. The fact that a recent judgement assessed such a contract

[12] Scientific Report on Exploratory Workshop „Regulation and Governance of Human Tissue Engineered Products in Europe", held at the University of West of England, Bristol, UK, June 23-24 2004. EW 03-189. www.esf.org.generics/1925/03189Report.pdf

[13] Genzyme, position paper on 2004 consultation paper: http://pharmacos.eudra.org/F2/advtherapies/stakehcom/tissue/pdf8.pdf

between manufacturer and patient to be unethical does not foster the position of companies engaged in ACI (Günter, 2005).[14]

The fragmentation runs opposite to recent European efforts to become a leading knowledge-based economy based on consolidation of the frontier technologies life sciences and biotechnology. In its strategy paper "Life Science and Biotechnology – A strategic vision" (European Commission, 2001; COM2001/454) the European Commission called upon measures to strengthen the European biotechnology sector's competitiveness while ensuring environmental and consumer safety. The Commission initiated a study on the human tissue engineering market in Europe. The study revealed that, while "European companies are at the same level of scientific and technological intelligence as their world competitors, they are disadvantaged by the fragmentation of the European market" (Bock et al., 2003).

4.1 A short history of the public consultation process

In order to harmonize the European procedures for granting market access to TEPs and to safeguard consumer and user protection a public consultation on requirements of a European regulatory approach for human tissue-engineered products was launched in June 2002 by the European Commission *(in the chapters below designated as "2002 Consultation paper")*. The web-based consultation[15] was accompanied by meetings with representatives of the pharmaceutical and medical device industry and experts from national authorities and flew into a "Proposal for a harmonized regulatory framework on human tissue engineered products: DG enterprise Consultation paper" published on 6 April 2004 *(in the chapters below designated as "2004 Consultation paper")*. Key points were the establishment of a third category of products beside medicinal products and medical devices and separate authorisation procedures for allogeneic and autologous products. The framework should have the character of a Regulation and borderline product should fall under the new regulation.

Again interested parties were invited to comment on this proposal. On the basis of the outcome of the consultation rounds in 2002 and 2004, the European Commission prepared a draft proposal for a Regulation, that abandoned the concept of a self-standing regulatory regimen for hTEPs but subsumed hTEPs to a comprehensive regulatory framework for advanced therapy medicinal products comprising somatic cell therapy, gene therapy and tissue engineering: "Regulation of the European Parliament and of the Council on Advanced Therapies and amending Regulation (EC) No 726/2004", dated 04 May 2005 *(in the chapters below designated as "May 2005 proposal")*. This proposal was constructed as an amendment to the Regulation on the Centralized Procedure.

After a final consultation round on this proposal DG Enterprise presented the final "Proposal for a Regulation of the European Parliament and of the Council on advanced therapy medicinal products and amending Directive 2001/83/EC and Regulation (EC) No 726/2004" on 16 November 2005 *(in the chapters below designated as "final proposal" or "proposed Regulation")*. The principal concept of this final proposal is

[14] see decision of Landessozialgericht Nordrhein-Westfachen, 2004.

[15] for an overview of the web-based consultation on a Regulation for advanced therapy medicinal products see website of the Commission: http://pharmacos.eudra.org/F2/advtherapies/index.htm

similar to the previous May 2005 proposal. But there have been some essential changes that affect the definition of TEPs, the scope of the Regulation, characteristics of the European body that will be in charge of TEPs and the grandfathering provision.

4.2 Key points

The genesis of the proposal reflects the highly controversial but also constructive discussion process and pays tribute to the understanding that the new proposal should address not only already existing TEPs but also future developments in this rapid evolving field of technology.
Key questions were:

- Separate legal framework or integration in existing legislation?
- How to define a tissue engineered product?
- Scope of the regulation?
- Market entry requirements?
- Which procedure will be appropriate to grant a marketing authorisation?
- Who will assess and decide?
- Which documentation is required?
- Which safety measures will be required post-marketing?
- Will there be any incentives offered to applicants?
- How are products regulated that are already on the market?

4.3 Separate legal framework or integration in existing legislation?

Before starting the public consultation rounds about a suitable regulatory framework for TEPs there was considerable uncertainty which regulatory regimen would be the best to address particulars of TEPs. There was a broad consensus that TEPs are neither pure medical devices nor conventional medicinal products. Dependent on the source of the cells – autologous or allogeneic – and on the intended use the TEP confers different risk potentials. As outlined above divergent risk levels are addressed by divergent regulatory approaches for the various classes of TEPs in the US and in particular European countries.
As the initiative aimed on creation of a comprehensive European framework that allows to follow a general regulatory regimen for management of TEPs and not case to case recurrence to existing frameworks three principal options for an appropriate regulatory regimen were discussed: to apply the principle of medical device law, to subject TEPs to the pharmaceutical product legislation or to create a separate legal framework.

Principle of Medical Device regulatory regimen

Medical devices have to fulfil the so-called essential requirements before being placed on the market. The general description of the essential requirements is laid down in the Annexes of the Directives 93/42/EEC, 90/385/EEC and 98/79/EC (see section 3.1.1).

A more detailed description of essential requirements to be fulfilled by particular products is given by national or harmonized EU-standards like the standards for quality

assurance ISO 9001 and ISO 13485 or the standards for testing the biological safety of medical devices (ISO 10993). A pre-market review for compliance of the medical device with the essential requirements is accomplished by notified bodies that have been designated (in Germany accredited) by the MS and can be of private or public nature. The choice which set of conformity assessment procedures is to be used depends on the level of risk associated with the device. Details on the conformity assessment route to be taken are outlined in the annexes of the Directives listed above.

The confirmation of compliance of a particular product with the essential requirements allows for CE marking of the product. For any product bearing a CE mark, each MS shall presume compliance with the essential requirements. This means the positive outcome of the conformity assessment performed by the notified body of one single MS allows for CE marking of the product and marketing of this product in all MS.

Principle of medicinal product regulatory regimen

EU regulation of medicines is a stringent regulatory system. Medicinal products can only be placed on the market when they have been granted a marketing authorisation by national or European regulatory authorities. Applicants can follow several procedures to be issued MA:

Table 1: *EU regulatory system for medicinal products*

Procedure type	**Market access**	**Legal basis**	**Preconditions**
National	Only national	National drug law	Any medicinal product that has not been granted MA previously in any MS – CP not compulsory
Centralized procedure	Community	Regulation (EC) No 726/2004 Techn. Requirements defined by Annex I of Directive 2001/83/EC	Compulsory for: high-technology medicinal products, particularly those derived from biotechnology Orphan medicinal products Products containing new active substances for particular therapeutic indications
MR procedure	Involved MS	Directive 2004/27/EC amending Directive 2001/83/EC	Any medicinal product that has been granted MA in at least one MS - CP not compulsory
DP procedure	Involved MS	Directive 2004/27/EC amending Directive 2001/83/EC (Art 28 (1), (3) (4))	Any medicinal product that has not been granted MA previously in any MS - CP not compulsory

All medicinal products – independent of any risk assessment - have to demonstrate quality, safety and efficacy. The analytical, pharmacotoxicological and clinical standards and protocols in respect of testing of the medicinal products suitable to demonstrate quality, safety and efficacy, are laid down in Annex I of Directive 2001/83/EC for European procedures respectively in the national legislation. More detailed requirements might be outlined by specific guidelines or other regulatory documents (the so-called soft-law). Harmonized standards like the European

pharmacopoeia might also be used as reference. The structure of data to be presented for application has also be defined by law as outlined by Annex I of Directive 2001/83.

Clinical testing requirements for medical devices have generally been less extensive than for medicines, although the European Commission's recent draft proposed amendment to the Medical Device Directive is likely to result in more extensive testing than in the past. [16]

Compliance with quality standards does not address high risk potential of TEPs

The principle of medical device legislation allows for high flexibility and rapid market entry, but already in the beginning of the discussion the medical device framework was not favoured as a model for a regulatory framework on TEPs.[17] In their "Opinion on the State of the Art concerning tissue engineering" the Scientific Committee on Medicinal Products and Medical Devices proposed adaptation of the regulatory control of TEPs dependent on the level of risk. Yet, also the Committee issued concerns that the declaration of conformity to quality assurance systems requirements and a CE marking process would not provide a sufficient regulatory framework for TEPs (SANCO/ SCMPMD/2001/0006).

During the 2002 consultation process the majority of contributors favoured establishment of a specific legislation for TEPs, assigning a differentiated approach for different types of products, depending on the perception of risk.[18] The 2004 consultation paper consequently set up a "risk-based" approach with a two-tier authorisation procedure dependent on the origin of the source cells. Yet, this approach was criticized as risk assessment should be dependent on the functional performance of a product and not on the origin of the source cells (e.g. Position paper of Natural Implant, April 2004)[19].

A further aspect should also be considered for the risk discussion: focussing on performance criteria of TEPs neglects the high risk potential inherent to any TEP due to the specific nature of the source material. Any transplantation or infusion of tissues, cells, or cell-derived material raise concerns of viral safety and transmission of infectious diseases or other diseases and of pyrogenicity. Even for autologous donations there might arise the risk of re-infection. Also, the manipulation of the cells could create new risks based on the modification of the cells (for example could render them carcinogenic). Furthermore, any unwanted cells isolated together with the target cells could escape any purification steps and invade the recipient (SANCO/ SCMPMD/2001/0006).

[16] Proposal for a Directive of the European Parliament and of the Council amending Council Directives 90/385/EEC and 93/42/EEC and Directive 98/79/EC as regards the review of the medical device Directives.

[17] Stakeholders' comments are included in the Summary of responses to the Commission's 2002 consultation paper: "Human tissue and cell engineering products"; available on the website of the Commission: http://pharmacos.eudra.org/F2/advtherapies/docs/2002%20Public% 20consultation%202002%20-%20summary%20of%20results.pdf

[18] http://pharmacos.eudra.org/F2/advtherapies/docs/2002%20Public%20consultation%202002%20-%20summary%20of%20results.pdf

[19] http://pharmacos.eudra.org/F2/advtherapies/stakehcom/tissue/pdf9.pdf

In the course of the several years taking consultation process the initial effort to set up a separate legislation for TEPs and to establish a clear boundary between TEPs, medical devices and medicinal products gave way to a more pragmatic approach. The medical device legislation clearly excluded cell derived products from the scope whereas the pharmaceutical product legislation has recently expanded its scope to cellular products. A regulatory framework for genetic cell therapies and somatic cell therapies has been arranged within the existing legislation for medicinal products. It became clear during the discussion that it would make no sense to put the focus on demarcation of tissue engineered cells from somatic cells to justify separate legal frameworks despite many similar characteristics. So, finally the subclass of advanced therapies that comprised genetically modified and somatic cell therapeutic products was amended by a third category of products: the TEPs. All advanced therapies are subsumed under the medicinal products legislation with special technical requirements as already defined by Annex I of Directive 2001/83/EC respectively as defined by future amendment of Annex I for TEPs.

4.4 Endeavour for a legal definition of TEPs

The definition of TEPs is the key factor to define the scope of the new Directive and to set the demarcation line to related product groups that will be addressed by other regulatory provisions or are intended to be left outside the scope of any medicinal product legislation. Demarcation problems arise from medical devices, somatic cell therapy products, and tissue allografts which are currently covered by the Tissue and Cells Directive 2004/23/EC as far as they are not intended to be used for industrially manufactured products and medical devices, and by separate national legal provisions.

The proposed definition of TEPs as outlined by the final proposal is composed of a structure-related and a function-related definition element:

final proposal Art 2(1b):

tissue engineered product means a product that:
- contains or consists of engineered cells or tissues and
- is presented as having properties for, or is used in or administered to human beings with a view to, regenerating, repairing or replacing a human tissue.

The structure related element “engineered human cells or tissues” mainly aims on demarcation from tissue autografts and allografts and went through increasing refinement. The function-based component “regenerating, repairing or replacing a human tissue” originally aimed on distinguishing TEPs from medicinal products and medical devices but finally mutated to a general description that classifies TEPs as medicinal products. The history of this mutation which is outlined below mirrors the evolvement of a completely new legal assessment of TEPs.

4.4.1 *The functional component – poor suitability as demarcation tool*

The question catalogue that was published 2002 as basis for a public discussion process about a legal framework for TEPs took reference to the terminology of the definitions of medical devices and medicinal products to establish a clear boundary to just these product groups:

2002 consultation paper:

"human BioOrgans, tissues and cells, autologous and allogeneic, both nonviable and viable, and including combined tissue/non-tissue type products that have been substantially modified by treatments, and that do not exert their effect through metabolic, pharmacological or immunological means"

Definition of medical devices:

According to Council Directive 93/42/EEC medical device "means any instrument, apparatus, appliance, material or other article, whether used alone or in combination….intended by the manufacturer to be used for human beings for the purpose of:

- diagnosis, prevention, monitoring, treatment or alleviation of disease
- dagnosis, monitoring, treatment, alleviation of or compensation for an injury or handicap
- investigation, replacement or modification of the anatomy or of a physiological process
- control of conception

and which does not achieve its principal intended action in or on the human body by pharmacological, immunological or metabolic means, but which may be assisted in its function by such means;"

Definition of medicinal products:

As defined by Art 1 of Directive 2004/27/EC a medicinal product is:

(a) any substance or combination of substances presented as having properties for treating or preventing disease in human beings; or

(b) any substance or combination of substances which may be used in or administered to human beings either with a view to restoring, correcting or modifying physiological functions by exerting a pharmacological, immunological or metabolic action, or to making a medical diagnosis.

The purpose of application may overlap in case of medical devices and medicinal products and also TEPs: all might aim on prevention or treatment of disease. Yet, the primary mode of action to accomplish this objective is different: typically the medical device function is fulfilled by physical means including mechanical action, physical action, replacement of or support to organs or body functions (MEDDEV 2.1/3 rev 2 July 2001) and not by pharmcacological, immunological or metabolic means as this is exerted by medicinal products. According to the 2002 consultation paper, the absence of these functional principles should also be the main criterion for characterizing the function of TEPs.

Naming the functions of TEPs

Stakeholders heavily disagreed with the approach to define the essential function of TEPs by exclusion of the three functional principles of medicinal products. Nearly all TEPs may have some metabolic, immunological or pharmacological mode of action – every product containing living cells, exhibits metabolic activity, but this will not be the

primary mode of action, but rather secondary or tertiary[20]. There is broad consensus about the main function of TEPs: repair, replacement or regeneration of human tissue or functions. Most contributions favoured inclusion of these essential functions into the definition of TEPs instead of the listing of inappropriate exclusion criteria.[21] These suggestions were included in the subsequent proposals.

The discussion process revealed that there may be an overlap of the primary mode of action of medicinal products and TEPs. The narrow relationship of both product groups already became obvious by having a look at the key principles characterizing somatic cell therapy products as laid down in Annex I, Part IV of Directive 2001/83/EC in comparison to the key elements of the initial TEP proposal:

Annex I, Part IV, section 2 of Directive 2001/83/EC

> "For the purposes of this Annex, somatic cell therapy medicinal products shall mean the use in humans of autologous (emanating from the patient himself), allogeneic (coming from another human being) or xenogeneic (coming from animals) somatic living cells, the biological characteristics of which have been substantially altered as a result of their manipulation to obtain a therapeutic, diagnostic or preventive effect through metabolic, pharmacological and immunological means."

Inclusion and exclusion criteria of somatic cell therapy products respectively designated TEPs are different (in contrast to the proposal somatic cell therapy products include xenogeneic cells, but exclude non-living cells). But both definitions target autologous and allogeneic cells and address the requirement of substantial modification by treatment respectively substantial alteration as a result of their manipulation (for definition of substantial manipulation see section 4.4.2). The similarity of both definitions made clear that demarcation of both product groups would need refinement of the definition of TEPs compared to the initial proposal.

The main criterion to distinguish medicinal products, especially somatic cell therapy products, from the new product group of TEPs was the primary mode of action: metabolic, immunological or pharmacological function in case of somatic cell therapeutics and the absence of a metabolic, immunological or pharmacological function in case of TEPs. As this criterion turned out to be obsolete, the boundary between somatic cells and tissue engineered cells was hardly to determine. This problem pursued with revision of the TEP definition presented in the consultation round in 2004:

2004 consultation paper:

"Human tissue engineered product 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 a human tissue or human cells, where the new tissue or the new cells,

[20] Position statement of Genzyme Europe on the 2004 Consultation paper: http://pharmacos.eudra.org/F2/advtherapies/stakehcom/tissue/pdf8.pdf

[21] Contributions are compiled in the Summary of responses to the Commission's 2002 consultation paper: "Human Tissue and cell engineering products"; http://pharmacos.eudra.org/F2/advtherapies/docs/2002%20Public%20consultation%202002%20-%20summary%20of%20results.pdf

in whole or in part, are structurally and functionally analogous to the tissue or the cells that are being regenerated, repaired or replaced."

This version implemented a positive description of the essential function of TEPs: regeneration, repair or replacement of a human tissue or human cells. The function-based component of the definition was complemented by a further structural and functional requirement: the TEP has to be structurally and functionally analogous to the tissue or the cells that are being substituted.

The requirement of both structural and functional analogy to the tissue or the cells to be substituted might have provided a measure for demarcation of somatic cell therapy medicinal products and TEPs. As somatic cell therapy medicinal products consist of cells which as a consequence of *in vitro* processing display prophylactic, diagnostic or therapeutic properties different from the original physiological and biological one (as laid down by Annex I, Part IV, No. 2a of Directive 2001/83/EC) they are not intended to be functional analogous to the source cells. But the requirement of structural and functional analogy for TEPs might have caused exclusion of a considerable number of products, which were intended for tissue replacement, from the scope of the proposed regulation as they would not fulfil both conditions.

Rather simple TEPs which currently build the main business like skin or cartilage substitutes fulfil both functional and structural analogy. But all those products that are not mere replacements of diseased tissues would be excluded. And many of the products that are currently in development would belong to this group:

- Any tissues derived from adult stem cells as these are neither finally differentiated nor are organized in a tissue like structure in the organism
- Any non-homologous use of autologous or allogeneic cells

  like: allogeneic processed acellular dermis for replacement and repair of damage periosteum or allogeneic amniotic membrane promoted for ocular surface reconstruction[22]

With the decision to subsume TEPs to the medicinal product legislation there was no further necessity to define a strict boarder between both product groups and putative divergent regulatory regimes. Therefore there was no further need to demand on any functional and/or structural analogy requirements. The 2005 proposals skipped off any analogy requirement and allowed for coverage of future TEP applications:

May 2005 proposal (Art 2(2) and final proposal of November 2005 (Article 2(1b)):

(Human)[23] tissue engineered product means a product that:

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

[22] examples from the annual report of the Tissue Reference Group of the FDA; accessible via internet: www.fda.gov/cber/tissue/trgfyrpts.htm

[23] "human" has been deleted in the final proposal

Indeed, the primary mode of action "regenerating, repairing or replacing a human tissue" implies that there must be any analogy between biological substitute and target tissue.

The term „is presented for" shall include those medicinal products that are presented as having particular medicinal functions by the manufacturer based on the marketing and labelling, independent of the question if these functions are objectively present. The separation into medicinal products that objectively fulfil special medicinal functions and others that might only be said to do so has its origin in the French legislation and is unknown in other European countries like Germany. It is thought as a measure to strengthen health care protection which has been introduced into medicinal product legislation with Directive 2004/27/EC but might be less relevant for the custom-made TEPs (Gassner, 2004).[24]

4.4.2 *The second branch of definition – the structural component*

TEPs usually contain cells – viable or nonviable – that may be organized in a natural-like 3D-structure and which are implanted into, infused in or applied to the human body. Tissue transplants or blood cell preparations also contain human cells and are introduced or reintroduced into the recipient. The main difference between both product groups is the degree of manipulation applied to the cells. The structure-based definition component of the 2002 proposal for TEPs aimed on emphasizing this difference.

2002 consultation paper:

"human BioOrgans, tissues and cells, autologous and allogeneic, both nonviable and viable, and including combined tissue/non-tissue type products that have been substantially modified by treatments, and that do not exert their effect through metabolic, pharmacological or immunological means"

The term "modification" has also been used by the CPMP document on somatic cell therapy: "Modification may result from the culture, expansion, isolation or pharmacological treatment of cells that alters their genotypic and phenotypic characteristics." (CPMP/BWP/41450/98).

The term "substantial modification" is rather unusual. The US system uses the term "more than minimally manipulated" as a demarcation tool of products that need product licensing or pre-market approval (see section 3.2). The SANCO-initiative considered medical techniques with "minimal manipulation" of cells as "a version of cell therapy and not tissue engineering" (SANCO/SCMPMD/2001/0006). Yet, this view has been superseded by the already mentioned CPMP document on somatic cell therapy (CPMP/BWP/41450/98). Here it is laid down that the manufacturing "process encompasses expansion or more than minimal manipulation which may be designed to alter the biological, physiological or functional characteristics of the resulting cells". It is obvious that somatic cell therapy products as well as TEPs are both characterized as products that result from more than minimal manipulation.

[24] position statement to the consultation paper 2004; http://pharmacos.eudra.org/F2/advtherapies/stakehcom/tissue/pdf29.pdf

The border to be defined is that between tissue and cell manipulations usually performed by tissue and blood banks without the requirement for any licensing procedure and those tissue and cell manipulations that qualify a product as TEP. A modification is any change of genotypic or phenotypic characteristics of a cell. When will a modification be a substantial modification? There are no objective criteria to qualify a change of the genotypic or phenotypic characteristics as a non substantial change. Nearly all cell culture techniques will produce cells with altered morphology. But there would be a need to determine when an isolated and *in vitro* cultured cell displays an altered physiology.

Tissue banks and blood services issued concerns that there might be a potential overlap with processes that are applied to treat tissue allografts (to disinfect, sterilise, preserve or remove unwanted components by washing processes or decellularisation) and that do not seek to add to, improve or alter any physiological function of the tissue cells. (e.g. position statement of the Tissue Section of the National Blood Service, UK).[25]

As a result of the initial discussion it became clear that it would be more appropriate to combine the term "substantial" with the degree of manipulation and not with the degree of modification. This means to define the kind of manipulation process and not the outcome of this process. For this purpose, in the 2004 consultation paper a definition for the term "engineered human cells and tissues" was presented:

2004 consultation paper:

"Engineering means any process whereby cells and tissues removed from a human donor (source materials) are substantially manipulated, so that their normal physiological functions are affected."

However, this definition still did not provide enough clarity. Nearly any cell culture process will affect the normal physiological function of a cell. As outlined e.g. by the contribution of the Forum Biotechnology and Genetics of the Netherlands[26], engineering is an issue in the event of: 1) manipulations which influence the physiological function of a cell population and/or 2) manipulations of a cell population which result in changes in the composition of the cell populations including procedures such as depletion and selection procedures.

The Tissue Bank of Bologna[27] subsumes "human tissues and human cells isolated and cultured for quantitative expansion, even on biomolecules or biomaterials" to the minimally manipulated products, if they are processed without substantial modification of physiological functions. All contributions showed that it would be necessary to define objective criteria which kind of manipulation would affect a substantial modification of the cell's physiology. [28]

The May 2005 proposal still left room for interpretation:

[25] http://pharmacos.eudra.org/F2/advtherapies/Stakehcom2005/Healthcare%20professionals/UK%20National%20Blood%20Service%20and%20European%20Association%20of%20Tissue%20Banks.pdf

[26] http://pharmacos.eudra.org/F2/advtherapies/stakehcom/tissue/pdf13.pdf

[27] http://pharmacos.eudra.org/F2/advtherapies/stakehcom/tissue/pdf19.pdf

[28] similarly: Hospital Clinic of Barcelone; http://pharmacos.eudra.org/F2/advtherapies/stakehcom/tissue/pdf14.pdf

May 2005 proposal Art 2(3):

Engineered human cells or tissues:
Cells or tissues removed from a human donor and manipulated via a manufacturing process, so that their normal biological characteristics, physiological functions or structural properties are substantially altered.

The final proposal, after all, implemented suggestions of diverse stakeholders[29] to set up a list of operations which are regarded as resulting in non-substantially manipulated products. Annex I(1) of the final proposal for a Regulation includes such a list of cell manipulations which are "not considered as substantial manipulations". The exclusion of these manipulations allows for definition of the term engineered and provides legal certainty to tissue establishments and hospitals by exempting the standard techniques applied for organ transplantation purposes from the scope of the Regulation.

Annex I(2) and (3) of the final proposal expand the definition of the term "engineered" by two further alternative components:

Final proposal Annex I:

Cells or tissues shall be considered "engineered" if they fulfil at least one of the following points:
(1) *list of non- substantial manipulations……..*
"(2) The cells or tissues are not intended to be used for the same essential function or functions in the recipient as in the donor;
"(3) The cells or tissues form part of a combined advanced therapy medicinal product."

Provision No (2) limits the field of applications which will be subject to Directive 2004/23/EC respectively national guidelines for transplantation.

Provision No (3) lays down the "lex specialis principle" for a combination of products that belong to different categories of advanced therapy medicinal products.

4.5 Refining the scope of the Regulation

The scope of a Regulation is determined not only by the definition of the subject of the Regulation and its integration into the general legal framework but also by defining conditions for putative exemptions and by providing guidance for the handling of borderline and combination products. During the consultation process, especially the conditions for exemptions from the scope of the proposed Regulation were in the focus of discussion.

4.5.1 *Expanding the scope by deletion of the "h" - from hTEP to TEP*

The proposal for a Regulation on advanced therapy medicinal products explicitly includes cells of animal origin as putative components of tissue engineered products.

[29] e.g. Forum Biotechnology and Genetics of the Netherlands; The Ministry of Health, Welfare and Sport of the Netherlands; Stem Cell Centre, Genua; contributions of the stakeholders are available at the Commission's websites: http://pharmacos.eudra.org/F2/advtherapies/Stakehcom.htm for the 2004 consultation and under: http://pharmacos.eudra.org/F2/advtherapies/Stakehcom.htm for the 2005 consultation.

Previously, xenogeneic tissues intended for human use should not be covered by the regulation due to the enhanced risk potential (e.g. animal pathogen transmission, enhanced immunogenicity). With the onset of the first consultation round there was a discussion how to treat TEPs that have been manufactured with the help of xenogeneic cells (e.g. mouse feeder cells in skin cell expansion for severely burned patients). The use of xenogeneic cells or tissues during manufacturing of cell preparations or tissue like structures should not affect classification of the finished product as TEP as long as xenogeneic materials were not present in the final product (2004 consultation paper). Yet, it will be difficult to make sure that xenogeneic products used during manufacturing will be completely excluded from the final product. Moreover, many products that are currently in development use acellularised dead matrices such as porcine small intestine submucosa or vessels. The May 2005 proposal already introduced a restriction to the exclusion of products containing xenogeneic material: human TEPs might contain xenogeneic cells and tissues which were used as ancillary elements in the manufacture if these were present in the finished product only in trace amounts and without being viable.

The final proposal on a Regulation of TEPs made a further step forward: it included animal derived TEPs into the scope of the Regulation. This expansion came not as a surprise as the technical requirements for somatic cell therapeutic products also include animal derived cells (see Annex IV of 2001/83/EC as amended by Directive 2003/63/EC). The inclusion of xenogeneic tissues and cells is furthermore a logical consequence of the pretension to establish a legal framework that allows for application to future technologies. A broad spectrum of current research activities in the academic and industrial area aims on usage of xenogeneic cells to be manipulated for tissue replacement in humans (e.g. development of acellularized xenogeneic tissue which act as a scaffold for the patient's own cells to regenerate damaged heart valves (Bader et al., 2000); or the encapsulation of xenogeneic cells in semipermeable membranes, capsules, or other devices, that are thought to protect transplanted cells from the immune system of the recipient, e.g. use of microencapsulated porcine islet cells for glucose-dependent insulin production (Schaffellner et al., 2005). Also some biotechnological companies are engaged in this kind of research: e.g. the Australian company CelxCel develops biological heart valve scaffolds from Kangaroo and bovine pericardium which are seeded with human fibroblasts. Several US companies are engaged in development of extracorporal liver systems using pig liver cells for artificial liver support.

Exclusion of TEPs that contain xenogeneic material from the scope of the Regulation due to an enhanced risk conferred by the xenogenic components would have the paradox effect that the products with the possibly highest risk potential would be left to a highly fragmented regulatory environment in the EU – the current setting for human TEPs which has been identified as serious impediment to the development of this innovative technology. This could become a serious obstacle as national expertise in this special area of tissue engineering might be even scarcer as for usage of human cells and tissues. It would furthermore be rather confusing to include xenogeneic living cells into the scope of somatic cell therapy products (see Annex I, Part IV section 2 of Directive 2001/83/EC and GCP Directive 2001/20/EC)[30] but not in the scope of TEPs despite the obvious overlap of both product categories.

[30] The GCP Directive 2001/20/EC considers xenogeneic cell therapeutics as a special case of somatic cell therapeutics. Art 9 (6) of the GCP Directive claims for written approval of clinical trials with these medicinal products before initiation of the trials

4.5.2 *Narrowing the scope by deletion of hospital made one-off products*

The majority of market players in the field of tissue engineering consists of small operators, mainly SMEs and a few hospitals and tissue banks that are engaged in manufacturing of autologous TEPs for skin or cartilage substitution. Any regulation on TEPs might heavily affect these market players. The consultation process reflects this balance act between strengthening of health protection and establishing respectively maintaining a regulatory environment that allows especially the small operators to keep and develop their business.

The discussion is tightly connected to the question if these products will need MA before application to the patient and will therefore be outlined in the chapter on marketing authorisation (see section 4.6). The discussion resulted in the exclusion of custom-made products that are fully prepared and used in a hospital from the scope of Directive 2001/83/EC as laid down by Art 28 of the final proposal. Thereby they are also excluded from the scope of the proposed Regulation on advanced therapy medicinal products as this Regulation will amend Directive 2001/83/EC.

4.5.3 *Expanding the scope by the Lex Specialis principle – combination and borderline products*

Combination with Medical Devices

Any combination of advanced therapy medicinal product and medical device will be assessed according the provisions set by the Regulation if the medicinal product does not have only ancillary function (Art 1(d) and Art 10 of the final proposal on advanced therapy medicinal products). This shall also be the case if the device part has already been assessed by a notified body (Art 10 (2) of the proposal). The Agency has the option but is not obliged to involve the notified body. According to Art 6 of the final proposal, the medical device shall meet the essential requirements laid down in the Annexes to the medical device Directives (see section 4.2). It does not need a CE-certification (see Impact Assessment, 2005; (SEC2005) 1444, Section 8.2.6.).

The final proposal allocates the full decision competence for both components – medical device and cell or tissue – to the Agency. Representatives of the medical device industry criticized these provision as a disregard of the expertise of the notified bodies (Eucomed, 2005 [31]; Gassner, 2005[32]; UK Bioindustry Association, 2005 [33]). On the other side, some stakeholders pointed out, that it would delay the whole procedure for gaining MA if applicants would have to involve a notified body for any medical device component, that has not already been CE-certified. As CE-certification covers only usage of the medical device for a particular purpose, the inclusion of the device into a combination product will often mean loss of the validity of the CE-certificate (see

[31] Eucomed, http://pharmacos.eudra.org/F2/advtherapies/Stakehcom2005/Industry/EUCOMED-Federation%20of%20Medical%20Technology%20Manufacturer-2.pdf

[32] http://pharmacos.eudra.org/F2/advtherapies/Stakehcom2005/Research%20community/Ulrich%20M%20Gassner.pdf

[33] UK Bioindustry Association; http://pharmacos.eudra.org/F2/advtherapies/Stakehcom2005/Industry/BIA-%20UK%20BioIndustry%20Association.pdf

Position paper of Natural Implant, 2004)[34]. The establishment of a one-stop-shop system for combination products might be suitable to confine regulatory burden for the applicant and to tighten the time schedule.

The option to take pattern of the consultation process established for combinations of medical devices and blood derived components has not been taken up. Art 1(4, 4a) MDD puts combination products of medical devices and medicinal products including blood derived and plasma derived medicinal products under the regime of the MDD if the action of the medicinal product derived from human blood or human plasma is ancillary to that of the device. The medicinal product has to fulfil provisions of Directive 2001/83/EC respectively Directive 2000/70/EC. Assessment is performed by national Health Authorities or – in case of blood or plasma derived products – by the Agency. But Authorisation of the combination product – this means CE-certification – is issued by the Notified Body. The result of the assessment by Health Authorities has to be taken into account for the final decision.

The suitability of the consultation model might be questioned as it is based on the medical device character of the combination product. The medicinal product component displays only ancillary function. In case of the combination of medical device and advanced therapy medicinal product the proposal describes just the reverse situation. The essential function of the combination product is a medicinal one and is only supported by the medical device. Whether a notified body has the expertise to assess the supporting function of the medical device as an integral part of the TEP seems rather unlikely due to the high complexity of advanced therapy medicinal products.

Borderline products

If a product falls within the definition of a TEP and of a somatic cell therapy medicinal product it shall be considered as a TEP (Art 2(3) of the final proposal). As it became obvious during the consultation that demarcation of both product categories might cause enormous problems this provision shall help to avoid any discussions on the nature of the products and clarify the legal basis for the assessment procedure which will be essentially similar for both product categories (Impact Assessment, 2005; (SEC2005) 1444;).

4.5.4 *No provision on use of embryonic stem cells*

The final proposal for a Regulation does not authorize for the use of embryonic stem cells. Yet, the proposed Regulation does not declare a total ban on the use of embryonic stem cells for the manufacture of advanced therapies. Art 28(2) puts the final decision on regulation of this issue into national responsibility as there is no European consensus on ethical assessment of use of this cell type.

4.6 Marketing authorisation requirement

As TEPs have been clearly defined as third category of advanced medicinal products the provisions of the pharmaceutical product legislation will fully apply. This means that all

[34] Natural implant, France; http://pharmacos.eudra.org/F2/advtherapies/stakehcom/tissue/pdf9.pdf

TEPs which shall be placed on the market of the European Community have to apply for MA. The MA has to be issued in accordance with Regulation (EC) No 726/2004 of the European Parliament and of the Council as laid down by Directive 2001/83/EC to be amended according Art 28 of the proposed Regulation on advanced therapies.

The principle of a compulsory Community marketing authorisation for all TEPs has been introduced with the May 2005 proposal, together with the decision on amendment of existing categories of advanced therapy medicinal products by a third one. Before coming to this basic decision different ways for obtaining MA for different types of TEPs were discussed.

The initial consultation, launched 2002, resulted in non-uniform responses to the option for national-based or centralized authorisation procedures. Concerns targeted especially the scarce availability of national expertise in the field of tissue engineering and the need for harmonised requirements, practice and post-authorisation controls. On the other hand, some stakeholders stressed expectation of more transparency and less bureaucracy with national procedures.[35]

The majority of market players in the field of tissue engineering consist of SMEs engaged in marketing of autologous TEPs (Bock et al., 2005). In order not to hamper the development of these small operators by establishing new cost and time-intensive regulatory hurdles and to take into account the lower risk potential of autologous products the 2004 consultation paper proposed a two-tier-authorisation procedure:

- autologous products should be assessed and authorised by the relevant national authorities under common guidance.
- allogeneic products should be assessed and authorised by the Community.

The two-tier concept offered clear criteria for the regulatory treatment of special TEPs but also allowed for permeability of the system if this is in the interest of involved parties:

- manufacturers of autologous products should have the possibility to apply also under the centralized procedure.
- national authorities should have the possibility to consult EMEA's scientific body for scientific advice.

Nearly all stakeholders appreciated the transparency of the concept but raised serious concerns focusing on the regulatory handling of in-house products and the risk of evolvement of different levels of competency and safety in the MS.[36]

- From a risk management perspective it does not make sense to treat allogeneic products that are produced individually for a single patient in a different manner as autologous products. Allogeneic products will always bear the risk that unknown pathogeneic factors will be conferred from the donor to the recipient. But standards for the donation, procurement and testing of all human tissues and cells intended for human applications shall minimise the risk of transmission of

[35] see: Summary of responses to the Commission's 2002 consultation paper

[36] for a summary of the discussion see: DG Enterprise consultation „Proposal for a harmonised regulatory framework on human tissue engineered products"; Summary of contributions; http://pharmacos.eudra.org/F2/advtherapies/docs/Summaryofresultsfinal2004.pdf

diseases or any inherited conditions. Furthermore, the major characteristic of any cell and tissue derived product is the manufacturing process. The risk of contamination during manufacturing does not depend on the source of the tissue or cells but on the manufacturing process itself . Therefore risk of contamination is similar for both product types (e.g. Tissue Banc France).[37]

- pharmaceutical batch control for autologous products is virtually impossible due to the intrinsic inter-patient variability and the marked time constraint of many of these individual treatments (e.g. *in vitro* cultivation of skin autografts for burned skin). The requirements of documentation for this type of product cannot be the same as for allogeneic products that are intended to be marketed over longer time periods throughout the Community. Yet, the two-tier approach assigns similar requirements for quality, safety and efficacy for both types of products (e.g. Council of Europe).[38]

- a decentralized approach would force all Member States to build up the infrastructure and expertise for assessment and authorisation of autologous TEPs. This obligation would raise enormous cost and might foster non-transparency and low efficacy of poorly proved national procedures. There is also the risk – despite Community guidance – of evolvement of divergent assessment standards and post-marketing surveillance standards resulting in different health standards in the Community (e.g. Genzyme Europe).[39]

The public consultation round 2004 made clear that the original idea to offer different procedural levels for different products respectively different operators could not be achieved by this model. The great majority of current TEP applications – autologous or dedicated allogeneic cells processed by SMEs or hospitals to be delivered to a pre-determined patient - will not benefit from any authorisation procedure and should consequently be exempted from the scope of the proposal. This suggestion was e.g. raised by the Council of Europe (Comments of the project of a European Regulation on human tissue engineered products, 2004[40]).

Exemption of these in-house products would not mean to surrender them into a regulatory gap as they were covered by the Tissues and Cell Directive 2004/23/EC. All Member States have to set up an accreditation system for tissue establishments and a control system to monitor compliance of these tissue establishments to the provisions of the Directive.

The second proposal of the Commission, published in May 2005 exhibited a pragmatic approach to this issue. Article 1 of the proposal excluded one-off products, which are made "according to a specific and non-industrial manufacturing process, in order to comply with a medical prescription for an individual patient" from the scope of the Regulation. All other TEPs – which were subsumed now to the group of advanced therapy products - would have to apply via the centralized procedure for MA (Art 14 of the proposal).

[37] http://pharmacos.eudra.org/F2/advtherapies/stakehcom/tissue/pdf10.pdf)
[38] http://pharmacos.eudra.org/F2/advtherapies/Stakehcom2005/Regulators/Council%20of%20Europe.pdf
[39] http://pharmacos.eudra.org/F2/advtherapies/stakehcom/tissue/pdf8.pdf
[40] http://pharmacos.eudra.org/F2/advtherapies/stakehcom/tissue/pdf33.pdf

The consultation paper of the 2005 May proposal gave examples for products falling inside or outside the scope of the Regulation:

- A hospital developing an in-house, non-industrial technology based on autologous cells to repair/regenerate cardiovascular tissue for a given patient. This case will not be covered by the Regulation.
- A large operator, developing a product based on autologous cultured chondrocytes , which are manipulated via a well validated and controlled industrial process. This case will be covered by the Regulation.

These examples make clear that there will a broad border between methods involving an industrial process and individual manufacturing protocols that have to take into account specifics of individual cell populations but also have to comply with standard operating procedures of the particular establishment. Compliance with the Tissues and Cell Directive 2004/23/EC necessitates, in general, usage of standardised, reproducible procedures. Almost all tissue engineering activities, whether performed by tissue banks and hospitals or by SMEs and global players, will be based on standardised, reproducible procedures and can be considered as industrial processes[41]. On the other hand some industry associations generally deny that simple cell and tissue preparation techniques like cell propagation with simple equipment should have industrial quality (EuropaBio position paper, 2005).[42]

This ambiguity has also been taken along with the final proposal published in November 2005. This last version has dispensed with an introducing statement on the scope of the Regulation and definition of exclusion criteria but it maintains exclusion of one-off products by laying down the exclusion of these products with Directive 2001/83/EC. The appropriate amendment of Directive 2001/83/EC is projected by Art 28 of the proposed Regulation. Any advanced therapy product, "which is both prepared in full and used in a hospital, in accordance with a medical prescription for an individual patient" will not be covered by Directive 2001/83/EC. This provision fully addresses characteristics of manufacturing but leaves out the source of the cells (autologous or allogeneic) as a criterion for application of the Regulation as this proved not to be appropriate for TEPs and has never been applied to somatic cells and genetically manipulated cells.

In addition, the provision makes clear that only custom-made products that are prepared by hospitals will be exempted from the requirement of obtaining MA.

4.7 A new body within the EMEA for TEPs

The lay-out of the evaluation procedure for advanced therapy medicinal products (Art 9 of the final proposal) implies that a new committee will have to be established at the EMEA: The CHMP shall consult the Committee for Advanced Therapies (CAT) on any scientific assessment of advanced therapy medicinal products necessary to draw up the scientific opinions issued by the CHMP. At present, only four committees have been established at the EMEA: the CHMP, the CVMP, the Committee on Orphan Medicinal

[41] MHRA, UK; http://pharmacos.eudra.org/F2/advtherapies/Stakehcom2005/Regulators/MHRA%20UK.-%20Medicines%20and%20Healthcare%20products%20Regulatory%20Agency.pdf

[42] EuropaBio; http://pharmacos.eudra.org/F2/advtherapies/Stakehcom2005/Industry/EuropaBio-European%20Association%20for%20Bioindustries-2.pdf

Products and the Committee on Herbal Medicinal Products, as laid down by Art 56 (1) of Regulation (EC) 726/2004. The CAT would have to be established as fifth committee at the EMEA.

The main task of the CAT will be to advise scientifically on any data related to advanced therapy medicinal products. The CHMP retains responsibility for the final scientific opinion.[43]This type of allocation of graded responsibilities to different bodies of the EMEA reminds of the relationship of the Committees and their scientific advisory groups as provided by Art 56(2) of Regulation (EC) 726/2004. This provision allows for the establishing of scientific advisory groups to which the CHMP may delegate certain tasks associated with drawing up the scientific opinions of the CHMP.

The May 2005 proposal still outlined that the CAT will be composed of 5 representatives of the CHMP, one representative of each MS, not represented by the CHMP delegates[44], and four representatives of the public appointed by the Commission (2 surgeons and 2 representatives of patient associations). The rapporteur or co-rapporteur, appointed by the CHMP, should be member of the CAT and act as rapporteur or co-rapporteur in the CHMP and in the CAT. The result of the evaluation process that has been performed by the CAT is given to the CHMP as an advice. If this advice is not in accordance with the opinion drawn up by the CHMP ground for differences should be outlined by the CHMP in the Annex.

The May 2005 proposal still displayed some features that implied a stronger position of the CAT as provided by the final proposal: e.g. the selection of the rapporteur was due to the CHMP, the selection of the co-rapporteur to the CAT; tasks of the CAT should be to assess data and to formulate an opinion.

Based on the May 2005 proposal some stakeholders recommended to strengthen the position of the CAT. The BPI recommended allowing for rapporteurship of any member of the CAT to avoid an overcharge of the 5 representatives that have to be members of the CHMP and of the CAT. The excessive workload could impact the time-lines.[45] Eucomed proposed the CAT to be a committee independent from the CHMP or, as less preferred option, to limit CHMP members within the CAT to one representative in order to advance the character of the CAT as a body of experts.[46] EuropaBio suggested that the CAT should formulate a draft opinion in accordance with Art 5 of Regulation (EC) 726/2004 and the CHMP should decide to endorse it or not.[47] However, none of these recommendations was implemented by the final proposal. This implies that the European Commission aims on confirmation of the leading function of the CHMP and only supporting function of the CAT.

[43] Explanatory Memorandum of the final proposal for a Regulation on advanced therapy medicinal products

[44] The PEI considered the delegation of representatives of the MS not to be necessary, as final evaluation will be performed by the CHMP, but this recommendation was not taken into account. http://pharmacos.eudra.org/F2/advtherapies/Stakehcom2005/Regulators/Paul%20Ehrlich%20Institut.pdf PEI 2005

[45] Position paper of the BPI – Bundesverband der Pharmazeutischen Industrie, Germany: http://pharmacos.eudra.org/F2/advtherapies/Stakehcom2005/Industry/BPI-German%20Pharmaceutical%20Industry%20Association-2.pdf

[46] Eucomed, http://pharmacos.eudra.org/F2/advtherapies/Stakehcom2005/Industry/EUCOMED-Federation%20of%20Medical%20Technology%20Manufacturer-2.pdf

[47] EuropaBio; http://pharmacos.eudra.org/F2/advtherapies/Stakehcom2005/Industry/EuropaBio-European%20Association%20for%20Bioindustries-2.pdf

Clearing house function

During the consultation process the establishment of a European body that would advice on the classification of borderline products (Clearing house function), analogous to the TRG in the US, has been subject of the discussion. Some stakeholders wanted this function to be allocated at the CAT (Eucomed[48], EuropaBio[49]), others preferred an independent body. The final proposal addressed this issue in Art 18, providing for "scientific recommendation on advanced therapy classification". The applicant may contact the Agency for product classification. The Agency shall consult the Commission before delivery of the recommendation. The proposal does not say anything about involvement of the CAT. Similarly, scientific advice and certification of quality and non-clinical data (submitted independent of application for a MA) are put into the responsibility of the Agency.

4.8 Which data are needed for MAA?

Applicants for MA will need exact definition of documentation requirements. The final proposal takes reference to requirements defined for products authorised via the centralized procedure. Specific requirements shall be laid down in Annex I of Directive 2001/83/EC. For the related product groups, somatic cell therapy and gene therapy medicinal products, particular requirements for analytical, pharmacotoxicological and clinical standards and protocols have already been laid down in Annex I, Part IV of Directive 2001/83/EC. The Annex needs an amendment specifying technical requirements for TEPs. These might partly overlap with those for other cell based therapies and might require also changes to the provisions. They will have to consider putative interactions of cells and non-cell components of TEPs. The legal provision for this amendment is defined by Art 8 of the final proposal. A concept paper for setting up a new guideline for human cell-based medicinal products to replace the existing CPMP document on somatic cell therapy (CPMP/BWP/41450/98) has recently been issued.[50]

As for somatic and for gene therapy medicinal products, conventional non-clinical pharmacology and toxicology studies may not be relevant for TEPs. Non-clinical testing is limited by the availability and relevance of animal models, especially for autologous treatments.[51] Quality control tests like tests for sterility or mycoplasma assays are not easily to apply to TEPs as required incubation periods will extend beyond the shelf life of many TEPs.

The principles of Good Clinical Practice laid down by Directive 2001/20/EC apply to all medicinal products authorised within the Community and should in principle be fully applicable to all advanced therapy products incl. TEPs. Yet, clinical testing procedures will need adaptation to specific needs of TEPs. Art 4(2) of the proposed Regulation mandates the Commission to amend Directive 2005/28/EC which lays down principles

[48] Eucomed, http://pharmacos.eudra.org/F2/advtherapies/Stakehcom2005/Industry/EUCOMED-Federation%20of%20Medical%20Technology%20Manufacturer-2.pdf

[49] EuropaBio; http://pharmacos.eudra.org/F2/advtherapies/Stakehcom2005/Industry/EuropaBio-European%20Association%20for%20Bioindustries-2.pdf

[50] Concept Paper on Guideline for human cell-based medicinal products, published 26 Jan 2006, to replace guideline CPMP/BWP/41450/98

[51] Natural implant, France; http://pharmacos.eudra.org/F2/advtherapies/stakehcom/tissue/pdf9.pdf

for GCP implementation. And Art 4(3) amends this order by the request for drawing up of detailed guidelines on GCP for advanced therapy medicinal products.

Usually the assessment of clinical trial data relies on evidence-based criteria and pertains to the creation of an adequate statistical basis. Tissue engineering typically is a customized process directed towards individual patients or a rather small number of patients. Efficacy criteria will have to be adapted to this situation and might take pattern from current procedures for orphan drugs.

In order to apply similar evaluation procedures for clinical trial applications to all categories of advanced therapy medicinal products, Art 4(1) of the proposed Regulation declares applicability of those provisions of Directive 2001/20/EC that refer to gene therapy and somatic cell therapy medicinal products also to TEPs. These are:

- Article 6(7) that allows for extension of the review time by the ethics committee from 60 to 90 days and option for extension by further 90 days for gene therapy and somatic cell therapy products.
- Article 9(4) lays down the corresponding expansion options for evaluation time periods by the competent authorities of the Member States.
- Article 9(6) lays down the requirement for written authorisation before commencing clinical trials involving medicinal products for gene therapy and somatic cell therapy.

For more specific requirements, the CHMP has already adopted guidance documents for somatic gene therapy products and xenogeneic cell therapy medicinal products. These guidance documents now shall be revised to better reflect the heterogeneity of cell-based drugs and address also particularities of TEPs. A concept paper on a guideline for quality, non-clinical and clinical requirements for human cell-based medicinal products has been issued in January 2006. Any quality guidelines will have to be in line with GMP acc. Art 5 of the final proposal but will need some adaptation.[52]

On one hand the scale of putative hazard caused by a TEP might be rather small compared to the mass produced conventional medicinal products or medical devices. On the other hand TEPs might cause a new quality of risk due to putative unexpected interactions of living cells with substrates and biomolecules which may not be easy to foresee (see also Impact Assessment, 2005; (SEC2005) 1444, No 8.2.3.1: “association with the device can significantly influence the properties of the cells and the overall safety of the product”). This risk potential is separate from risks mediated by somatic therapy, gene therapy or xenogeneic cell therapy products as only TEPs are based on the interaction of tissue cells and supporting non-tissue structures. A common guideline for the non-clinical and clinical development of all advanced therapy products will have to consider this speciality of TEPs.

[52] for example see: Centro Nazionale Trabianti; http://pharmacos.eudra.org/F2/advtherapies/Stakehcom 2005/Healthcare%20professionals/Centro%20Nazionale%20Trapianti.pdf

4.9 Traceability and risk-assessment

The requirement for establishing a system that allows for long-term traceability from the source cells to the patient has always been accepted by all stakeholders in the consultation process. Such a provision has also been installed by the Tissue and Cells Directive 2004/23/EC. Art 8(1) of this Directive determines that „Member States shall ensure that all tissues and cells procured, processed, stored or distributed on their territory can be traced from the donor to the recipient and vice versa." A donor identification system shall assign a unique code to each donation and to each of the products associated with it (Art. 8(2)). Data required for full traceability shall be kept for a minimum of 30 years after clinical use (Art. 8(4)).

The May 2005 proposal on advanced therapies assigned all responsibility for this system to the MA holder. This has been criticized due to data protection reasons and due to the fact that the manufacturer of a TEP often does not have access to patient's data. These data are only available to the hospital or institution that is in charge of isolation of the cells and infusion or transplantion to recipients.[53]

The final proposed Regulation takes account of these considerations and breaks down responsibility to manufacturers and hospitals. The MA holder has to establish a system of full traceability from sourcing till delivery to the hospital, institution or private practice where the product is used. The hospital, institution or private practice shall establish and maintain a traceability system for the patient and the product (Art 16 of the final proposal).

A further requisition regarding safety of advanced therapy medicinal products is the requirement of a post-authorisation risk management system designed to identify, prevent or minimise risks including an evaluation of the effectiveness of that system. The design of the risk management system has to be provided with the marketing authorisation application. The evaluation of the effectiveness as well as putative specific post-marketing studies shall be included in the PSUR (Art 15 of the final proposal). The requirement of including a description of a risk-management system to be introduced by the applicant in the marketing authorisation application has also been laid down by Directive 2001/83/EC, Art 8(3) No (ia). The restriction "where appropriate" is missing in the final proposal. Obviously, setting up of such a system is considered to be indispensable due to the high risk potential of TEPs. Presentation of risk-benefit data of the medicinal products as part of the PSUR is also common practise.

4.10 Incentives

The final proposal includes a separate chapter titled "Incentives". It comprises 3 Articles:

- Art 17 on scientific advice
- Art 18 on scientific recommendation on advanced therapy classification
- Art 19 on certification of quality and non-clinical data

[53] EuropaBio; http://pharmacos.eudra.org/F2/advtherapies/Stakehcom2005/Industry/EuropaBio-European%20Association%20for%20Bioindustries-2.pdf

Art 17 provides for a 90% fee reduction for scientific advice (7.000 EUR instead of 70.000 EUR).[54] Art 18 and 19 introduce two items that have not been addressed in European legislation before:

- a clearing house function for borderline products will be established in analogy to the function of the TRG in the US. Like in the US, a list of recommendations shall be published for information.

- Evaluation and certification of quality and non-clinical safety data in advance to an application for MA. This might provide for reduced approval times of future applications, based on the same data, and shall strengthen the marketing position of companies that are not interested in clinical development of the products but will sell them to third parties.[55]

4.11 Transitional period

Art 29 of the final proposal addresses the problem of grandfathering of existing products. The final proposal is granting a transitional period of 2 years after entry into force for TEPs that are currently marketed in accordance with national or Community legislation. Compared to the May 2005 proposal that offered 3 years as transition time this is a very strict time schedule. Stakeholders pleaded for a more expanded transitional period especially as many guidelines that will define data requirements for application for marketing authorisation have still to be published.[56]

5. Discussion

The initial objective of the proposal was the establishment of a harmonised European framework for TEPs that would be appropriate to fill the regulatory gap for this type of product. During the consultation process the proposal changed to a legal framework for advanced therapy medicinal products comprising not only TEPs but also somatic cell therapy and gene therapy medicinal products. Four key objectives to be fulfilled by the final proposal were outlined by the Commission:

1. to provide a high level of health protection
2. to harmonise market access
3. to provide overall legal certainty
4. to foster the competitiveness of European undertakings

As outlined in the chapters above the final proposal was the result of an intensive consultation process involving representatives of national authorities, industry, tissue establishments, healthcare professionals, research communities, patient interest groups and ethics related organisations. Interests of these diverse stakeholders are often contrary and some parties will benefit from provisions that might become a disadvantage for others. The Commission pursued with the proposal a pragmatic

[54] Numbers cited in: Impact Assessment of the Commission; (SEC2005) 1444
[55] Impact Assessment of the Commission; (SEC2005) 1444
[56] BPI: http://pharmacos.eudra.org/F2/advtherapies/Stakehcom2005/Industry/BPI-German%20Pharmaceutical%20Industry%20Association-2.pdf

approach. As it became obvious that TEPs share significant properties with medicinal products the Commission decided to amend existing legislation for medicinal products instead of setting up a separate legal framework for TEPs.

However, tissue engineering is still in its infancy and subjection under a legal framework that has been designed for an established industry might bear a risk of overregulation for this young discipline.

5.1 High level of health protection

Provisions of Directive 2001/83/EC and Regulation (EC) No 726/2004 proved to be appropriate to secure a high level of health protection in the EU. These provisions are fully applicable to advanced therapy medicinal products. As these products are derived from human or animal tissues they bear a high risk of transmitting communicable diseases or to transfer infectious agents to the patient due to bacterial or fungal contamination during manufacturing. Therefore additional provisions for traceability – similar to the provision for blood and blood derived products – have been set up. The model of shared responsibility of the TEP producing company and the hospital that is in charge for application of the TEP to the patient limits obligations of the manufacturer who already has to fulfil requirements of Directive 2004/23/EC.

5.2 Harmonisation of market access

As the new regulatory framework for TEPs is embedded in the legal construct of a regulation it will become binding law in all Member States and does not need – or does not allow for – transformation into national law. Therefore the regulatory handling of any TEP should be identical in each European country. Establishment of a European body for assessment of marketing authorisation applications secures adherence to predetermined procedures and time frames independent of the availability of national experts. From a legal point of view there should be no hurdle to pan-European marketing of TEPs and pan-European accessibility of innovative products to the patient.

However, the question if a product is put on the market does not only depend on the provision of an appropriate regulatory environment, but also on the possibility to sell the product and have a return for the investment. As long as the reimbursement situation has not been tackled companies – SMEs and big players – will hesitate to make big investments in this technology at all or at least to offer products in markets where they are not reimbursed. Harmonised access of patients to this technology will therefore need measures that expand the improvement of the regulatory situation.

Another aspect jeopardizing the harmonisation of market access has been scrutinized during the EuropaBio Industry Hearing.[57] The Directive 2004/23/EC regulates donation, procurement and testing of the source cells for TEPs. Art 152 of the Treaty allows Member States to add extra measures on top of that. This means that access to the primary materials of TEPs will remain in the disposition of the MS: A similar problem might arise from the decision of the Commission to leave "the application of national legislation prohibiting or restricting the use of any specific type of human or animal cells" unaffected by the Regulation of advanced therapy medicinal product (Art 28(2) of

[57] Objection raised by N. Veulemans, TiGenix; Report of the EuropaBio Industry Hearing, 2005.

the final proposal). This could impede harmonisation of the market for products that contain embryonic stem cells. On the other side, it would hardly be possible to achieve adoption of a European framework that would generally allow for usage of embryonic stem cells.

5.3 Legal certainty

The decision to bring together all therapies using living cells, which have been substantially manipulated, under the same legal umbrella makes sense as these products share similar characteristics, a similar risk potential, and similar market features.

The legal character of the final proposal – a Regulation – is an appropriate instrument to implement the legal framework as rapidly as possible as no transformation into national law is required. The layout of the new regulation as amendment to existing regulations will accelerate the approval process and reduce the time till the proposal will become law.

Crucial for the question whether the proposed regulation will be an appropriate instrument to fill the current gap in the regulatory environment will be

- if the subject and scope of regulation has been clearly defined.
- if the handling of borderline and combination products has been addressed in a way, that classification is transparent and predictable.
- if the conditions to be fulfilled for market entry and post-market surveillance are clearly defined and if transparency of the procedure and a predictable time schedule are provided.

5.3.1 *Definition of TEPs and scope of the Regulation*

Definition of TEPs

As outlined in sections 4.4.1 and 4.4.2 the main problem for definition arose from a putative overlap of TEPs with somatic cell therapy products and tissue and organ transplants that shall not be changed in their physiology by any manipulation steps before transplantation to the recipient. Compilation of a list with non-substantial manipulations in Annex I of the final proposal seems to be a suitable measure to distinguish TEPs from tissue and organ transplants. Formulation of exclusion criteria should be more useful than compiling a catalogue of substantial manipulations due to the rapid development in this innovative sector.

Demarcation from somatic cell therapy seems rather difficult based on the definition of the final proposal. Many contributions of the 2005 consultation round criticized that there is still no clear distinction between TEPs and somatic cells.[58] The fruitless struggle

[58] Agence Biomedicin France; http://pharmacos.eudra.org/F2/advtherapies/Stakehcom2005 /Healthcare%20professionals/Bernard%20Loty-%20Agence%20de%20Biom%E9decine.pdf; Spanish Agency of Medicines and Medical Devices, http://pharmacos.eudra.org/F2/advtherapies /Stakehcom2005/Regulators/Agemed%20Spain%20-%20SPANISH%20AGENCY%20OF%20 MEDICINES%20AND%20MEDICAL%20DEVICES.pdf;
BPI: http.//pharmacos.eudra.org/F2/advtherapies/Staehcom2005/Industry/BPI-German%20Pharmaceutical%20Industry%20Assocaition-2.pdf

for a better definition shows both product categories share so many properties that separation into two different product categories seems to be an academic exercise and does not confer any benefit for the regulatory handling of these products.

The description of the composition of TEPs lays down that only products that contain cells or tissues – viable or non-viable – are considered as TEPs. This means that derivatives of cells or tissues that do not contain engineered cells or tissues at the end of the manufacturing procedures are not covered by the definition. They would be covered by Directive 2004/23/EC, but this does not provide for safety, efficacy and quality of the final substantially manipulated product. The Ministry of Health of the Netherlands proposed to amend the definition: "human tissue engineered products are derived from living cells with the final product containing viable or non-viable cells or no cells at all".[59]

Scope of the Regulation

Inclusion of TEPs that include xenogeneic cells or tissues is a necessity due to ongoing research in this area. It would not make any sense to delay the decision on regulatory requirements for this product group as the lack of a regulation would produce similar legal uncertainty and fragmentation as it is currently the case for all TEPs. Inclusion is also a logical consequence of the establishment of one common subgroup for all cell-based therapies as xenogeneic cells had already been included in the scope of somatic and gene therapy medicinal product regulation.

One of the most discussed issues expanding the presentation of the final proposal is the exclusion of any advanced therapy medicinal product "which is both prepared in full and used in a hospital, in accordance with medical prescription for an individual patient." (Art 28(1) of the final proposal).

The exclusion aims on avoiding unnecessary burden from institutions that are considered to act on a non-profit base and that do not offer their products on the market. Usually, they act locally and are not interested in expanding their business to other sites and even not to other countries. Imposing regulatory requirements of the final proposal to these institutions would obviously mean an overburden that could cause the hospitals to stop this service. This is not in the interest of improving public health.

However, from a scientific point of view it is hardly to explain why an autologous tissue culture which is prepared in the hospital will be regulated by Directive 2004/23/EC and the same tissue culture prepared by a SME will be subject to the new regulation. One of the main objective of the new regulation, to provide a high level of health protection, will be questioned by this measure. Both products carry the same risk but only the product which is manufactured by the SME will be assessed and authorised by the European authorities. If the product is considered to confer only low risk – due to the autologous character – that will be sufficiently addressed by the provisions of Directive 2004/23/EC it is hardly to justify why one product needs manufacturing authorisation and marketing authorisation before applied to the patient and the other product needs only the manufacturing authorisation. The exclusion seems to be a political decision and will for sure cause a lot of discussions and objections.

[59] Ministry of Health, NL; http://pharmacos.eudra.org/F2/advtherapies/Stakehcom2005/Regulators/Dutch%20Ministry%20of%20Health.pdf

Furthermore, questions arise which sceneries might be covered by the exemption:

- Will exemption apply to hospitals that prepare the TEP for an individual patient but implantation is done by another hospital – Art 28 of the final proposal only says "in a hospital", not "in the same hospital"?
- How will those TEPs be regulated that are prepared and used in a hospital but the manufacturing is performed by a private company that might be associated with the hospital and uses laboratories within the hospital?

- What about TEPs that are manufactured by TPMs but the responsibility for the final product remains with the hospital by contractual agreement?

- What about tissue engineering in hospitals that are owned by private investors and aim on achieving profits? End of 2006 there was the first example of a university hospital that has been acquired by a private corporation in Germany.

Adherent to these questions is another question: Will the fact that the manufacturer of a TEP is a hospital override the fact that the TEP is manufactured by industrial processes?

5.3.2 *Borderline products and combination products*

The principles of subsidiarity have been clearly defined. The difficulty to distinguish somatic cell therapy medicinal products and TEP has already been discussed but should not give rise to any regulatory gap.

Art 2(1d) of the final proposal stipulates subjection of combination products of medicals devices and advanced therapy medicinal products to the scope of the proposed Regulation as long as the medical device is an integral part of the combined product and does only fulfil ancillary function. This provision should mediate rather comprehensive guidance for combination products. However, repeated discussions on classification issues for particular borderline products between medicinal products and medical devices show that this question cannot be finally addressed and needs case by case decisions.

The setting that a medical device fulfils essential function and tissues or cells of human or animal origin fulfil ancillary function has not been addressed by the final proposal. This situation is also not covered by Directive 93/42/EEC as Art 1(5f and 5g) exclude products that contain human or animal derived (living) cells or tissues from the scope of the Directive.

5.3.3 *Conditions for market entry and post-market surveillance*

Marketing authorisation

Setting up of the new regulation as amendment to the existing medicinal product legislation – Directive 2001/83/EC and Regulation (EC) No. 726/2004 – clearly determines conditions for the market entry of advanced therapy medicinal products: no product might be placed on the market unless a marketing authorisation has been issued by the national authorities or by the Commission (Art 6(1) of Directive 2001/83/EC).

Exclusion criteria as defined by Art 3 of Directive 2001/83/EC also apply, the most important one might be exclusion of medicinal products that are intended for research and development trials.

Additionally, the final proposal lays down exclusion of hospital-made customized products from the scope of the regulation and therewith from the obligation to apply for MA. Problems inherent to this provision have already been discussed above.

Data sets to be provided for marketing authorisation application of TEPs will depend on the elaboration of particular technical requirements that will come as an amendment to Annex I Part IV of Directive 2001/83/EC and might require changes to the existing provisions on somatic cell therapy medicinal products. Furthermore, adaptation of GMP and GCP guidelines will be required. Setting up and adoption of amendments or revisions of existing Directives and guidelines or of new guidelines will need time. Taking this into account a transitional period of 2 years (Art. 29) of the final proposal seems rather ambitious.

Safety requirements – traceability and risk management

Provisions for traceability and risk management take pattern from similar provision for other medicinal products and do not come as a surprise. Claiming the establishment of a post-authorisation risk management system by the MA-holder could cause problems as patient-specific data are only accessible to the hospitals. This fact has been taken into account for regulating traceability. It might be necessary to involve the hospitals not only in traceability but also in setting up of a risk management system.

Transparency of procedures

The final proposal gives a rough description of tasks taken over by the CHMP and by the CAT. The Commission could not win through to a separate competent body beside the CHMP but left final responsibility for any decision with the CHMP. Considering the limited tasks of the CAT and the strong influence of the CHMP on its composition, it might provide more transparency to dispense with the establishment of a new Committee with rather imprecise allocation of tasks and to delegate the advisory function to a scientific advisory group in line with Art 56(2) of Regulation (EC) 726/2004.

From a practical point of view it might be unfavourable to confine the possibility of a rapporteurship to those five CAT members that are also members of the CHMP. This might lead to overburden of these representatives and jeopardize the maintenance of time schedules.[60]

The final proposal does not claim special expertise of the CAT members in the field of advanced therapy medicinal products. The Committee will only be able to deliver scientific input if selected representatives are experts in this field.

[60] See comments of the BPI: http://pharmacos.eudra.org/F2/advtherapies/Stakehcom2005/Industry/BPI-German%20Pharmaceutical%20Industry%20Association-2.pdf

The final proposal announces specific procedures for the evaluation of data submitted by the applicant. 270 days for evaluation of marketing authorisation applications might be too long for products that have only days, weeks or few months of shelf life. Constructs like PMF or VAMF could serve as a model for appropriate provisions.

5.4 Fostering competitiveness of European companies

Bigger companies are assumed to be familiar with regulatory requirements and procedures and to have sufficient financial and personal resources at their disposal to fulfil the provisions set by the new regulation. They will benefit from harmonised conditions for market entry throughout Europe as they will not need any more local specialists who know the country specific requirements. They do not longer have to prepare individual data packages for each European country and enter into negotiations with each national Health authority. Market entry barriers for global players will become much lower causing increased competition within the national markets. In the short term, patients might benefit from improved accessibility of TEPs and possibly from lower prices. But, in the medium and long term the growing presence of big players in national markets could become a serious threat to the diversity and innovative force of the current market.

The majority of market players in the field of tissue engineering consist of small operators, mainly SMEs, hospitals, tissue establishments and universities. Generally, medicinal products which are intended for research and development are not in the scope of medicinal product legislation. Universities and research driven hospitals will not be affected by the new Regulation. As revealed by the Commission's research report (Bock et al., 2005) tissue establishments currently are not engaged in production of TEPs. But for SMEs and treatment-driven hospitals the new Regulation will present a real challenge.

Operators will be obliged to establish standards for safety, quality and efficacy and for post-authorisation vigilance even for those low-risk products which they currently market without MA. In many countries, e.g. Germany, low risk-products like autologous skin or cartilage transplants need only a manufacturing authorisation for being applied to the patient. Manufacturing and marketing of autologous products has been the entrance gate for small start up-companies into the business. Revenues could be used for investments in R&D with the option to broad the product portfolio and to expand the business beyond national frontiers. To cope with the new requirements some companies might be obliged to shift investments from R&D to establishment of quality systems and setting up of product dossiers to be submitted to the EMEA for gaining marketing authorisation. Forced investment in the "bread and butter" business might be a kick-down factor for further development of some small companies and cause them abandoning the business or purchasing it to other market players or to merge to bigger units.

The consolidation of the market might enhance the over-all profitability of the business and improve the general goodwill for investments into this technology. But in some cases the knock-out of a company might be associated with loss of promising research activities. This will in the long run impede the innovative force of this new technology.

Setting up of high regulatory hurdles might also impair further evolvement of the start-up scene in this sector. Many undertakings originate from scientists that have long been associated with universities before taking over the risk to enter the market as a private company. The step from research to practice will now afford much more capital and administrative and strategic know-how. This could mean an overburden to many start-ups.

The Commission provided for a range of incentives that are intended to support efforts to arrange with the new legislation. These incentives are an add-on to incentives and competitiveness-related provisions which are already laid down in existing Community legislation (e.g. designation as orphan medicinal product, fast-track approval, or conditional marketing authorisation). Special incentives for advanced therapy medicinal products comprise financial benefits like fee reduction for scientific advice of 90 % - independent of the economic size of the applicant -, or waiver of fees for an application for MA, if the application fails – this makes up 232.000 EUR [61] -, scientific support for classification of the product and certification of quality and non-clinical data, independent of an application for a MA. The latter offer is a true innovation and could indeed be very interesting for research-based companies or hospitals that do not want to promote their development candidates into the clinic but want to purchase them to bigger players for further development. They might indeed achieve better prices if they can back the quality of their products on EMEA certificates.

Any benefits for companies regarding scientific advice, data protection or market exclusivity are granted in connection with application for MA. Yet, till this point is reached manufacturers of advanced therapy medicinal products will have to adapt their internal systems to new requirements. And new chances will not always offset the compliance costs.

[61] numbers excised from the Impact assessment (SEC2005) 1444

6. Conclusion and outlook

The decision to subsume the products of all therapies that are backed on usage of living cells, namely gene therapy, somatic cell therapy and tissue engineering products, under one common framework allowed for a pragmatic approach to the regulation of TEPs. Redrafting of existing provisions was not necessary and the new framework can take reference to the well proved regulatory framework for medicinal products.

The proposal still contains a range of items that have been heavily discussed and for which the discussion is still ongoing. But it is important to proceed with this approach in order not to loose further ground to non-European competitors.

The final proposal will be delivered to the European Parliament and to the council for co-decision. In parallel it will be submitted to the European Economic and Social Committee and to the Committee of the Regions, for consultation. The whole decision process will take further 1 or 2 years. This time should be used for working out technical requirements and amending guidelines.

7. Summary

Tissue engineering is an innovative approach in the field of regenerative medicine. Principles of life sciences and engineering are applied to create biological substitutes that are functionally, structurally and mechanically equal or better than the tissue that is to be replaced. A range of tissue engineered products (TEPs) are already on the market for the treatment of skin, cartilage and bone diseases. Products of higher complexity like blood vessels, heart valves, nerve tissues or artificial livers are in the pipeline.

TEP-sales could not fulfil high-flying market projections. Only few TEPs have reached the market during the last years and existing TEPs have not achieved broad acceptance in clinical practice. The European Commission identified the lack of a pan-European regulatory framework covering TEPs as one of the main hurdles for a rapid progression of this technology in Europe. Therefore they initiated a public consultation round to stipulate the regulatory principles of such a framework and work out provisions regulating market access and post-marketing requirements.

The first approach, published 2002, favoured a self-standing regulatory framework for TEPs, separate from the medical device and medicinal product legislation. But in the course of the discussion on appropriate definition for TEPs and the scope of a TEP-regulation it became obvious that there is a broad overlap with existing legislation for tissues and cells regulated by Directive 2004/23/EC and somatic cell therapy medicinal products regulated by Directive 2001/83/EC. In order to avoid any re-drafting of already-existing and proved concepts the final proposal for a regulation on TEPs was absorbed by an integrated approach addressing all advanced therapies - gene therapy, somatic cell therapy and tissue engineering - in one single framework.

The new regulatory framework will come as a regulation amending the Directive 2001/83/EC and the Regulation (EC) 726/2004. The latter one sets the framework for achieving marketing authorization for TEPs. The previous concept of national marketing authorisation for autologous products and European marketing authorisation for allogeneic products has been abandoned in favour of a centralized procedure for all TEPs as this has already been the case for gene therapy and somatic cell therapy medicinal products. This approach takes into account that the risk potential of TEPs is not only determined by the source of the cells, but also by the manufacturing process and the performance of the finished product. Therefore all types of TEPs should be assessed and approved via the same procedure. The centralized approach should further secure availability of high level expertise for this kind of products as national expertise is rather scarce in this field. Directive 2001/83/EC will lay down the basic commitment of TEPs as a third category of advanced therapies. Annex I will have to be amended to specify technical requirements for TEPs.

The new regulation on advanced therapy medicinal products provides a rather clear definition of TEPs by separating them from those tissues and cells that have not been substantially manipulated and that are covered by Directive 2004/23/EC. This Directive will only apply to TEPs as far as donation, procurement and testing are affected. The new regulation does not provide a clear demarcation from somatic cell therapy products but aims on avoiding borderline products by subjecting them to the TEP provisions. Xenogeneic tissues and cells have been included into the definition for TEPs to cover also future product developments incorporating animal derived source cells.

The exclusion of advanced therapy medicinal products which are both prepared in full and used in a single hospital, in accordance with a medical prescription for an individual patient, might give rise to further discussion. Exemption of hospitals but not of SMEs from the obligation to apply for marketing authorisation for custom-made one-off products could lead to regulatory overburden of the SMEs.

The proposal for a Regulation on advanced therapy medicinal products provides legal certainty to all players in the field and secures a high level of health protection to the patients based on the applicability of proven principles of the Community legislation on medicinal products. The regulation might cause a consolidation of the tissue engineering sector that in the long run might foster competitiveness of the European market players.

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9. Annex

9.1 Legal provisions of the EU, the MS and US provisions

(listed in the order of release)

EU

Council Directive 90/385/EEC of 20 June 1990 on the approximation of the laws of the Member States relating to active implantable medical devices (AIMD)

Council Directive 93/42/EEC of 14 June 1993 concerning medical devices as amended by Directive 98/79/EC, Directive 2000/70/EC, Directive 2001/104/EC and Regulation (EC) No 1882/2003

Directive 98/79/EC of the European Parliament and the Council of 27 October 1998 on in vitro diagnostic medical devices (IVDD)

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

EMEA CPMP Document, 31 May 2001. Points to consider on the Manufacture and Quality control of Human Somatic Cell Therapy Medicinal Products (CPMP/BWP/41450/98)

Directive 2001/83/EC of the European Parliament and of the Council of 6 November 2001 on the *Community code relating to medicinal products for human use*, as amended by Directive 2002/98/EC, Directive 2003/63/EC, Directive 2004/24/EC and Directive 2004/27/EC

Directive 2001/20/EC of the European Parliament and of the Council of 4 April 2001 on the approximation of the laws, regulation 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

Directive 2003/63/EC of 25 June 2003 amending Directive 2001/83/EC of the European Parliament and of the Council on the Community code relating to medicinal products for human use

Regulation (EC) No 726/2004 of the European Parliament and of the Council of 31 March 2004 laying down "Community procedures for the authorisation and supervision of medicinal products for human and veterinary use and establishing a European Medicines Agency"

Directive 2004/23/EC of the European Parliament and of the Council of 31 March 2004 on setting standards of quality and safety for the donation, procurement, testing, processing, preservation, storage and distribution of human tissues and cells

Directive 2004/27/EC of the European Parliament and of the Council of 31 March 2004 amending Directive 2001/83/EC on the Community code relating to medicinal products for human use

Commission Directive 2005/28/EC of 8 April 2005 laying down principles and detailed guidelines for good clinical practice as regards investigational medicinal products for human use, as well as the requirements for authorisation of the manufacturing or importation of such products

Concept Paper on Guideline for human cell-based medicinal products, published 26 Jan 2006, to replace guideline CPMP/BWP/41450/98

Commission Directive 2006/17/EC of 8 February 2006 implementing Directive 2004/23/EC of the European Parliament and of the Council as regards certain technical requirements for the donation, procurement and testing of human tissues and cells

MS

Human Tissue Act 2004, 2004 Chapter 30 (UK)

German Medicines Act (AMG), 14th Amendment, 1 December 2005

US Regulations

Section 361 of the PHS Act; Public Health Service Act, effective 1999, 42 U.S. Code Section 264.

64 FR 52696, September 30, 1999; Suitability Determination for Donors of Human Cellular and Tissue-Based Products

66 FR 1508, January 8, 2001; Current Good Tissue Practice for Manufacturers of Human Cellular and Tissue-Based Products; Inspection and Enforcement

66 FR 5447, January 19, 2001; Human Cells, Tissues, and Cellular and Tissue-Based Products; Establishment Registration and Listing

Code of Federal Regulations 21 CFR Part 1271, "Human Cells, Tissues, and Cellular and Tissue-based Products", April 2005

9.2 Commission documents published during the consultation process

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