Chapter 44
Regulatory Frameworks for Cell and Tissue Based Therapies in Europe and the USA

Gudrun Tiedemann and Sebastian C. Sethe

Abstract Whereas some basic therapies based on tissues and cells have been in clinical use for years, regulatory regimes applying to such applications have recently been revised and extended in Europe and in the US. Moreover, advances in regenerative medicine present new challenges and new types of products for regulation.

Both European and US regulators have developed rules to distinguish 'complex' cell therapies from their more established predecessors. In Europe, regulation of medicines and tissues and cells has now been supplemented by the regulation of 'Advanced Therapies' that is specifically relevant for regenerative medicine. We discuss the European legislative framework with reference to Germany and the UK as examples how the common rules are implemented. We also show how similar distinctions are made in the United States and consider the stance of the FDA on clinical development of novel cell therapies.

In conclusion, we briefly discuss whether the proposed regulatory regimes strike the appropriate balance between protecting patient safety and promoting innovation in regenerative medicine.

44.1 Introduction

Legal and regulatory provisions shape the medical innovation trajectory in major ways. To safeguard public and patient health, legislation is laid down to control the testing, manufacture, marketing and use of therapeutic products for human use.

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G. Steinhoff (ed.), *Regenerative Medicine: From Protocol to Patient*,
DOI 10.1007/978-94-007-5690-8_44,

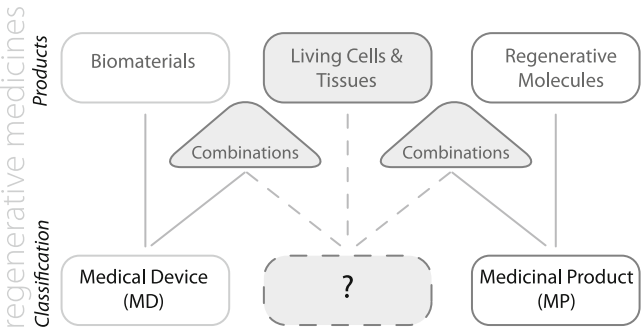

Fig. 44.1 Classification of regenerative products

Over the years, regulatory provisions have evolved to cover the medical sector more and more comprehensively and regulators are also struggling to keep up with novel scientific, technical and economic developments.

Advances in regenerative medicine result in a group of innovative and complex products that may involve living cells and tissues, regenerative molecules and biomaterials. These approaches to potential new treatments and long-term health protection stand for a step change in medicine.

A general distinction has traditionally been drawn between medical devices, pharmaceuticals and transplants. Some therapeutic approaches that could be classed as 'regenerative medicine' fit with existing regimes of regulatory oversight. For example, small molecules enhancing the regenerative capacity of endogenous stem cells would be classed as pharmaceuticals; a donated liver is a transplant. For others, the product classification may be ambiguous or confusing. For example, are genetically modified stem cells seeded on an implantable scaffold that contains a slow-release capsule which secretes chemical factors to promote angiogenesis a device (because of the scaffold), a drug (because of the factors), a transplant, a gene therapy or something else entirely? Moreover, can the new regenerative treatments be 'made to fit' existing categories or are there new and different considerations that innovators and regulators need to pursue?

Here, we will focus on the regulation of cell therapy and tissue engineered products (cell therapies in shorthand). Cell and tissue based therapies have long been left relatively unregulated, in part because these treatments were seen as more closely aligned to surgical interventions than the pharmaceutical market. Driven by scientific progress in regenerative medicine which has produced new and different types of the above 'borderline' complications, new legal provisions have been developed to regulate the cell therapies sector.

In this context, there has been considerable debate about what makes a regulatory regime in cell therapies regulation fit for purpose (see Fig. 44.1).

In this chapter, we will give a summary introduction to the regulatory regimes applicable to cell based therapies in Europe and the US and conclude with a brief discussion regarding the adequacy and effectiveness of these regulations.

44.2 Regulation of Cell and Tissue Based Therapies in Europe

In the European Union (EU) recent legislative efforts have specifically addressed cell and tissue engineering approaches. In order to understand how these initiatives take practical effect, a basic appreciation of European Law is required: A distinction can be made between European **Regulations** and European **Directives**. Whereas European Directives are considered to have direct *effect*, they first require implementation by national legislation in the individual Members State (MS). In contrast, European Regulations are *directly applicable* (yet may still be in need of substantiation in a national context). Therefore, although European Law may proscribe the regulatory parameters, the interpretation and implementation of these stipulations in individual MS may differ.

For this reason, after discussing the EU regulations in cell and tissue based therapies, we will look briefly at two MS – Germany and the United Kingdom (UK) as case studies for national implementation.

44.2.1 Basic Regulatory Domains

The three basic domains of medical products referenced in the introduction also exist in Europe:

Medical Devices
The core legal framework for medical devices consists of 3 directives **(the Device Directives)**: Directive 93/42/EEC covers medical devices generally. Directive 90/385/EEC concerns specifically active implantable medical devices. Many regenerative medicine approaches will fall under this scope. Also of interest is Directive 98/79/EC regarding in vitro diagnostic medical devices, such as tissue engineered toxicology assays. These directives have been supplemented over time by several modifying and implementing directives, including the last technical revision brought about by Directive 2007/47/EC.

A key regulatory component of bringing a medical device to the European market is the so called 'CE marking' to indicate conformity with the essential health and safety requirements. Depending on the class of product, conformity can be proven by the manufacturer or with the involvement of a **notified body**.[1]

Whether clinical trials are necessary to demonstrate safety and efficiency depends on the class of the product. Authorization for clinical trials is given by the competent authorities of the MS.

Pharmaceuticals
The nexus for regulation of small molecule drugs, complex biologics, and even herbal products, vitamins and minerals where used for medical treatment is

[1] A list of notified bodies can be found at http://ec.europa.eu/enterprise/newapproach/nando/

Directive 2001/83/EC (the Medicines Directive) which applies to medicinal products for human use intended to be placed on the market in Member States and either prepared industrially or manufactured by a method involving an industrial process. Under this legislation, all medicinal products in its scope require a Marketing Authorisation (MA) from the European Commission or the national competent authority of the MS to ensure quality, safety and efficacy before they can be sold commercially. Similar to the devices legislation, the Medicines Directive has also been extensively amended in order to incorporate new legislative agendas including, most recently, initiatives on regenerative medicine as will be discussed below.

Transplantation

Whole organ transplantation is not currently regulated at EU level, although efforts are underway to address this sector.[2] **Directive 2002/98/EC (the Blood Directive)** sets standards of quality and safety for the collection, testing, processing, storage and distribution of human blood and blood components. Although some blood products may be very relevant in regenerative medicine, we will not focus on this area here. **Directive 2004/23/EC (the Tissues and Cells Directive)** sets standards of quality and safety for the donation, procurement, testing, processing, preservation, storage and distribution of human tissues and cells. This Directive is complemented by two technical directives (2006/17/EC and 2006/86/EC), which specify further detailed requirements. The Tissues and Cells Directive set standards that must be met when carrying out any activity involving tissues and cells intended for 'human application' (medical treatment of human patients). It could be thus be thought that the Tissues and Cells Directive is the relevant European regulatory instrument for cell therapies – however, the Directive only relates to cells which have been minimally manipulated such as in whole bone marrow transplantation and in fertility treatment. As we will see, most stem cell and tissue engineering therapies in regenerative medicine involve substantially manipulated cells or tissues and thus form part of a new regulatory paradigm on 'advanced therapies' which are regulated similar to pharmaceuticals under the Medicines Directive.

44.2.2 Legislation on Advanced Therapy Medicinal Products (ATMP)

After discussion and stakeholder consultation about regimes applicable to living cell based therapies, and in particular tissue engineered products, the European Commission established as *'lex specialis'* **Regulation (EC) No 1394/2007** on advanced therapy medicinal products (**the ATMP-Regulation**) as shown in Fig. 44.2.

From a legal implementation perspective, the ATMP Regulation has several elements: it amends other aspects of European medicines law most notably the

[2] Press release: MEMO/08/774, 08/12/2008.

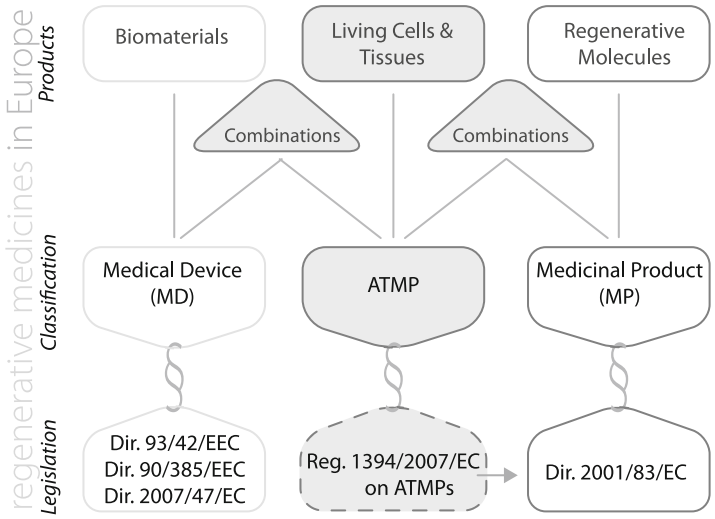

Fig. 44.2 Regulatory regimes for regenerative medicines in Europe

Medicines Directive; it contains some provisions which have direct applicability; and it contains some instructions for MS to establish further regulatory provisions and also tasks the European Commission and the European Medicines Agency with specific implementation steps. Figure 44.3 gives an overview of the follow-up amendments, legislation, guidelines and provisions engendered by the ATMP Regulation.

44.2.2.1 Types of Advanced Therapies

The ATMP Regulation establishes the concept of **Advanced Therapy Medicinal Products** (ATMP) – a category that is meant to encompass gene therapy, certain types of cell therapy and tissue engineering. With a circular cross-reference to Annex I Part IV of the Medicines Directive, (which has since been amended by Directive 2009/120/EC) the ATMP Regulation refers to products in these areas as 'gene therapy medicinal products' (GT), 'somatic cell therapy medicinal products' (SCT), and 'tissue engineered products' (TEP).

A comparison of the three ATMP-product-classes GT, SCT and TEP regarding definition, indication and active substance is shown in Fig. 44.4.

It should be pointed out that these definitions are regulatory constructs and not necessarily in line with scientific terminology (e.g. SCT may well include stem cell based treatments, even though the word 'somatic' is used).

The ATMP Regulation also recognises 'Combination Products' which are ATMP that incorporate, as an integral part of the product, one or more medical devices (Art.2 (d)).

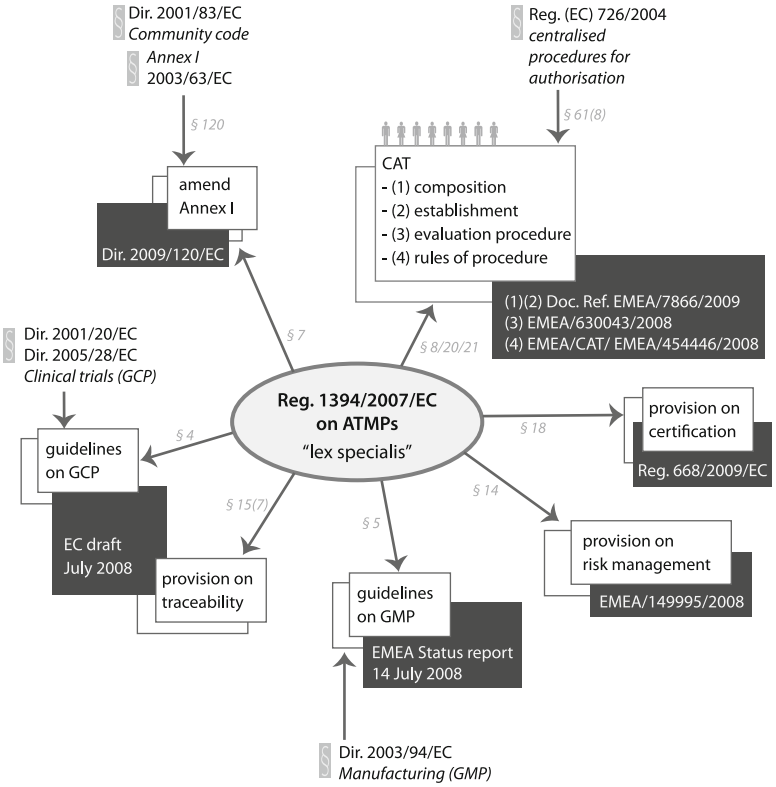

Fig. 44.3 Integration of Regulation (EC) 1397/2007 into the European regulatory framework: Implementation plan (black font on white background) and the current implementation status (white font on dark background)

The ATMP Regulation has no impact on national legislation prohibiting or restricting the use of certain type of human or animal cells (for example embryonic stem cells) and aims not to interfere with MS policy on whether to allow the use of any specific type of human cells. Products modifying the germ line genetic identity of human beings and products derived from human-animal hybrids or chimeras are excluded from the ATMP Regulation, but Xenotransplantation is specifically included.

As one can see from the definitions listed in Fig. 44.4 a lot turns on a decision of whether cells/tissues are 'substantially manipulated'. TEP make a similar reference to cells/tissues which are 'engineered'.

The ATMP Regulations specify that manipulations which shall **not** be considered as 'substantial manipulations' include: cutting, grinding, shaping, centrifugation, soaking in antibiotic or antimicrobial solutions, sterilization, irradiation, cell separation, concentration or purification, filtering, lyophilisation, freezing, cryopreservation and vitrification.

	gene therapy medicinal product GT	somatic cell therapy medicinal product SCT	tissue engineered product TEP
full definition	Directive 2001/83/EC Annex I Part IV –2.1	Directive 2001/83/EC Annex I Part IV –2.2	Reg. (EC) 1394/2007/EC Art.2(b)
indication	administered to human beings with a view to regulating, repairing, replacing, adding or deleting a genetic sequence;	treating, preventing or diagnosing a disease through pharmacological, immunological or metabolic action	regenerating, repairing or replacing a human tissue
active substance	recombinant nucleic acid	(engineered) cells or tissues that have been subject to substantial manipulation so that biological characteristics, physiological functions or structural properties relevant for the intended clinical use have been altered, or that are not intended to be used for the same essential function(s) in the recipient and the donor	
exclusions	vaccines against infectious diseases		products containing or consisting exclusively of non-viable human or animal cells tissues, which do not contain any viable cells or tissues and which do not act principally by pharmacological, immunological or metabolic action

Fig. 44.4 Definitions of ATMPs: GT-, SCT-, and TE-products

A similar classification problem can exist where tissues and cells are not intended to be used for the same essential function (so called 'non homologous use').

In summary, tissues and cells are 'elevated' to ATMP when they EITHER are 'substantially manipulated' OR 'for non-homologous use (see Fig. 44.5) – or both.

In effect, this means that the great majority of regenerative medicine therapies will be covered by the ATMP Regulation. Nonetheless, this determination must be made for each product individually. The Commission anticipated that such classification questions may lead to problems initially and CAT have established a free classification procedure which is supposed to feed back a classification recommendation to the questioner within 60 days. The results of these determinations are published to provide other innovators with a list of examples.

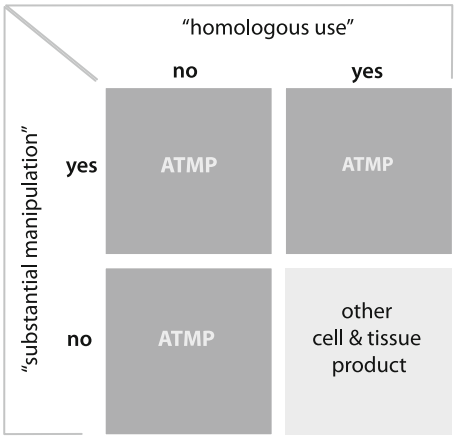

Fig. 44.5 Cells or tissue products in and out of the definition of an ATMP

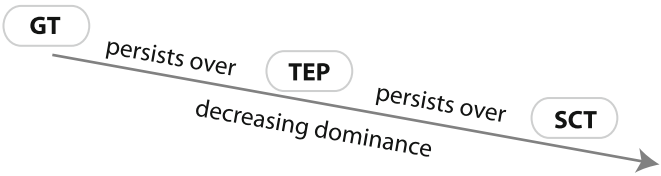

Fig. 44.6 'Dominance' of ATMP classification

44.2.2.2 Dual Classification

The ATMP-Regulation provides some general rules on classification of an ATMP that fulfils multiple characteristics:

Where a product contains viable cells or tissues, the pharmacological, immunological or metabolic action of those cells or tissues shall be considered as the principal mode of action of the product. A product with mixed characteristics is classified only by according to the dominant characteristic in the following order (Fig. 44.6):

Whereas it is important to point out the primacy of GT in this arrangement, we focus here on TEP and SCT products. In both cases, it may sometimes be difficult to determine whether a product qualifies as covered by the ATMP Regulation or whether it is covered 'only' by the Tissues and Cells Directive.

44.2.2.3 'Exemption §28(2)' from the Scope

Because the ATMP regulations builds on the Medicine Directive, its scope is limited to products which are intended to be placed on the market in MS and which are

either prepared industrially or manufactured by a method involving an industrial process. If an ATMP is **not** prepared industrially or manufactured by a method involving an industrial process, **and not** intended to be placed on the market in the Member State it is out of the scope of the ATMP-Regulation.

In order to avoid these cell-and tissue-products to be completely exempted from pharmaceutical legislation, the ATMP-Regulation (Art. 28(2)) amends Art.3 of Directive 2001/83/EC with the so-called 'Hospital Exemption' related to ATMPs which are prepared on a non-routine basis according to specific quality standards, and used within the same Member State in a hospital under the exclusive professional responsibility of a medical practitioner, in order to comply with an individual medical prescription for a custom-made product for an individual patient (see Fig. 44.7).

Member States are requested to lay down rules for authorising these products by the national Competent Authority whilst at the same time ensuring that relevant Community rules related to quality and safety are not undermined.

While searching for 'exemptions' to the process of marketing authorisation, another, similar provision may be of interest that predates the ATMP Regulation and applies equally to all other medicines: According to Art.5.1 of the Medicines Directive, a MS may, in order to fulfil special needs, exclude a medicinal product from the provisions of the Medicines Directive altogether if that product is supplied in response to a bona fide unsolicited order, formulated in accordance with the specifications of an authorised health-care professional for use by an individual patient under his direct personal responsibility (see Fig. 44.8).

Whether this provision is useful and applicable will depend not only on the circumstances of the individual case but also on the extent that the individual MS has recognised and interpreted the provision.

44.2.3 Interactions with Regulatory Bodies

44.2.3.1 Marketing Authorisation

In order to place an ATMP product on the market in the EU, the manufacturer needs to obtain marketing authorisation (MA) from the European Commission.

All ATMP are subject to a centralised MA procedure which involves a single scientific evaluation of the quality, safety and efficacy of the product which is carried out by the European Medicines Agency (EMEA)[3] as established by Regulation (EC) No 726/2004.

For ATMPs which were 'legally on the market' in accordance with national or Community legislation on 30 December 2008 a transitional period of 3 years for SCT and GT (30 December 2011) and 4 years for TEPs (30 December 2012) is granted.

[3] Following a recent rebranding, the European Medicines Agency is no longer using the acronym EMEA, but is also not using EMA. Here we have opted for EMEA to avoid confusion for those used to the old abbreviation.

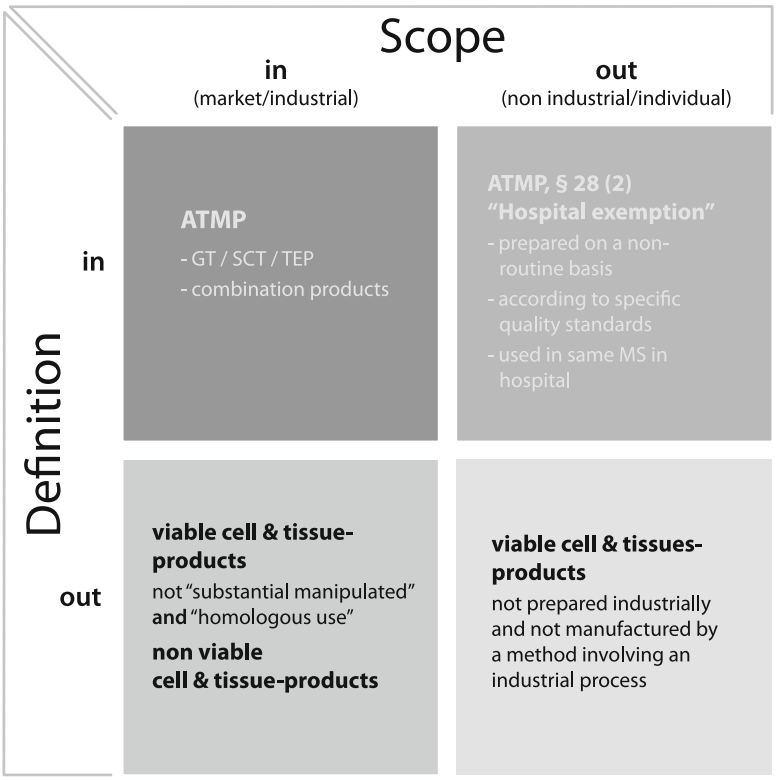

Fig. 44.7 Cells or tissue products in and out of the definition of an ATMP

	2001/83/EC	2001/83/EC Art. 3(7)	2001/83/EC Art.5.1.
Authorised by	European Commission	treating medical practitioner	treating health care professional
Conditions	marketing /manufacturing authorisation	-individual medical prescription -custom-made product -individual patient	-bona fide unsolicited order -individual patient
Requirements	safety, efficacy etc	non-routine basis	special needs
Location of treatment	/	a hospital	/
Location of manufacture	any accredited facility anywhere	prepared and used in the same MS	manufactured in an eligible MS or imported to an eligible MS

Fig. 44.8 Some of the main differences in scope between ATMP produced under the standard provisions, Art. Directive 2001/83/EC Art. 3(7), and Art.5.1

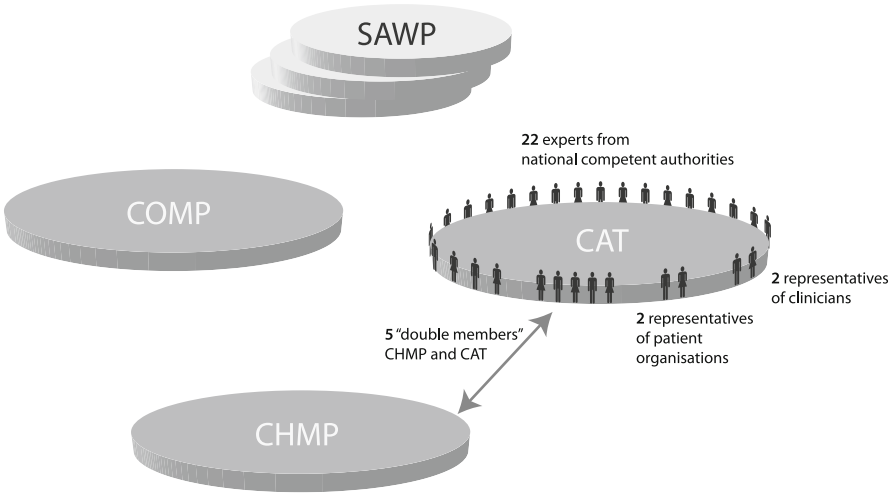

Fig. 44.9 Committees involved in evaluation of ATMPs

MA is not required where the product is still undergoing development in clinical trials.

44.2.3.2 Committee for Advanced Therapies (CAT)

The evaluation of ATMPs often requires very specific expertise. For this reason a new and multidisciplinary expert committee 'Committee for Advanced Therapies' (CAT) within EMEA has been established, to assess ATMPs and to follow scientific developments in the field (see Fig. 44.9). The names and scientific qualifications of the members are made public by the Agency. The CAT is responsible for preparing a draft opinion on the quality, safety and efficacy of each ATMP – including combined ATMPs – for final opinion by the Committee for Medicinal Products for Human Use (CHMP). The CHMP delivers this opinion to the Commission for final approval.

For scientific consistency and the efficiency of the system, the coordination between the CAT and the other Committees, advisory groups and working parties, notably the CHMP, the Committee on Orphan Medicinal Products (COMP), and the Scientific Advice Working Party (SAWP) must be ensured.

44.2.3.3 The Role of National Regulators

Whereas ATMP have to pursue the centralised European route, for other regenerative medicine products it may be possible to gain national approval in individual MS and subsequently European-wide approval under the mutual recognition procedures. EMEA has no scientific assessors on its own and relies on outsourcing its licensing

activities to national authorities. In the young field of regenerative medicine, arguably the most important role for national regulatory authorities however, is in regulating the conduct of clinical trials. Clinical trial authorisation – as well as manufacturing authorization of the clinical trial samples – is required in each MS where a trial is being undertaken. Some MS further differentiate between national and regional authorities.

44.2.3.4 Fee Reductions

Specific incentives for small and medium sized enterprises (SMEs) exist in the ATMP area. Additional procedures are offered to support applicants in the development process.

Any applicant or holder of a marketing authorisation may request advice from the Agency on the design and conduct of pharmacovigilance and of the risk management system. There are specific incentives of 90% fee reduction for SMEs and 65% for others. If an applicant is SME or a hospital and can prove there is a particular public health interest in the Community he can get additional fee reductions: 50% fee reduction on MA fee and 50% post authorisation activities for 1 year.

44.2.3.5 Certification of Quality and Non-clinical Data

A new certification system aims at giving SMEs an incentive to develop ATMPs. Under this scheme, the Regulator can 'certify' data as being of sufficiently high quality for regulatory consideration. It is expected that innovators will then be able to raise capital for further R&D. The scope of the evaluation is to certify that each submitted study complies with the relevant scientific and technical requirement set out in the Annex I to Directive 2001/83/EC and adequately follows state-of-the-art scientific standards and guidelines.

SMEs may submit to the Agency all relevant quality and, where available, non-clinical data required in accordance with modules 3 and 4 of Annex I to Directive 2001/83/EC, for scientific evaluation and certification.

The Commission has laid down provisions for the evaluation and certification of the data.

Not a marketing authorisation: The certification procedure is independent from a future application for MA. But it could facilitate the evaluation of any future application for clinical trial authorisation or a marketing authorisation application (MAA), provided that these applications are based on the same data.

Not 'legally binding' for the Agency: A certificate is not binding with regard to any future regulatory procedure and all relevant data should be submitted again for the purpose of any future regulatory procedure.

Mostly quality and, where available, non clinical data: The certification procedure covers only a scientific evaluation of experimental data (quality/non-clinical) already generated. Advice for further development will have to be obtained by the Scientific Advice procedure.

The certificate cannot conclude on the adequacy of the studies submitted to be further developed in a clinical trial. This is under the responsibility of the National Competent Authorities where the clinical trial will be conducted.

Whether such a certification scheme will prove a worthwhile investment for innovators remains to be seen. Until 2012 there was only one certification procedure conducted by the CAT. The reason may be that the procedure is not open for Academia where about 60% of the early development is done. This has to be changed in future.

44.2.3.6 Specific Requirements

Part IV, Annex I of the Directive 2001/83/EC lays down detailed scientific and technical requirements regarding the testing of medicinal products for human use and describes the format requirements (Modules 1–5) for MA. This section was recently amended by Directive 2009/120/EC specifically to address ATMP. Member States shall bring into force the laws, regulations and administrative provisions necessary to comply with Directive 2009/120/EC by 5 April 2010 at the latest.

The regulations specify a number of requirements. A few examples:

Cell sources: Information on donation, procurement and testing shall be provided. Animal cells or tissues are expressly not excluded but specific acceptance criteria must be provided. If 'non-healthy' cells or tissues are used as starting materials, their use shall be justified. Problematically, if allogeneic cell populations are being pooled, the pooling strategies and measures to ensure traceability shall be described. It is still unclear what constraints this imposes on 'rollover' cell pools.

Pre-clinical development: The Regulations suggest that 'The use of homologous models (e.g. mouse cells analysed in mice) or disease mimicking models shall be considered, especially for immunogenicity and immunotoxicity studies'. Different scientific opinions exist on the value of such studies. The regulations state that 'conventional pharmacokinetic studies to investigate absorption, distribution, metabolism and excretion shall not be required'. However, parameters such as viability, longevity, distribution, growth, differentiation and migration of cells shall be investigated, unless otherwise duly justified. Given the reported difficulties in cell tracking, this requirement alone may provide a significant barrier to development.

Risk analysis: Risk factors that may be considered include: the origin of the cells (autologous, allogeneic, xenogeneic), the ability to proliferate and/or differentiate and to initiate an immune response, the level of cell manipulation, the combination of cells with bioactive molecules or structural materials, the long time functionality, the risk of oncogenicity and the mode of administration or use.

The manufacturing process involves the emulation of the concept of a 'production batch' used in the context of mainstream pharmaceuticals. Manufacturing must be validated to ensure "batch consistency" and "the proper differentiation state and the cell function with additional substances throughout the manufacture" – this would

seem to place significant technical requirements on manufacturers in handling an inherently heterogeneous product. The regulations suggests that normally, the functional integrity of the cells should be tested at the moment of application/administration, but specify that if certain release tests cannot be performed on the active substance or finished product, but only on key intermediates and/or as in-process testing, this needs to be justified.

Risk-based Approach: in January 2012 the CAT came over with a new draft guideline on the risk-based approach according to Annex I, part IV of Directive 2001/83/EC applied to ATMP. It is a strategy aiming to determine the extent of quality, non-clinical and clinical data to be included in the Marketing Authorization Application (MAA), in accordance with the scientific guidelines relating to the quality, safety and efficacy of medicinal products and to justify any deviation from the technical requirements. It is not the intention to provide a rigid classification system of different risks but rather to exemplify the concept by using several examples with different risk profiles. This may be a worthwhile instrument leading through the complex development process in a fruitful dialog with the authorities.

44.2.3.7 Specific Guidelines on Good Clinical Practice (GCP) and Traceability

Clinical trials on ATMPs have to be conducted in accordance with the overarching principles and the ethical requirements laid down in Directive 2001/20/EC for good clinical practice. However, Commission Directive 2005/28/EC laying down principles and detailed guidelines for good clinical practice, as well as the requirements for authorisation of the manufacturing have to be adapted to ATMPs. Draft Guidance by the Commission thus far simply references 2005/28/EC and CPMP/ICH/135/95 without adding many further specifications regarding, inter alia, the investigators brochure, the clinical protocol, ethics quality control etc. However, this approach brings a particular emphasis to the requirements for traceability that the document selectively focuses on.

The system has to ensure coherence and compatibility with traceability requirements in the Tissue and Cells Directive. Notably, the traceability system must also respect the provisions laid down in Directive 95/46/EC on data protection, which are considered to be particularly stringent in international comparison. For example, because the European Commission does not regard the privacy laws in the US as adequate, the transfer of patient data, to the USA is prohibited except under special 'safe harbour' agreements.

44.2.3.8 Guideline on Safety and Efficacy Follow Up – Risk Management of ATMPs

In addition to the requirements for pharmacovigilance laid down in Articles 21 to 29 of Regulation (EC) No 726/2004, the MA-application for an ATMP shall lay

down measures envisaged to ensure the follow-up of efficacy of ATMPs and of adverse reactions thereto. The Commission requires a risk management system designed to identify, characterise, prevent or minimise risks related to AMPs, including an evaluation of the effectiveness of that system, be set up. EMEA may stipulate that specific post marketing studies be carried out.

If serious adverse events or reactions occur in relation to a combined ATMP, there is an obligation for EMEA to inform relevant national competent authorities.

44.3 Examples: Germany and United Kingdom

As explained above, although European Regulations on regenerative medicine impose an ever greater degree of uniformity on regulatory standards across Europe, Members States retain some leeway in implementing those provisions into national law. We have also seen that the ATMP 'Hospitals Exemption' is expressly delegated to National Competent Authorities. Here, we will briefly provide two illustrations on how European regulations are incorporated into the national framework by brief reference to Germany and the UK.

44.3.1 Germany

There are two main Competent Authorities in Germany: the *Bundesinstitut für Arzneimittel und Medizinprodukte (*BfArM – Federal Institute for Drugs and Medical Devices) and the *Paul-Ehrlich-Institut* (PEI – Federal Institute for Vaccines und Biomedical Drugs). The latter is responsible for cell and tissue products. In addition to these federal authorities there are cooperating local authorities, which have specific functions. The German approval and authorisation requirements are laid down in the German MP-Act the *'Arzneimittelgesetz'* (AMG).

For living cell and tissue based medicines the relationship between Community and German legislation is shown in Fig. 44.10.

44.3.1.1 Basic Tissue and Cell Treatments in Germany

Since 2007 the Tissues and Cells Directive has been transposed to the German law, as amendments to the transfusion-, transplantation- and pharmaceutical regulation. The definitions and specific rules for classic tissue-preparations (*'Gewebezubereitungen')* have been laid down in the 14th Amendment ('14te Novelle') of the AMG.

'Classic' tissue/tissue-preparations are defined as MP in §4(30) AMG, regarding the German Transplantation Act §1a Nr. 4 (TPG). If these products are **produced industrially** the requirements are – as for any other MP – the manufacturing

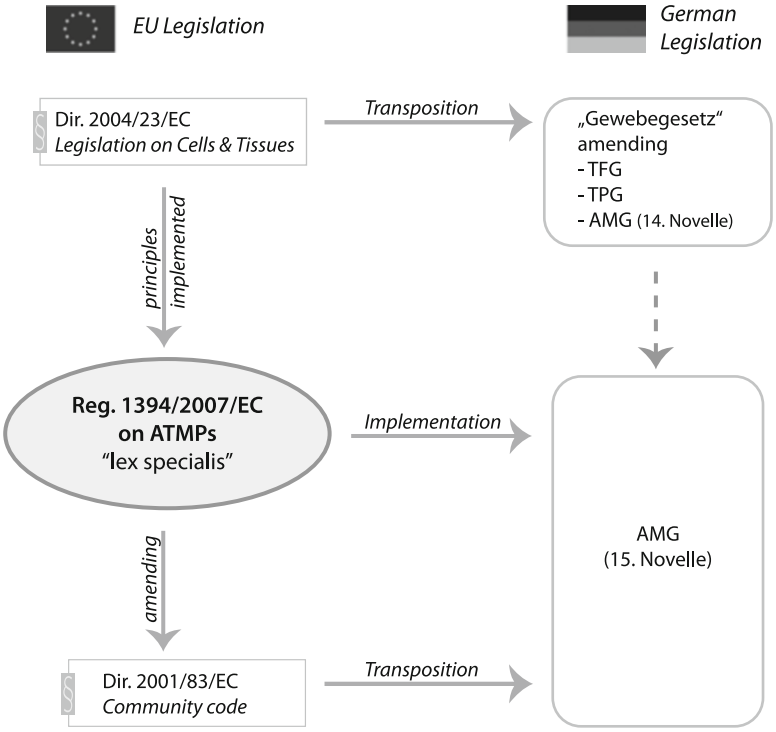

Fig. 44.10 Relationship between Community and German legislation

authorisation regarding §13(1) AMG by the local authority (after consultation with the PEI) and MA through §21(1) AMG, including clinical trials.

If the tissue preparations however are **not processed with industrial methods and where the methods are well-known in the Community**, specific national authorisation provisions for manufacturing as well as for use are laid down in the AMG.

For **manufacturing** again the respective local authority is responsible but the manufacturer has to fulfil only reduced requirements for processing and testing (§20c AMG) – in addition to the general requirements for donation, procurement and testing laid down in §20b AMG (which is also applicable for the procurement of autologous blood, often required for the preparation of TEPs).

The **authorisation for use** is the so called *'Genehmigung'* (§21a AMG), issued by the PEI. The requirements are – compared to the 'normal' dossier for MA – rather similar but reduced, particularly regarding clinical trials.

According to §20d AMG tissues/tissue preparations are **excluded** from these provisions, if they are not placed on the market and are processed and applied under the responsibility of a physician (*'Einhandprinzip'*). Tissues, which are procured and re-applied within the medical operation without any change to their material composition, are entirely excluded from the scope of the AMG (§4a (3)).

44.3.1.2 ATMP in Germany

The implementation of the ATMP Regulation with its follow up effects has led to new further amendments to the AMG. Since July 2009 ATMPs are implemented in the '15th Novelle' under the term '*Arzneimittel für neuartige Therapien*' (§4(9) AMG). GMP-manufacturing (§13(1) AMG) and centralised MA (§21 AMG) are required.

For the exemption according to Article 28(2) of the ATMP-Regulation for 'non-routine' ATMPs §4b AMG lays down *'Sondervorschriften für Arzneimittel für neuartige Therapien*'. In the following we will focus on the German provisions for this 'Hospitals Exemption'.

44.3.1.3 'Hospital Exemption' in Germany

The specific 'non routine' provisions are laid down in §4b (1 and 2) of the AMG and apply to ATMPs, which are:

- prescribed by a physician for an individual patient as a custom-made preparation,
- applied under the responsibility of a physician in a specialised health care unit
- ***manufactured on a non-routine basis*** according to specific quality standards.

  Here *'manufactured on a non-routine basis'* means in particular ATMPs

  - which are manufactured on a small scale and where – on the basis of routine production – the product has to be ***individually modified because of a medical indication for a single patient***, or
  - products not yet manufactured in a sufficient number to lay down the necessary results for a comprehensive evaluation.

  The German provisions for these 'non-routine' ATMPs are in detail:

- **no** need for MA according (§21 AMG) (as there is **no** placing on the market (§43 AMG))
- traceability and pharmacovigilance administered via competent local authority and/or PEI (but equivalent to the rules on Community level)
- quality standards for production by manufacturing authorisation (*'Herstellerlaubnis')* regarding §13 AMG via local authority and PEI (same authorisation as for 'routine ATMPs')
- if the ATMPs are "handed over to others" authorisation through '*Genehmigung*' (§21a(2–8)AMG) via PEI (specific quality standards: template for authorisation corresponds in general with the Common Technical Document (CTD) for approval but the 5 CTD-modules for quality, preclinical and clinical data, summaries and registration are abbreviated versions) is required.

If there is doubt whether an ATMP falls under the provision *'Genehmigung'* or not, the relevant local competent authority is responsible to decide this on request of the applicant and after consultation with the PEI.

The authorisation will be withdrawn, when the prerequisites for the 'exemption' are not or no more fulfilled. At defined time points the owner of the authorisation has to report to the PEI about the scale of production and/or the consolidated findings for the evaluation of the MP.

44.3.2 United Kingdom

44.3.2.1 Basic Tissue and Cell Treatments in the UK

The regulation on tissues and cells which are not classified ATMP is largely covered by the Human Tissue Act 2004 (HTA). Following a national scandal into unauthorised retention of organs for research, the Human Tissue Act is unusual in a European context in covering the storage of human tissue not just for purposes of the Tissue and Cells Directive but also for clinical and other research.

The UK Human Tissue Authority has issued Directions under Art.26(7) of the Human Tissue Act to address the European requirements: HTA Directions 001/2006 implement the requirements of the Tissue and Cells Directive and technical Directive 2006/17/EC including standards relating to procurement, distribution, donor selection and evaluation, and the transport of tissues and cells. HTA Directions 002/2007 implement technical Directive 2006/86/EC on facilities and equipment, quality management and review, confidentiality, processing and storage and the reporting of serious adverse events and reactions. HTA Directions 004/2007 regulate to the import of tissues and cells from outside the EU.

44.3.2.2 ATMP in the UK

Cell therapies which are classed as ATMP on the other hand are primarily regulated as normal medicines under the Medicines Act 1968 which – with its vast number of amendments – "has become a very complex and fragmented set of legal provisions" the structure of which is currently under review.[4] Clinical trials for ATMP will be regulated mainly under the Medicine for Human Use (Clinical Trials) Regulations 2004 by the UK Medicines and Healthcare products Regulatory Agency (MHRA).

44.3.2.3 Hospitals Exemption in the UK

MHRA has consulted in this context not only on the implementation of the 'Hospitals Exemption' (Art.3 (7) 2001/83/EC as amended) but also on the re-framing of the UK 'Specials' regime (ie the national arrangements set up under a derogation in Article 5.1 of Directive 2001/83/EC).

[4] MHRA Concept paper on the project to consolidate and review medicines legislation; Jan 2009.

Where a number of different products are under consideration the question of whether preparation is non routine will be considered separately in relation to each product prepared by that operator.

MHRA will take into account the overall numbers of the product prepared by the operator, the regularity/frequency of production, and the time period over which the preparation of that product has become established. The Agency would not, for example, accept an argument that depended on the premise that all autologous ATMPs were by definition different products, where their intended use, manufacturing processes and final product presentation are the same.

MHRA suggests that it should typically be possible to determine within a period of 1–3 years where the scale and frequency of production means that preparation has become routine, but where some months are elapsing between each preparation, a significantly longer period may need to elapse before the preparation could be reasonably regarded as routine.

A manufacturer needs to obtain a hospitals exemption manufacturer's licence from the MHRA. The licence will authorise the manufacture of particular categories of ATMPs (gene therapy, somatic cell therapy or tissue engineered product) rather than individual products. ATMPs made and used under the exemption must comply with the principles of GMP as stipulated by the European Commission. The MHRA will inspect for compliance with GMP and review an annual return on this activity.

44.4 Regulation of Cell and Tissue Based Therapies in the USA

44.4.1 Legislative Framework

We have seen that for Europe, an understanding of the relationship between Community and Member States legislation is useful for a perspective on the regulation of cell therapies. Similarly the US constitution provides a basis for medicines regulation in the USA. Congress regulates interstate commerce, and in this context the authority to regulate drugs, devices, and biological products was delegated to the Food and Drug Administration (FDA) by the federal Food, Drug and Cosmetics Act.

As shown in Fig. 44.11 the FDA divides regulatory oversight in this area among the Center for Drugs, Evaluation and Research (CDER) which deals with 'chemical' pharmaceuticals, the Center for Biologics, Evaluation and Research (CBER) which deals with 'complex' biological treatments and the Center for Devices and Radiological Health (CDRH) that deals with medical devices.

CBER will likely be the most important centre for innovators in this area and within CBER the Office of Cellular, Tissue and Gene Therapies (OCTGT) is comprised of three Divisions:

- Division of Cellular and Gene Therapies (DCGT)
- Division of Clinical Evaluation and Pharmacology/Toxicology (DCEPT)
- Division of Human Tissues (DHT)

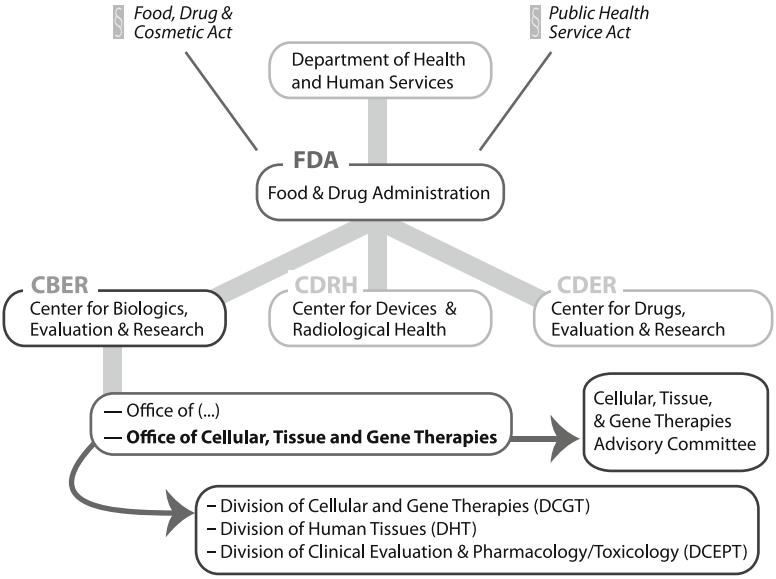

Fig. 44.11 Organigram of FDA with focus on cellular therapies (Note that this is a snapshot, other FDA institutions may be of relevance, e.g. within CBER the Office of Compliance and Biologics Quality, or the Office of Communication, Outreach and Development)

Contact details of relevant personnel can be accessed at the FDA website.[5]

Whereas FDA is the ultimate respondent on regulatory affairs, also of interest in this sector is the important role of voluntary accreditation and certification programs such as by the American Association of Tissue Banks (AATB) and Foundation for the Accreditation of Cellular Therapy (FACT).

FDA considers "articles containing or consisting of human cells or tissues that are intended for implantation, transplantation, infusion, or transfer into a human recipient" as **human cellular-and tissue-based products (HCT/Ps)**. However, the designation as HCT/P in itself does not determine how the product will be considered by the FDA. In the past, cell and tissue therapies have been exempt from product regulation because of their stronger association to medical practice than to industrial manufacture. During the last decade however, steps were taken to bring the sector under stronger regulatory supervision.[6]

In the regenerative medicine area, the first determination will be whether the product requires marketing authorisation. The product's classification determines the regulatory scrutiny of clinical R&D and marketing authorisation. It also determines the FDA branch with lead responsibility for the product.

[5] Currently at http://www.fda.gov/AboutFDA/CentersOffices/CBER/ucm123224.htm

[6] Beginning with the "Reinventing the Regulation of Human Tissue" discussion paper CBER February 1997.

44.4.1.1 Unaltered or Manipulated

Organs, blood products and tissues do not require marketing authorisation, but they still require compliance with regulatory standards.

CBER does not regulate the transplantation of **vascularised human organ transplants** and blood vessels recovered with an organ. These are overseen by the Health Resources Services Administration (HRSA) (although the position in the case of a vascularised tissue engineered human organ may 1 day be of interest).

Blood and Blood Products are sui generis products covered under CP 7342.001 "Inspection of Licensed and Unlicensed Blood Banks, Brokers, Reference Laboratories, and Contractors"; and CP 7342.002 "Inspection of Source Plasma Establishments".

Also excluded are secreted or extracted human products, such as milk, collagen, and cell factors; (semen *is* considered an HCT/P); Cells, tissues, and organs derived from animals other than humans; and in vitro diagnostic products.

Tissues: Some HCT/Ps are regulated solely under section 361of the US Public Health Service (PHS) Act and the regulations in 21 CFR Part 1271 (see Fig. 44.12).

Tissues and cells under this category include bone (including demineralized bone), ligaments, tendons, fascia, cartilage, ocular tissue (corneas and sclera), skin, arteries and veins (except umbilical cord veins), pericardium, amniotic membrane (when used alone, without added cells for ocular repair), dura mater, heart valve allografts, semen, oocytes and embryos (but not embryonic stem cells). The category also includes "hematopoietic stem/progenitor cells derived from peripheral and cord blood" – this is likely a significant borderline area in the context of regenerative medicine, not least because with these cells there is no consensus on what entails an original and relevant characteristic. However, the Administration advises that 'propagation' and 'pharmacological treatment' are at any rate 'kick-up factors' that constitute 'substantial manipulation' and bring blood stem cells into the area of products requiring marketing authorisation.

Where doubt exists, the FDA Tissue Reference Group (TRG) aims to provide a single reference point for HCT/Ps classification questions – however, an alternative and ultimately more authoritative route exists through the Office of Combination Products (OCP). The TRG is composed of representatives from CBER and CDRH and attended by a liaison from OCP. The group will issue guidance to applicants within 60 days on whether the product is regulated solely as a tissue. Similarly, a request for designation to OCP will yield a response within 60 days, with an opportunity to request reconsideration after 15 days of receiving the opinion, to which OCP must respond within 15 days.

44.4.1.2 Drug, Biologic or Device

If the HTC/P is considered substantially manipulated, so as to be regulated as a medicinal product the question arises what type of product it would then be. FDA seeks to determine this by focusing on the 'primary mode of action' of the therapy.

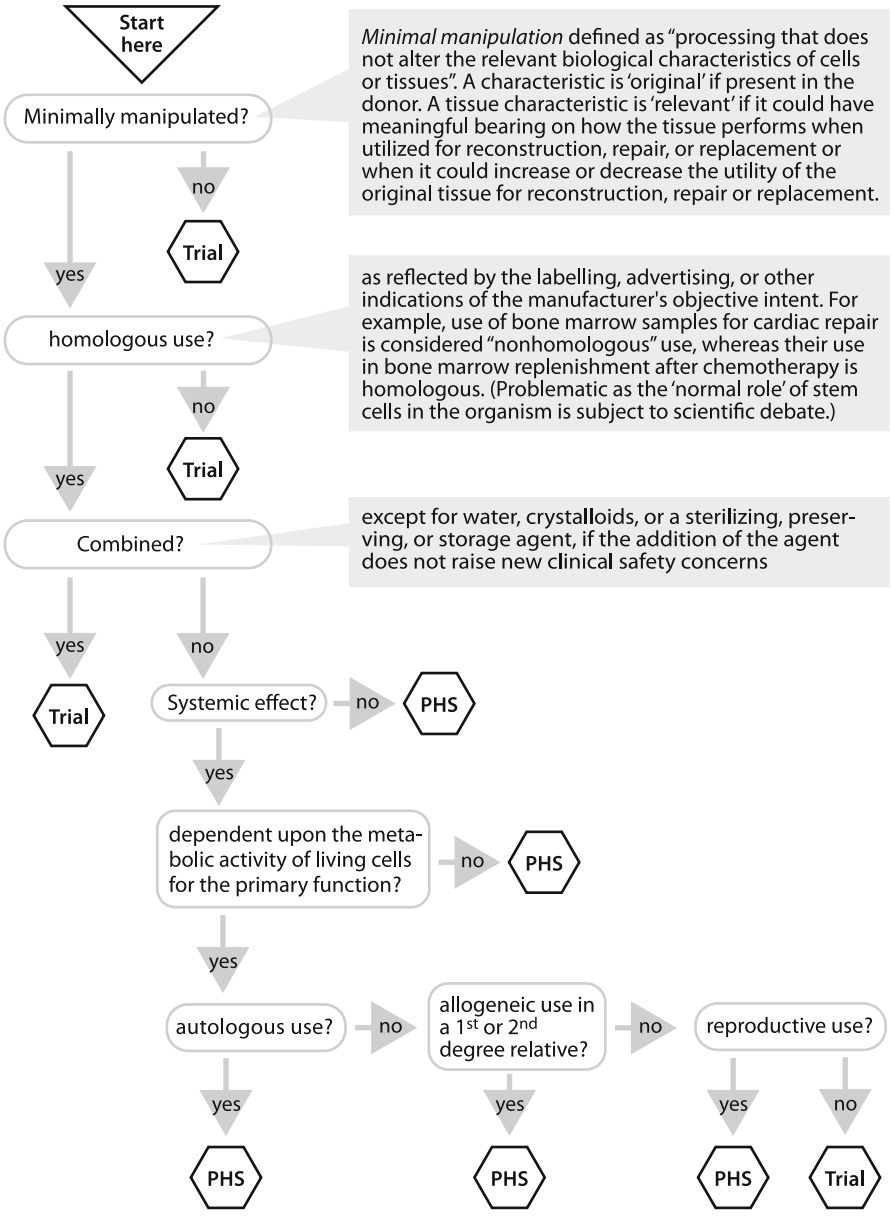

Fig. 44.12 Decision tree relating to whether a human tissue or cell product is regulated exclusively under Sec.361 of the US Public Health Service Act (PHS) or requires a license, approval, or clearance as part of a premarket review (Trial)

If the 'primary mode of action' is that of a drug, the product is assigned to CDER, if that of a device to CDRH, and biologics to CBER.

Drug is an article intended for use in the diagnosis, cure, mitigation, treatment, or prevention of disease in humans or animals, and an article (other than food) intended to affect the structure or any function of the body (42 USC 262(a)).

This category is oriented towards 'established', 'pill-type' products. Thus, very few products in regenerative medicine will be considered as drugs.

Device means an instrument, apparatus, implement, machine, contrivance, implant, in vitro reagent, or other similar or related article, including any component, part, or accessory, which is intended for use in the diagnosis of disease or other conditions, or in the cure, mitigation, treatment, or prevention of disease, (…) or intended to affect the structure or any function of the body (…) and which does not achieve any of its principal intended purposes through chemical action within or on the body and which is not dependent upon being metabolized for the achievement of any of its principal intended purposes (21 USC 201(h)). The latter provisions seem to preclude certain bioresorbable scaffolds.

Biologic is defined as a virus, therapeutic serum, toxin, antitoxin, vaccine, blood, blood component or derivative, allergenic product or analogous product, (…) applicable to the prevention, treatment, or cure of diseases or injuries of man (42 USC 262(a)). Most HCT/Ps that have been substantially altered will fall into this category.

There is no statutory definition of what constitutes primary mode of action. FDA has issued guidance[7] where the mode of action is defined as the means by which a product achieves its intended therapeutic effect, and –for combination products– the single mode that is expected to make the greatest contribution to the overall intended therapeutic effects. Sponsors can instigate a 'Request for Designation' (21CFR §3.7 – all §§ in this section are under 21 CFR) but in the past the classification of a product as either a device or biologic has sometimes appeared arbitrary. To complicate matters CDER now review certain biologics including: monoclonal antibodies for in vivo use; cytokines, growth factors, enzymes, immunomodulators, and thrombolytics; proteins intended for therapeutic use that are extracted from animals or microorganisms, including recombinant versions of these products (except clotting factors); and other non-invasive immunotherapies.

OCP publishes jurisdictional updates of decisions rendered on sample products.

44.4.1.3 Regulation of 'Unaltered' Tissue

Although, as we have seen, the issues of classification are not always clear-cut, it is unlikely that many advanced tissue or cell based products will be treated as tissue in this category. However, the regulations relating to tissues are still of prime relevance

[7] Definition of primary mode of action of a combination product. Fed Regist 70(164, Aug 25):49848–49862.

to innovators who –perhaps in a trans-Atlantic collaboration– use tissues and cells as 'raw material' for further or future development (e.g. blood stem cells as a component, or embryos for the derivation of embryonic stem cell lines). Similar to the European situation, the regulatory provisions that apply to the procurement of tissue will also be relevant for the further development of cell therapy and tissue engineered products. For example, the donor testing and eligibility criteria will apply to both contexts.

In the past, innovators have sometimes been able to convince regulators of the acceptability of a tissue component (e.g. a cell line) 'post hoc' with safety data, but the preferred approach will be one of integrating regulatory standards throughout the product development chain. We will therefore quickly reference some of the relevant provisions in this section.

Domestic or foreign establishments that manufacture or import HCT/P into the US must register with FDA and submit a list of each a HCT/P manufactured. CBER maintains a listing of registered HCT/P establishments on which over 100 foreign stem cell procurement facilities are listed.[8] Satellite recovery establishment only provide temporary storage of recovered HCT/Ps and may perform no other activity or manufacturing step.

HCT/P establishments must screen and test HCT/P donors for risk factors for, and clinical evidence of, relevant communicable disease agents and diseases and communicable disease risks associated with xenotransplantation. These procedures must be designed to ensure compliance with the requirements of subpart 21 CFR 1271 C. Donor eligibility determination must be based upon the results of donor screening (§ 1271.75) and donor testing (§§ 1271.80 and 1271.85). Certain records must accompany the HCT/P at all times once a donor eligibility determination has been made (§ 1271.55). For such tissues, FDA compliance programme 7341.002 – Inspection of Human Cells, Tissues, and Cellular and Tissue-Based Products applies.

Each HCT/P that is manufactured must be assigned and labelled with a distinct identification code that relates the HCT/P to the donor, to all records pertaining to the HCT/P; and to the recipient. The code may not include an individual's name, social security number, or medical record number (§ 1271.290c).

Manufacturers must investigate any adverse reactions and deviations related to an HCT/P they made available for distribution. Reportable adverse reactions must be submitted to FDA within 15 days of receipt of information as a MedWatch Form 3500A. Adverse reaction means a noxious and unintended response to any HCT/P for which there is a reasonable possibility that it was caused by the HCT/P (Part 1271.3(y)) and deviations relate to events that represent a deviation from applicable regulations, standards or established specifications that relate to prevention communicable disease transmission (§ 1271.3(dd)).

[8] Currently at http://www.fda.gov/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/EstablishmentRegistration/TissueEstablishmentRegistration/FindaTissueEstablishment/ucm110270.htm

44.4.1.4 Regulation of 'Manipulated' Tissue

Only very few cell therapy products are on the market to date, many products of relevance in this sector are currently in early stages of development. We will concentrate on the regulatory requirements for conducting clinical trials in this sector.

The Food, Drug and Cosmetic (FD&C) Act requires demonstration of safety and effectiveness for new drugs and devices prior to introduction into interstate commerce. The Public Health Service Act (PHS) requires demonstration of safety, purity, and potency for biological products before introduction into interstate commerce.

Consequently, pre-marketing authorization clinical studies must be performed under exemptions from these laws.

For drugs and biologics, a Investigational New Drug (IND) application must be filed (§ 312), for devices an Investigational Device Exemption (IDE, § 812).

44.4.2 Interactions with FDA

Once the responsible FDA division has been identified as outlined above, sponsors may take advantage of a pre-IND meeting opportunity to seek Agency guidance (§ 312.82). However, an important distinction should be made between 'official' and 'informal' pre-IND meetings. The Sponsor may request a formal pre-IND meeting from FDA which should be scheduled to occur within 60 days of FDA receipt of the meeting request. The former provides the investigators with formal advice that reflects 'current thinking' –it will subsequently be very difficult for the team to deviate from that advice without extremely good justification. Generally, FDA will not grant more than one pre-IND meeting for each potential application.

Informal advice can often be sought by interactions with the regulators.

44.4.2.1 Preclinical Data

The sponsor of a clinical trial should provide "…adequate information about the pharmacological and toxicological studies…on the basis of which the sponsor has concluded that it is reasonably safe to conduct the proposed clinical investigations." (CFR 21 Part 312.23 (a)(8)).

The kind, duration, and scope of animal and other tests required vary with the duration and nature of the proposed clinical investigations. Potential for tumorigenicity and the potential for inappropriate differentiation at a non-target location are significant safety concerns especially with hESC derived products.[9] Selection of the

[9] CTGTAC Meeting #45, April 10, 2008 Briefing: "Cellular Therapies Derived from Human Embryonic Stem Cells – Considerations for Pre-Clinical Safety Testing and Patient Monitoring".

most appropriate animal species and models is a major unresolved issue. In addition to the species used, the safety assessment of many cellular therapies has also made use of animal models of disease/injury that mimic some aspect of the pathophysiology of the proposed patient population. Such models help provide insight regarding dose/activity and dose/toxicity relationships. Thus, the applicability of such models in the context of species-specific immunology should be addressed. Cell survival, migration/trafficking, differentiation/mRNA or protein expression profile, integration (anatomical/functional), and proliferation also may need to be considered when selecting appropriate preclinical models.

44.4.2.2 Application

The contents of IND and IDE applications are similar. Beyond a description of the product and its manufacturing they will contain an account of preclinical studies including patient inclusion and exclusion criteria, study end points, patient follow-up, data monitoring and stopping rules. A list of standard operating procedures (SOP) will normally suffice for submission but critical SOP should be supplied in detail.

A Drug Master File (DMF) may be used to provide confidential detailed information about facilities, processes, or articles used in the manufacturing, processing, packaging, and storing of the product. Facility design and layout, production steps, contingency arrangements and personnel records must be relayed and may be referenced in a 'Type 5' DMF where such information already exists with FDA.[10]

Both IND and IDE investigations require Institutional Review Board (Ethical) assessment and approval. FDA must respond to the IND application within 30 days.

44.4.2.3 Phase 1

Phase I clinical trials (§ 312.21(a)) are typically designed to assess tolerability, or feasibility, for further development. In many situations, conducting the first-in-man study under an IND or IDE as a 'classis' phase1/feasibility study in healthy volunteers will be inappropriate for cell therapies.

FDA confirms: "We recognize that it may not be possible to follow each recommendation. For example, with some cellular products, it may be impossible to retain samples of the final cellular product due to the limited amounts of material available. Therefore, we recommend that you include your justification for adopting additional controls or alternative approaches to the recommendations in this guidance in the records on the phase 1 investigational drug."[11]

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[10] http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm122886.htm

[11] FDA Draft Guidance for Industry: INDs—Approaches to Complying with CGMP During Phase 1.

An investigational cell therapy for use in a Phase 1 study, is subject to the statutory requirements set forth at 21 U.S.C. 351(a)(2)(B). The production during Phase 1 is exempt from compliance with the cGMP regulations in part 211 but the exemption ceases if the investigational cell therapy has been made available for a Phase 2 or Phase 3 study or been lawfully marketed.

44.4.2.4 cGMP Criteria

The legislative framework for GMP requirements is set in §§210 and 211 for pharmaceuticals and for devices (Quality Systems Regulations) in §§820.

Staff qualifications and continued professional training need to be specified and recorded (§ 211.25).

Release criteria in 21 CFR 610 include sterility (§ 610.12) as common in biologics[12] including growth-promoting properties of the culture medium (note that some stem cell lines are reportedly compromised by mycoplasma[13]), identity (§ 610.14, established either through the physical or chemical characteristics of the product, inspection by macroscopic or microscopic methods, specific cultural tests, or in vitro or in vivo immunological tests) and potency – in vitro or in vivo tests, which have been specifically designed for the product so as to indicate its specific ability to effect a given result (§ 610.10; § 610.10; § 600.3(s)). This can be problematic in some cell therapies where the mode of action is a complex systemic interaction, but FDA representatives have given verbal indication of being alert to this complexity. Of particular interest for advanced therapies are the stipulations on culture (§ 610.10; § 610.18) which must be stored by a method that will "retain the initial characteristics of the organisms" – this obviously has to be reconsidered for complex cell derivation protocols. Moreover, the regulations talk about "source strains" and "seed lots" – which equates to 'master cell banks' and sub-cultures. Periodic tests must be performed to verify the integrity and purity of the culture and these results must be recorded and retained (§ 211.188; § 211.194).

Cell lines used for manufacturing biological products shall be:

(i) Identified by history;
(ii) Described with respect to cytogenetic characteristics and tumorigenicity;
(iii) Characterized with respect to in vitro growth characteristics and life potential; and
(iv) Tested for the presence of detectable microbial agents.

These rules do not apply to primary cell cultures that are subsequently subcultivated for only a very limited number of population doublings.

[12] Pharmaceutical Inspection Co-operation Scheme. Recommendation on sterility testing, Pharmaceutical inspection convention (1 November 2002) PI 012-1.

[13] Cobe et al. (2007) Microbiological contamination in stem cell cultures. Cell Biol Int 31(September)991–995.

FDA recognised that investigational cell therapy products may be manufactured as one batch per subject,[14] nonetheless testing of each batch for viability, cell number, mycoplasma and endotoxins close to the moment of application will usually be expected. Moreover, regulators ask for metrics on identity and potency but it is recognised that these may be 'moving targets'.

44.4.2.5 Expeditions and Facilitation

There are ways to expedite the process: Firstly FDA will 'fast track' the review if the product is intended for the treatment (or, in the case of devices, diagnosis) of a serious or life-threatening condition and it demonstrates the potential to address unmet medical needs.

When there is sufficient clinical experience to establish the safety of a product after use outside the US or in a different patient population, the FDA may review data from clinical studies performed outside the US in both the IND/IDE application or in an application for marketing approval. For devices, the sponsor can demonstrate substantial equivalence of the device to a legally marketed predicate device (510(k)).

Another way to speed up the process is to gain a Humanitarian Device Exemption (HDE) for certain devices (FD&C Act, §520 m) or an orphan drug designation (FD&C Act, 525, et. seq.). A device may be marketed under the humanitarian exemption for treatment or diagnosis of a disease or condition that affects fewer than 4,000 individuals per year in the US. The exemption relates to the effectiveness requirements for devices (FD&C Act, 529(m)(1), as amended February 1998). Several engineered skin constructs have been approved for market under the humanitarian exemption. Orphan drugs are those intended to treat a disease or condition affecting fewer than 200,000 individuals in the US for which there is little likelihood that the cost of development will be recovered from sales in the US. Other benefits of an orphan drug designation include grants and tax credits for clinical trials, FDA fee waivers and marketing exclusivity in the US for a period of 7 years from the date the compound is approved.

44.4.2.6 Vigilance

Manufacturers and clinicians should report adverse events through the FDA 'MedWatch' process. Post marketing studies may be a condition of the FDA approval, which may often be the case for novel cell therapies. Devices manufacturer may be required to conduct postmarket surveillance for any device which is a class II or class III device the failure of which would be reasonably likely to have

[14] FDA Guidance for Industry CGMP for Phase 1 Investigational Drugs; July 2008.

serious adverse health consequences or which is intended to be implanted in the human body for more than 1 year, or for a life sustaining or life supporting device (SEC. 522. [21 USC § 360 l]).

44.5 Regulatory Policy

It is implicitly clear that all discussions on 'Advanced Therapies' concern regimes of scientific, clinical and commercial conduct that do not fit the mould of existing medicines.

- Advanced therapies depart from a focus on 'simple' ligand-receptor interactions, but often also do not present a product the effect of which can be defined purely by its presence (such as whole-organ transplantation). Both safety and functionality of the product cannot be assessed with any significance in vitro.
- Cells and tissues are very complex entities that react very sensitively to a variety of stimuli, some of which cannot be replicated in vitro. Cell populations in many therapies are necessarily heterogeneous. The search for optimal purification protocols which is applicable for other contexts may not be appropriate for ATMP.
- Stem cells are often used precisely for their ability to differentiate into a variety of cell types and to engender changes in surrounding tissue. Thus any isolated assessment of proliferation profile and reactivity will always be insufficient. Almost all cells harbour a potential to proliferate in unexpected ways.
- Whereas in established 'pill-type' and biologics manufacture large 'lots' and 'batches' are released and tested, ATMP are often produced specifically for a particular patient. This means that regulatory provisions on product release testing may not only be inappropriate but also create a disproportionate burden.

44.5.1 Different Protagonists

Clinical trials require in-depth discussions between manufacturers, clinicians and regulators. Traditionally, only large pharmaceutical companies are equipped to shoulder the burden of maintaining GMP manufacturing facilities, of coordinating complex trials to the requisite standard and to meet the considerable bureaucratic requirements. The European ATMP regulation established special provisions and cost benefits for SMEs. However, it is sometimes overlooked that a great proportion of ATMP are not pioneered by industry but as individual ventures at a single (university) hospital, often on the initiative of clinicians collaborating with local academic groups.

It has been observed that for many ATMP products, especially cell-based and patient-specific treatments, the pharmaceutical industry has limited interest (and know how) in playing its 'usual' role of financing development and of acting as a sponsor in clinical trials.

Several reasons have been suggested:

- Many ATMP are manufactured very differently from mainstream medicines.
- It is often not possible to conduct trials on a large patient population.
- Many ATMP are seen to be more closely related to transplantation, an area that does not interface much with industrial R&D.

In many instances, the 'spin out' of ATMP development from the academic GMP facilities also meets technical difficulties: Purification of a specific ATMP product requires a highly specialised skill mix which combines elements of scientific expertise, with technical know-how and a strong clinical link to the treatment protocols of the individual patients.

Consequently, academic facilities are major contributors to the development of ATMPs. Not only do they have an important function in the translation of pre-clinical academic research into GMP, but many products may only reach clinical application by relying exclusively on academic facilities.

44.5.2 cGMP – Trying to Make Fit

Although the ATMP regulations are oriented towards the granting of a marketing authorisation its reach does not just extend to the 'launching' of a finished product on the Common Market. As we have seen, regulatory stipulations apply to every stage of development in clinical trials and even reach into pre-clinical development. One effect of the recent regulatory initiatives is to extend considerations of GMP to the area of ATMP. Rules on GMP have evolved over decades to ensure standards of quality, safety and efficacy in the development of pharmaceutical products. They stipulate a 'clean room culture' where every step is carefully monitored, controlled, validated and recorded. It is universally acknowledged that established GMP standards cannot simply be imposed on cell therapies without modification.

In fact, the ATMP Regulations in Europe were partially created to address this issue, but judging by the picture that emerges in this area, there remains a real concern that standards and practices in other fields are imported and imposed to advanced cell therapies without a careful assessment of whether these standards are appropriate and effective.

44.5.3 Some Examples

44.5.3.1 'Biomolecules'

The revised Annex 4 of 2001/83/EC contains the innocuous sounding provision: "For somatic cell therapy medicinal products and tissue engineered products, producing systemically active biomolecules, the distribution, duration and amount of expression of these molecules shall be studied." (4.3.2b)

This requirement could be interpreted as putting an unwarranted and unobtainable burden on complex ATMP. As an analogy: in organ transplantation, the 'biomolecules' emitted by the whole organ are not generally studied let alone exhaustively understood. Anyone familiar with recent scientific discourse in cell therapy will recognise that some perspectives are ascribing therapeutic benefit to the systemic interactions that the cell therapy induces, rather than to particular functions of the transplanted cells in situ. The mission to chart in detail every 'systemically active biomolecule' that a cell may produce in vivo is one that may well occupy generations of scientists for decades. The requirements of this provision could be seen to depart from the risk-based approach that the regulations posit.

44.5.3.2 Tumorigenicity

An issue that has created a great deal of concern for regulators in the US is the proposition of using cells with a multipotent differentiation profile, as such cells may 'revert' and grow uncontrollably in the recipient.

Where tumorigenicity is a theoretical concern, it is necessary to validate these applications using animal testing and ultimately in clinical trials. It is worth bearing in mind that decades of stem cell transplants have not produced large scale incidences of cancer. In situations where ATMP represent the only option to halt or mitigate the progression of a serious life threatening condition, lingering concerns about the long-term neoplasia risks must be weighted against a patients chances of survival without the intervention.

44.5.3.3 Hospital Exemption

It is clear from the proceedings that led to the Advanced Therapies Regulations, that the issue of a 'Hospitals Exemption' involved protracted discussion among Member States with very different positions and perspectives. The current wording therefore represents a baseline consensus, from which Member States are called to develop their own regimes. The context developed here is one that seeks to protect patients, but acknowledges that particular types of bespoke treatment are firmly a category apart.

The law support a clinician's unique right and responsibility to determine the best course of treatment for an individual patient. Many unlicensed stem cell therapies are only an option in very seriously debilitating or life-threatening conditions where no effective, licensed treatment alternative is available. In such cases, regulators must not encumber the decision making process but instead facilitate it by providing guidance about the management of situations in observance of appropriate safety standards.

Thus, where Art.3 (7) 2001/83/EC as amended states "Member States shall ensure that national traceability and pharmacovigilance requirements as well as

the specific quality standards referred to in this paragraph are **equivalent** to those provided for at Community level in respect of advanced therapy medicinal products for which authorisation is required" (our emphasis) we suggest that the level of equivalence required is approximate similarity, not one of identical application. While it is not yet clear how these requirements will be interpreted across Europe, what we have seen emerging in the UK and Germany may give rise to concern, where they allow no leeway on GMP standards. The aim of charting and enforcing (current) Good Manufacturing Practice is to operate high standards in the production of medicinal product. Often these regimes aim at establishing protocols that are robustly applicable in defined conditions over extended periods of time and generate products of comparative makeup, for example to avoid batch inconsistency. Where a treatment is inherently "non routine", these considerations of GMP are not as pertinent. For example, whereas GMP assessments focus strongly on Standard Operating Procedures (SOP), there is, by definition, no "standard" in non-routine ATMP production.

A further complication is introduced by the fact that data generated by relying on the Exemption cannot be generated for the purpose of analysing it scientifically – otherwise the treatment may be considered a clinical trial, which introduces a new set of regulatory requirements. This is clearly at odds with much of the discussions surrounding the exemption where it was assumed by many parties that small scale, proof of principle trials could be conducted under the exemption.

44.6 Summary Outlook

When considering the regulatory approach to novel cell and tissue based therapies, regulators in both Europe and the US have embarked on a precarious road: on the one hand copious new regulatory provisions and guidance suggest that the Regulators are responsive to the different nature of these therapies and aware of their potential. On the other hand there is a clear tendency to make the new regimes fit the existing mould as much as possible. In the US, greater discretion seems to be left with the regulatory authorities whereas in Europe the approach is officially more text-based while it remains uncertain how specific provisions will be interpreted by assessor and inspectors for EMEA and at Member State level.

By 30 December 2012, the European Commission shall publish a general report on the application of the ATMP-Regulation. By then it may already become apparent whether the regulatory approaches are sustainable or whether the concerns of inappropriate regulation we have alluded to here are justified. Until then, researchers, clinicians and entrepreneurs pioneering regenerative medicine treatments are in the position of not just scientific but also regulatory trailblazers – at dire risk of colliding with emerging rules but also with an opportunity to shape regulatory attitudes and regimes. In turn, regulators must be aware that in an emerging field even

'little things' such as inability to access appropriate guidance or rigid application of inappropriate standards can have an instant 'ripple' effect on the entire fledgling community and can inadvertently stifle all innovation at least in that particular branch of regenerative medicine.

Acknowledgements We are grateful to Dr. Anke Wagner (RTC Rostock), for her expert advice, craftsmanship and patience in designing the illustrations in this chapter.