



Technology Report – an English Abridgement

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Regenerative Medicine in Berlin-Brandenburg

BioTOP is a joint initiative of the state of Berlin and the state of Brandenburg under the umbrella of the TSB Innovationsagentur Berlin GmbH and part of the cluster management Health Capital. BioTOP is funded by the federal state of Berlin, the federal state of Brandenburg and the Investitionsbank Berlin, cofunded by the European Union (European Fund for Regional Development).

The Berlin-Brandenburg Center for Regenerative Therapies (BCRT) is run by the Charité – Universitätsmedizin Berlin, the Max Delbrück Center Berlin, and the Helmholtz Center Geesthacht, represented by the Teltow Institute of Polymer Research. The center pursues a highly interdisciplinary research program. It is funded as a translational research center by the German Federal Ministry of Education and Research, the Helmholtz Association, and the federal states of Berlin and Brandenburg.



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Introduction into Regenerative Medicine in the German Capital Region Berlin-Brandenburg

Ina Krüger

Regenerative medicine is an important field on the interface between biotechnology and medical engineering. Research in this area is advancing rapidly worldwide, and the public, too, views this development as positive. In February 2010, some 27,000 people in the 27 member states of the European Union were asked for their opinion in the Europabarometer Biotechnology study. The results showed that Regenerative Medicine is supported by the majority of EU citizens and finds broad approval.^[1]

Defining Regenerative Medicine

Regenerative Medicine is one of the most advanced specialised life science disciplines. Its aim is to understand and stimulate the self-healing powers of the body. To do so, it investigates the mechanisms of tissue formation and regeneration in embryonic, adult and aged tissues. The methods used are based on interdisciplinary approaches from clinical medicine, molecular and cell biology (genomics, proteomics, stem cell research), biochemistry, macromolecular chemistry, pharmacology, as well as physics, the engineering and materials sciences (e.g. cell culture systems, biomaterials), bioinformatics, medical engineering and nano- as well as biotechnology. Regenerative Medicine develops and applies innovative medical therapies to restore dysfunctional cells, diseased or injured tissues and organs by biological substitution (transplantation medicine), using cultivated cells and/or tissues (Tissue Engineering) and/or by stimulation of the body's own regeneration and repair processes.

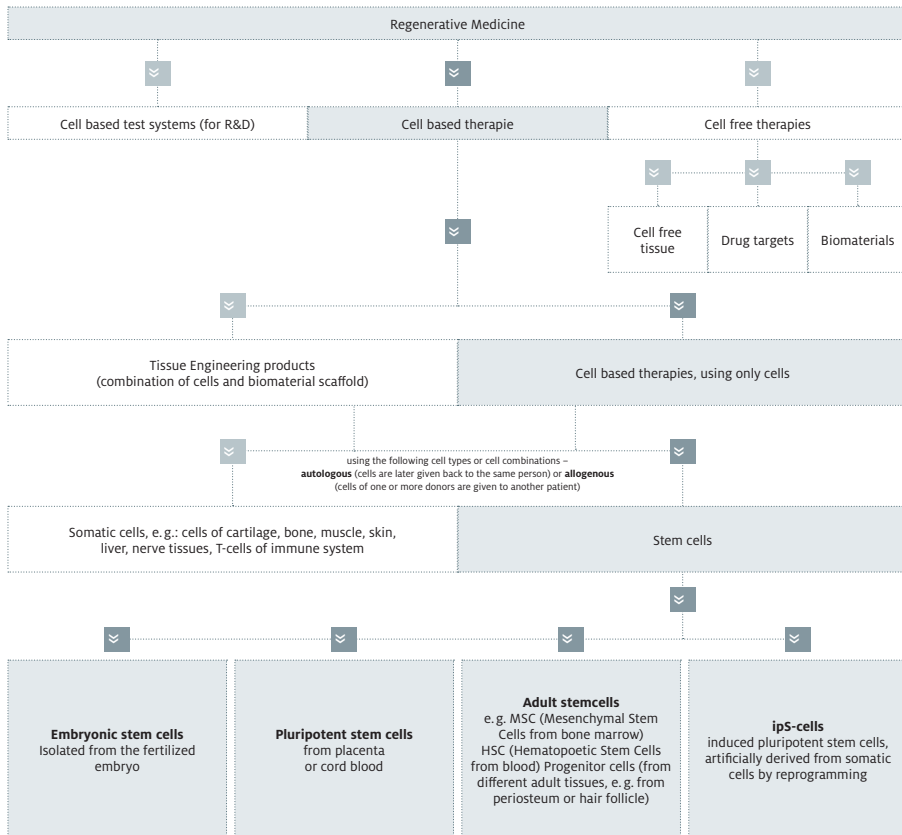
NIH Definition Regenerative Medicine:

Regenerative Medicine/Tissue Engineering is a rapidly growing multidisciplinary field involving the life, physical and engineering sciences that seeks to develop functional cell, tissue, and organ substitutes to repair, replace or enhance biological function that has been lost due to congenital abnormalities, injury, disease, or aging.

Regenerative medicine in Berlin-Brandenburg

Companies

The Berlin-Brandenburg region acquired an outstanding national and international reputation in the field of Tissue Engineering and Regenerative Medicine at an early stage. Starting in the early 1990s, researchers at the Charité performed pioneer work and developed the first 3D Tissue Engineering products as well as systems to support cell regeneration (Liver Cell Reactor). They also founded the first German companies in the field of Regenerative Medicine.

Overview of Regenerative Medicine matters, advanced^[2]

In the corporate sector, Regenerative Medicine trailblazers include the companies Co.don, Autotissue and Biochrom. Co.don AG in Brandenburg developed the world's first production technology and system which set the benchmark standard for clean room technology in biotechnological and pharmaceutical production under GMP guidelines. As early as 1997, the company was the first in Germany to receive approval for the production of autologous cartilage cell transplants under Section 13 of the German Pharmaceuticals Act (AMG).^[3]

AutoTissue GmbH was founded in summer 2000 by scientists from the Department of Cardiovascular Surgery at the University Medical Centre Charité. The company manufactures cardiovascular implants based on its patented decellularisation and sterilisation technologies. The focus is on decellularised implants which are used to substitute the pulmonary valve in patients with

congenital or acquired heart defects. From 2002 until 2009 more than 1,200 of these pulmonary valves were already implanted successfully in a number of countries.^[4]

The company Biochrom AG in Berlin was founded in 1981 and is now one of Europe's biggest manufacturers of media and serums for the culturing of human and animal cells. Biochrom supplies culture media for cell cultures, sterile solutions for pharmaceutical production and animal serums such as foetal bovine serum (FBS), which are needed by almost every research group engaged in the cultivation of cells, to customers worldwide. Biochrom has cooperated with scientists intensively for many years to keep developing the new media formulations required under the respectively current state of the art.^[5]

Science

The scientific foundation of Regenerative Medicine in Berlin-Brandenburg is provided, in particular, by the clinical expertise at both the University Medical Centre Charité and the German Heart Institute Berlin (DHZB), the biomedical basic research at the Max Delbrück Centre for Molecular Medicine (MDC), the Max Planck Institute for Molecular Genetics as well as the biomaterials research and technology platform at the Centre for Biomaterial Development of the Helmholtz Centre Geesthacht in Teltow.

The Berlin University Medical Centre Charité is one of Europe's largest university hospitals. Its 103 clinics and institutes which are organised in 17 Charité Centres employ more than 13,000 people. Every year, the Charité treats some 133,000 in- and 570,000 out-patients. At the same time, the hospital is a leading force in medical innovation. Based on its scientific research, it develops new methods for diagnosis, prevention and therapy – to the benefit of patients. More than 3,000 scientists and physicians at the Charité procure some 130 million Euros annually in external research funding. This is impressive proof of the research performance of this institution and creates additional income and jobs for the city of Berlin.^[6] The Charité is therefore also an ideal partner for research and clinical studies in the field of Regenerative Medicine.

The German Heart Institute Berlin (DHZB) is an internationally renowned high-performance clinic for the treatment of heart, thorax and vascular diseases and performs artificial heart implantations as well as heart and lung transplants. In addition to transplantation medicine and artificial heart technology, the Regenerative Medicine of the cardiovascular system forms one of the pillars of the DHZB research programme. Innovative cardiac cell therapy procedures are tested in experimental and clinical trials at the DHZB, which is also engaged in the preclinical development and clinical translation of heart valve and vessel implants produced by Tissue Engineering processes.^[7]

Researchers at the Centre for Biomaterial Development of the Institute of Polymer Research at the Helmholtz Centre Geesthacht in Teltow are engaged in the development of innovative, poly-

mer-based biomaterials for medical applications. The centre analyses and characterises polymer materials systematically, focussing on three types of material systems: stimuli-sensitive polymers, biomimetic systems and (co-)polymers which are cell- and tissue-specific. The polymer libraries so created form the basis for specific therapy developments. The polymer synthesis processes (including up-scaling technologies) and the processing, functionalisation and sterilisation of the materials are combined in the technology platform “Biomaterial Science and Bioactive Environments”. The aim is to implement multifunctional materials by combination of different functions. The Centre for Biomaterial Development provides the most advanced synthesis and processing systems. Clean rooms and a customised QM system guarantee the highest process quality. The centre’s up-scaling capabilities permit provision of the required material quantities and small series for clinical trials.^[8]

Network Activities

The first initiatives to network scientific workgroups in the field of Regenerative Medicine in Berlin-Brandenburg were launched in 1995 with the founding of the “Association for the Promotion of Tissue Engineering” under the auspices of the Tissue Engineering Laboratory at the Charité. The national “Tissue Engineering Interest Group” (IGTE) including both research groups and companies was founded in spring 1996 on the initiative of an Experimental Surgery Working Group. The IGTE has been coordinated by BioTOP since 1998. The “Interdisciplinary Research Association Biomedical Technologies” (IFV) was founded in 1999 and then integrated in 2002 into the “IFV Regenerative Medicine – Cellnet.org”. These activities have been supported by the Berlin Senate since 1999, while the German Federal Ministry of Education and Research (BMBF) has funded research in the focus areas “Tissue Engineering” since 2000, “Biological Substitution of Organ Functions” since 2001 and “Cell-Based Regenerative Medicine” since 2004.^[9]

In 2003, the IFV, BioTOP, TSB Medici, Charité and the “International Foundation for Regenerative Medicine” founded the cooperation platform “Regenerative Medicine Initiative Berlin” (RMIB) with support from many working groups and companies in the Berlin-Brandenburg region. The aim of this initiative was to establish a research alliance in the field of Regenerative Medicine. In 2006, it gave birth to the “Berlin-Brandenburg Centre for Regenerative Therapies” (BCRT) which is supported by the BMBF.

The BCRT^[10] expanded the R&D activities in the field of Regenerative Medicine considerably. It is sponsored by the Charité, the Max Delbrück Centre for Molecular Medicine (MDC) in Berlin and the Helmholtz Centre Geesthacht, represented by its Teltow Institute for Polymer Research. The BCRT pursues a highly interdisciplinary research programme, is supported by a wide range of internationally recognised experts from basic and clinical research and cooperates closely with industry. The BCRT is funded by the BMBF, the Helmholtz Association and the states of Berlin and Brandenburg and performs the role of a translation centre.

Research at the BCRT concentrates on the analysis and stimulation of autologous regeneration processes to support natural healing. The focus is thereby on the endogenous regeneration of bones, muscles, cartilages, the heart, vessels and the immune system based on the use of cells, bioactive molecules, biomaterials or combinations of them. The BCRT research programme comprises three indication areas (the musculoskeletal system, cardiovascular system and immune system) which are intermeshed closely with the platforms basic research, polymer-based biomaterials and translation research. They in turn are supported by internal Business Development services (market and patent research, targeted project management and partnering activities) and Clinical Development / Regulatory Affairs services (including the preparation of clinical studies and approval strategies).

The aim of the BCRT is to promote the translation of findings from basic research into clinical applications and near-market product developments such as cell- or biomaterial-based therapies.

To support the qualification of young scientists, the BCRT cooperates closely with the Berlin-Brandenburg School for Regenerative Therapies (BSRT) which offers an international post-graduate programme in Regenerative Medicine.

The RMIB (www.rmib.de) which was renamed “Regenerative Medicine Initiative Berlin-Brandenburg” in 2008 promotes networking in research and industry as a communication platform for Regenerative Medicine and adjacent disciplines and therefore also seeks to stimulate interdisciplinary cooperation between the BCRT, other research institutes, companies and organisations in the science and technology sector. In addition, it supports new activities and developments in Regenerative Medicine and conducts public relations initiatives to promote this field. The aim is also to extend the importance and success of Berlin-Brandenburg as a science and business location for this sector. Cooperation in the network concentrates on the regional focus areas in Regenerative Medicine.

In Berlin-Brandenburg, a range of organisations are also devoted to networking at the national and international level. In response to a regional initiative, the “Working Group Regenerative Medicine” was launched in summer 2003 with the aim of enhancing the competitive position of German research and industry internationally. In November 2004, it presented the position paper “Perspectives for Regenerative Medicine in Germany”, which included both a status report on the field in Germany and strategies for its successful further development in the form of detailed recommendations.^[11]

As one of its initiators, the BCRT participates intensively in the activities of the “Regenerative Medicine Initiative Germany” (RMIG).^[12] In addition, the research groups of the BCRT are involved in many cooperation projects and activities, including the founding of the “Indo-German Forum on Regenerative Medicine” in early 2010. Intensive contacts were already established with Korean research institutions, including Seoul National University, in the late 1990s. One result was the location of Pharmicell Europe GmbH, a subsidiary of the South Korean company FCB Pharmicell Co. Ltd.,

in Brandenburg. In 2009, the BCRT initiated a German-Californian cooperative venture resulting in 2010 in a tender invitation of the German Federal Ministry of Education and Research (BMBF) for funding applications for cooperation projects with the California Institute for Regenerative Medicine (CIRM) in San Francisco. The BCRT is also engaged in cooperation with partners in Britain, China, the Netherlands and other countries.

Regional Politics and Regenerative Medicine

Promoting the growth of Regenerative Medicine as a highly advanced technology segment with the aid of translation and networking activities can create new jobs, support the expansion of existing small- and mid-sized companies and attract new companies to Berlin-Brandenburg. With the BCRT and Charité, the region already has a strong science and clinical cluster, alongside a range of SMEs which have successfully positioned themselves on the market with their first products. Berlin-Brandenburg is therefore clearly the leading German region for the development of Regenerative Medicine. While some other states also possess research and/or clinical facilities in this segment, none of them provide the SME density and range of potential suppliers or specialised service providers available in Berlin-Brandenburg.

The regulatory environment for product approvals in the field of Regenerative Medicine has changed markedly since 2006. Cell-based therapies now require drug approval which involves high costs and extended timelines due to the associated clinical studies. The clinical groups and SMEs who are fighting hard to overcome this barrier to market entry urgently require support from the region. It can take many forms. What is important is, among other things, the establishment of a regulatory infrastructure which enables the research groups to translate their results into applications quickly and affordably. This includes an efficient translation structure at the BCRT, close cooperation with the Charité infrastructure in the implementation of clinical studies, efficient coordination with the state authorities to procure manufacturing permits. Also includes the exchange of information and experiences between the affected SMEs and clinical working groups as regards applications for product approvals to the EU authorities and Paul Ehrlich Institute (PEI) as well as intensive discussion about the available options under refund law. Attention thereby focuses on networking between the young SMEs and research teams as well as clinical users with the aim of promoting technology transfer and developing R&D cooperation projects to enhance the standing of Berlin-Brandenburg as a Regenerative Medicine location.

The financing of the required clinical trials is the biggest problem currently facing the Regenerative Medicine sector. The situation is set to improve as soon as the new approval regulations have been implemented, so that experiences become available for the first time which will help make the approvals procedure predictable. At the same time, the health insurance funds will need to define their reimbursement policies. Once these hurdles have been taken, an innovation surge in the health sector will be possible which will not cause any additional costs.

Introduction

In the Master Plan for the Health Capital Berlin-Brandenburg, Regenerative Medicine was allocated to the Field of Action 5 “Biotechnology and Biomedicine”. “The central task of the Field of Action is to develop long-term road maps with those involved and establish transfer centres for joint product development on the interface between business, science and clinical practice. The value chains for the key product categories of (...) Regenerative Medicine must be enhanced considerably. Health sector users must be involved in product development at an early stage. (...) The success of biotechnology companies therefore depends decisively on efficient technology transfer, the availability of funds and appropriately qualified experts.”^[13]

The foundations for the successful development of Regenerative Medicine in this region are in place: The translation centre BCRT is unique in bringing together basic research and clinical application; the region’s many small innovative companies provide both tissue-based and machined medical products, as well as cell-based therapies and necessary auxiliary products like cell culture media, bioreactors and analytics; the infrastructure for clinical trials at the Charité and many other hospitals in Berlin is of outstanding quality; the BSRT provides excellent training for specialists; the region provides a wide range of information, further education and consulting services; and, last but not least, the communication platform RMIB brings together the different players involved. The region’s advanced network structures in other disciplines ensure that interdisciplinary cooperation can take place, not only within the field of Regenerative Medicine, but also with adjacent disciplines. This creates the basis for developing new technological concepts, for example for the “biologization of medical engineering”. The different partners involved utilise the network synergies and work together to overcome market entry barriers. Good opportunities therefore exist to put into practice the visions Regenerative Medicine opens up and seize the tremendous opportunities for growth offered by the market for innovative therapies. As Matthias Wilken from the German Federal Pharmaceutical Industry Association said in an interview in April 2010 published at www.biotop.de: „The bigger the medical successes become, the greater both the pressure to remove the barriers and the interest in investing in the corresponding companies will be.“^[14]

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The Regulatory Framework

Barbara Pfüller

The complexity and dynamism of the regulatory environment for Regenerative Medicine products described in the Capgemini Report^[1] have by no means lessened, although the implementation of the EC Regulation on Advanced Therapy Medicinal Products (ATMP, 1394/2007/EC, effective since 31.12.2008) closed the gap between pharmaceutical and medicinal product legislation (Fig. 1). That it is often still not easy to classify the many Regenerative Medicine (RegMed) products and allocate them to the respectively applicable laws is reflected in the introduction of a special classification procedure for them by the EMA.^[2]

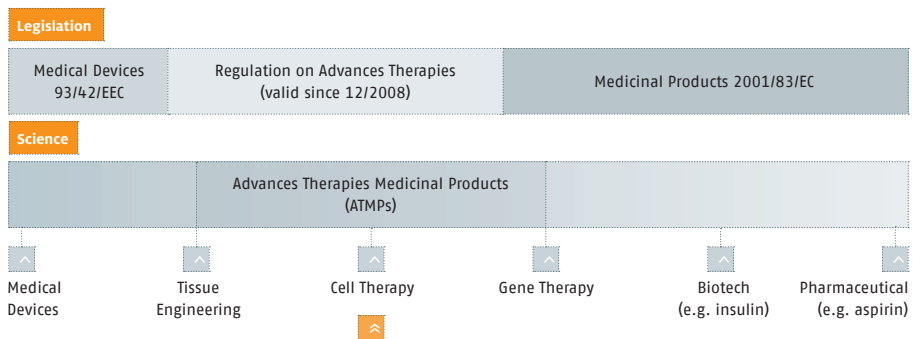


FIGURE 1 Presentation of the scope of the ATMP Regulation

Figure 1 shows which product groups are governed by the ATMP legislation:

- » Somatic cell therapy agents
- » Biotechnologically processed tissue products (Tissue Engineering)
- » gene therapeutics

In addition there are combination products (e.g. of pharmaceuticals and medicinal products) which are automatically governed by the ATMP Regulation and hence subject to a central approval procedure, if they contain cells.

ATMP legislation regulates the market admission and monitoring of products in the fields of gene therapy, somatic cell therapy and bio-engineered tissue products in the EU and is superior to country law. The central approval procedure is performed by the European Medicines Agency (EMA) and facilitates market access in all countries of the European Community.

National Implementation of the ATMP Regulation

Since the 14th amendment of the German Pharmaceuticals Act (AMG) entered into effect in 2005, clinical trials which examine the efficacy and/or safety of somatic cell therapy agents must not only be reported to the competent federal authority – the Paul Ehrlich Institute (PEI) in the case of cell-based medicines – but also be approved by it. To obtain approval for a clinical trial, the applicant must guarantee the greatest possible patient security achievable in the state of the art. This is demonstrated, among other things, by:

- » a manufacturing permit which presumes the quality of the medicine according to the GMP standard (good manufacturing practice), and
- » a pharmacological-toxicological examination corresponding to the respective state of the art which must conform with the GLP standard (good laboratory practice);
- » implementation of the clinical trials in compliance with GCP (good clinical practice).

The legal foundation for this procedure is the German “3rd Announcement for Clinical Trials of Medicines in Humans”.^[3] Compliance with these requirements is a time- and cost-intensive process for applicants, which can not be mastered without corresponding expertise. Not only university research facilities come up against barriers here.

The definition of ATMP in the ATMP Regulation with their partly difficult allocation to the field of pharmaceuticals or otherwise mentioned above was implemented in German law with the 15th AMG amendment which entered into effect in July 2009. Among other things, it includes a limitation of the so-called ‘point-of-care’ exemption (§4a par. 3 AMG) to “tissues obtained from a person in the course of a treatment procedure to be retransferred to the same without any change in its physical composition.” In addition, par. 4b implements the so-called ‘hospital exemption’ of the ATMP Regulation (§28). It includes “pharmaceuticals for innovative therapies, which:

- 1) are prescribed for an individual patient as a personal preparation;
- 2) are produced routinely according to specific quality standards; and
- 3) are used in a specialised patient care facility under the professional responsibility of a physician”

and concerns the 4th section (Approval) and 7th section (Delivery of Medicinal Products) of the AMG. The holder of the approval and of the market admission is replaced by the holder of the authorisation under §4b par. 3 sentence 1 (Authorisation by the Competent Federal Authority (PEI)).

As regards medicinal products destined for clinical trial, a permit for their extraction, processing and examination as well as marketing must have been procured in the case of tissues and tissue preparations (§20b, §20c, §20c).

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Production Requirements

Ina Krüger

The many different products that can be classed as belonging to the Regenerative Medicine (Reg-Med) segment present shared requirements as regards their production processes. Since these products are generally introduced into the human organism, they must be manufactured in compliance with special safety and quality regulations. The abbreviation GMP is generally used in this context. GMP is a term introduced by the US Food and Drug Administration (FDA) in 1962 and stands for a collection of behavioural measures and rules that must be observed in the production and handling of certain products (e.g. pharmaceuticals, veterinary medicines, active ingredients, foods, cosmetics) to ensure that these products are manufactured reliably, in replicable manner and traceably in the desired quality, and that every kind of contamination is prevented.

The obligation to observe the GMP rules is enshrined in corresponding laws (e.g. the German Pharmaceuticals Act and European Directives) or by intergovernmental conventions. There is no such thing as ‘the’ GMP rules/requirements/guidelines, but a large array of GMP requirements with supplementary or additional guidelines. Which GMP requirement is to be applied largely depends on the nature of the product (e.g. cell-based product, acellular tissue), the pharmaceutical form, the specification (sterile, low bacterial count, non-sterile), the stage of development (development or production), the process step (critical or non-critical) and the sales location (e.g. USA, Europe, Asia). Only once these factors are clarified can the appropriate GMP guidelines be selected and applied.^[1]

Strictly speaking, this GMP concept in the narrower sense of the term does not apply to the entire production process of RegMed products – especially if, for example, the process of cell extraction and the transplantation of the tissue substitute in Tissue Engineering belongs to the actual production process, but can naturally not be implemented exclusively in the classical GMP environment, but e.g. in an operating theatre. This is why the term “Good professional practice” (Gute fachliche Praxis, GFP) was introduced for cell-based therapies in Germany. It refers to the extraction of the tissue sample, its storage and the actual production process in the laboratory and product confectioning (see figure below).



FIGURE “Good professional practice” (GPP) in the production process of cell-based medicinal products

The actual GMP process (centre of the graph) depends on the product concerned and is consequently very product-specific. This applies to both the processes and the physical facilities involved, which are by no means replaceable. This means that a GMP area meeting the requirements of the manufacturing process of a specific product must be planned and established. It therefore follows that products which are (and are permitted to) be produced in a particular GMP area can not easily be replaced by others.

Depending on the production process requirements (e.g. clean room class, sterility requirements, security requirements, room heights, etc.), the costs of the establishment of a GMP area are in the five- to six-digit range. Current operating expenses (power for air and water purification and sterilisation and the use of single-use goods in the production process, maintenance of the operating permit, etc.) should not be underestimated. The planning of GMP plants is therefore adapted very precisely to the planned production capacity of an enterprise. Sub-letting of GMP capacity is rarely an option due to product specificity and risk. Contract manufacturing under GMP conditions is generally only worthwhile for large, stable sales volumes, but not for small product volumes with changes in product type. Companies can theoretically only make free GMP capacities available if (very) similar product categories are to be produced there. The required similarity in most cases precludes cooperation of this kind, however, because this would then tend to involve competitors with whom the security of process know-how has to be observed. The establishment of dedicated specialised GMP plants will always be less expensive than the provision of unused GMP areas.

To ensure sustainability of a spin-off or greenfield development in a region, it is essential that companies can fill their product pipeline from the cooperating science landscape, e.g. that they find an environment in the regional university and clinical research and development scene which enables

them to validate their own product developments in proof-of-concept studies in the form of animal trials or different stages of clinical validation. Hence funds for corresponding clean room and/or GMP infrastructures should be made available, especially also for research and development. The use of services from the public research organisations in the field also result in more external funding income and, in turn, ensure that companies remain in the region.

The availability of appropriate GMP production facility in a company alone, however, is not sufficient to bring a product to market successfully. To obtain permission to manufacture products in this GMP facility for testing in clinical studies or for use as therapies, the competent regional government authority of the state in which the facility is located must grant a manufacturing permit.

[1] www.gempex.de/d/wegweiser/wasistgmp.htm

Special Quality Control Requirements

Rainer Seubert

Regenerative Medicine is gaining in importance in science and increasingly also in business. High research and development subsidies, in particular in the university environment, also permit targeted product developments in new indication areas. The concept of translation, which is increasingly significant especially in Berlin, is important because the results of academic research and development are to result in a product or therapy for patients. In Germany and across Europe, marketing and ongoing development in the field is performed mainly by start-ups or smaller biotech companies. In Germany, the subsidies available to small biotech firms are excellent, but the respectively required private co-financing is a major problem.

Regenerative Medicine products in the form of skin, bone, cartilage and disc substitutes are already on the market with very good clinical results. A new development from the Charité University Medical Centre Berlin is a cell therapy of specific heart cells (CAPcells) for the treatment of chronic myocardial insufficiency. This therapy was developed in cooperation with the Berlin-Brandenburg Centre for Regenerative Therapies and led to successful animal trials. The Charité spin-off CellServe GmbH is now continuing the university development and is licensing for this product development. A clinical study is to be launched as soon as possible. With reference to the example of this 'CAPcell' product development, some of the generally applicable quality control requirements are described below.

Quality control requirements

Since cell-based therapies are governed by the German Pharmaceuticals Act (AMG) the highest quality standards must be guaranteed in development, production and logistics. Quality Management Systems (QMS) are increasingly in operation even in academic research. One example are ISO certified QM systems such as those used in the Tissue Engineering Laboratory at the Charité of Prof. Dr. M. Sittinger, where the heart cells were first isolated.

The production processes in companies pose the highest demands regarding quality and safety. Production is performed in a GMP or ultra-clean laboratory. GMP refers to the guidelines for quality assurance of the production processes and environments in the manufacture of medicines, active ingredients and medicinal products. In pharmaceutical manufacturing, quality assurance plays a central role since any divergence from the assured quality here can have direct influence on the health of patients. A GMP-compliant quality management system serves to ensure product quality and fulfilment of the public health authority regulations governing the marketing of the products concerned.

In the clean room laboratory, tissue-specific cells are isolated from a tissue sample (in this case a biopsy from the heart muscle of the patient), cultivated and then returned to the physician using advanced transport logistics. Strictly defined examination procedures are applied to ensure that the cells used preserve their required characteristics during the production process and are not contaminated, e.g. by viruses. The examination and analysis methods used are subject to continuous improvement. Here, too, there is great demand for the translation of scientific findings into validated test methodologies available to the market. During the transport of cell preparations, especially their stability, purity and safety must be ensured by use of special refrigeration containers. Like all production process steps, the logistics are regulated by standard operating procedures (SOP). Such SOPs are also used, in particular, in pharmaceutical processes and clinical studies where it is vital that compliance with identical process sequences is always ensured and documented.

Outlook

The innovative market for cell-based therapies is a huge growth market which will provide treatment options for diseases that could not be treated to date. Given strong support from the region and subsidies from the German federal and state governments, new products and therapies can be expected in the foreseeable future if investment activity hopefully revives again.

Reimbursement Options for ATMP

Ina Krüger

As Capgemini already noted in 2005 ^[1], the technological superiority of TE/RegMed (Tissue Engineering/Regenerative Medicine) products alone is not sufficient to ensure their competitiveness. It is indispensable to demonstrate their efficiency and efficacy. The efficiency of medical health services and activities can be measured by economic evaluation (economic efficiency analyses). Here, the costs and benefits of a medical intervention are compared. The measurement of medical efficacy is performed by a proof of efficacy examination. Randomised clinical trials are now the “gold standard”.

The regulations governing refunds are complex both in Germany and other European countries and regulated nationally. There are, on the one hand, private refunds by the private health insurances (PKV), patients (self-payers) and other forms of provision and, on the other, budgeted cost reimbursement by the governmental health insurers (GKV). All citizens subject to mandatory statutory insurance are covered by the governmental health insurance (§ 5 German Social Code V (SGB V) and/or § 2 German Farmers' Health Insurance Act (KVLG) 1989). Measured in the percentage of insured (app. 90%), the statutory health insurance (GKV) is most predominant by far. In accordance with SGB V, the GKV may only refund services which were provided in compliance with the non-discrimination precept and the economic efficiency precept.

The out-patient segment

The use of ATMP products in the out-patient segment (practice-based doctors) is eligible for GKV cost refund only if a settlement code number under the uniform evaluation standard (EBM) has been awarded. If there is no appropriate EBM number, an extensive application procedure must be implemented. ATMP are regarded as innovative therapies. Hence they generally do not fall under any EBM number and require authorisation by the Federal Joint Committee (G-BA) (§ 135 SGB V).

The G-BA (www.g-ba.de) defines which medical care services are eligible for refund by the statutory health insurers. It consists of representatives of the health insurances, the medical profession, patient representatives (with submission, but no voting rights) and so-called neutral members. An application must be filed for a diagnostic or therapeutic method to be discussed in the G-BA. Such applications may be filed only by the neutral members of the G-BA, the German National Federation of Health Insurance Funds, the National Association of Statutory Health Insurance Physicians (KBV), the National Association of Statutory Health Insurance Dentists (KZBV), the German Hospitals Association (DKG) and the patient representatives. In addition, all statutory medical and statutory dentistry associations and the federal associations of the hospital operators may also submit respective applications.^[2]

For the case that there is no accounting code allowing ATMPs and medical products from the Reg-Med segment to be submitted for reimbursement, then an applicable representative must be found who will apply for the product refund. The G-BA then examines the therapeutic utility of the method (§35 SGB V), its medical necessity and economic efficiency, as well as the required qualifications of doctors and necessary documentation, in cooperation with the Institute for Quality and Efficiency in Healthcare (IQWiG). These processes may take years. Following a positive decision of the G-BA, the product or treatment method may then be eligible for EBM refund by the statutory health insurers.

The in-patient segment

When using the products or methods in the in-patient segment (hospitals), funding is provided under the DRG system (diagnosis related groups). This system is based on the provision of financial budgets for the entire complex treatment of each disease. The hospital decides on the use of the treatment methods selected based on the benefit for the patient and the costs of the products and/or methods used. If the RegMed product provides convincing patient benefit and can be financed reasonably in the context of the respective budget, it will be refunded as part of the relevant DRG. Problems arise if the costs incurred do not cover the entire treatment. In this case, an adjustment or the introduction of a new DRG is required.

The DRG are newly agreed annually for one year respectively by the German National Federation of Health Insurance Funds, the German Hospitals Association (DKG) and the Federation of Private Health Insurers. They grant industry associations the option of submitting amendments to a proposal procedure. The proposals are then examined by the Institute for the Hospital Remuneration System (InEK GmbH).^[3]

Since 2005, under § 6 par. 2 KHEntgG, companies have also been able to agree temporary, case-related payments or additional payments for new diagnostic and treatment methods (NUB) with individual hospitals^[4]. This application procedure may also take several years.

In addition, transitional formats between the out- and in-patient segments increasingly exist, such as out-patient operations in hospitals. Every manufacturer must therefore devise its own strategy depending on the nature of its product and organise the corresponding activities.

Contract-based healthcare provision

Financing of the products in the context of contract-based healthcare provision (including integrated care) is one alternative to these principal refund options.

Since the German law on reorganisation of the pharmaceuticals market (AMNOG) entered into effect, manufacturers have the option of introducing products into complex treatment strategies under individual regional agreements which generally only apply for a single healthcare provider. The focus here is on patient need. To meet it, healthcare packages are assembled from the offers of

different service providers along the therapy chain which, in total, are cheaper for the sponsor. Such healthcare packages are organised by management companies which provide the corresponding contract structures. These companies are the contract partner for the healthcare sponsor and the individual service providers.

What do you suggest young companies which develop medicinal products for innovative therapies should do?

“They should begin to look at the legal regulations as early as possible. They should document all data carefully. They should not treat patients outside clinical trials if possible. And they should be prepared to subdivide the approval process into smaller packs by using the certification procedure to receive support from the relevant authority along with milestones to be taken step by step, so that they are sure and can also document externally that they are on the right road...”

Extract from an interview with Matthias Wilken, Head of Drugs Approval Europe at the German Federal Pharmaceutical Industry Association (BPI e.V.) at www.biotop.de/interview/index+M59c9a72267d.html

The first contract-based healthcare formats are currently being tested in model projects. No conclusive statement can therefore currently be made regarding the possibility for participation of ATMP manufacturers. However, participation in the budget negotiations already in progress between healthcare funding agencies and different stakeholders on the service provider side should be a swift option for procuring access to statutory insurance cost refunding for a new RegMed product without the EBM or DRG. The precondition is the clear health economic benefit of the RegMed products for a defined patient group and therapy strategy.

Competition in the reimbursement system

In the struggle for a reimbursement code number it must also always be noted that innovative therapies compete with the recognised classical therapies over one and the same capped budget of the health insurers. The economic efficiency of products and treatment methods will therefore play an increasingly important role. If new products can treat diseases that could so far not be treated, their benefit is certainly greater than if the new product is ‘only’ better than the existing one. In every case, however, more financial volume would need to flow into the refund system for a new method or better and more expensive product, or other services be cut. Since our society is neither prepared nor able to continue increasing the funding of the healthcare system significantly, however, a new product always has to compete for refunds with existing products and services. For this reason, the new product should always be better. Its equivalence or superiority must be demonstrated. Only then is there any prospect of reimbursement in the statutory (GKV) or private (PKV) health insurance system.

Personal healthcare services

Only the offer of an approved personal healthcare service (IGel) to self-paying patients can circumvent this health insurance system (GKV and PKV). The level of the costs to be charged to the patient is thereby guided by the medical fee schedule for physicians (GOÄ) which governs refunding in the private health insurer segment. Personal healthcare services can only be invoiced if “they were provided at the request of the payer” (§ 1 par. 2 GOÄ). According to the federal master agreement governing (contract) medical care, statutory insurance (GKV) patients must confirm in writing before treatment begins that they expressly request treatment at their own expense.^[5]

There is a clearly recognisable readiness among Germans to participate in financing a treatment with TE/RegMed products. Almost 50% of those surveyed, however, are not prepared to pay more than €1,000 for a TE/RegMed product. The survey conducted by Capgemini in 2005^[6] also showed that the preparedness to pay rises with familiarity with the subject and with the scope of health insurance cover (insurance with a statutory health insurance with or without supplementary or additional private insurance). The high TE/RegMed product acceptance among doctors is also positive. For them, the costs of a TE/RegMed treatment are also an important criterion.

It should accordingly be the task of all involved to increase familiarity with the current possibilities of Regenerative Medicine, without raising wrong expectations with excessive visions for the future. Greater familiarity generates trust in the technology and may lead to broad acceptance both in the population and among public and private funders in the medium term.

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Financing Options

Holger Klemm

On their road to success, innovative technologies and therapies must take the hurdles development, international approval, health insurance refund and market launch. This generally also applies

for RegMed projects which include revolutionary technologies from stem cell research. Whether a new technology really does find broad application eventually depends on how successfully these four partly unpredictable hurdles can be scaled. This presents major financing challenges, especially for the most innovative RegMed projects, in particular during the early stage since equity financing options were already far more scarce in Germany than the USA or Britain even before the current financial crisis.

RegMed projects are often characterised by expensive and long research and development phases and are financed essentially by a combination of the instruments subsidies and equity procured from investors. Financing by debt capital is generally relevant for life sciences companies only for the provision of operating funds. For many RegMed projects, internal funding of development activities by generating own sales revenues is not an alternative to equity or subsidy financing because these companies generally do not yet sell own products, but are only developing them. In international comparison, there are not many differences regarding the most common financing instruments for RegMed projects. But the share of subsidies relative to equity in total financing is usually higher in continental Europe than in the USA or Britain since the Anglo-American financial markets are more developed.

Research and development subsidies

In Germany, the conditions for procuring subsidies for research and development projects in the field of Regenerative Medicine are especially attractive in the Berlin-Brandenburg region. This strong government support compared to other German states, especially as regards projects at research institutes, is provided mainly in the form of funding by the Berlin Centre for Regenerative Therapies (BCRT). The BCRT currently supports some 100 projects with co-financing from the Charité and Helmholtz Association. The investment banks IBB and ILB also provide very attractive R&D funding programmes to companies.

The German Research Foundation (DFG) and the German Federal Ministry of Education and Research (BMBF) also provide financially robust RegMed specific programmes which are partly also accessible to companies. Founders can obtain financial support for their R&D projects from programmes like Go-Bio, EXIST-Forschungstransfer, EXIST or the spin-off funds of the DFG. Research organisations like the Max Planck Society, Fraunhofer Society or Helmholtz Association support spin-offs from their organisations with R&D grants.

At the international level, funding conditions for RegMed projects are even more attractive. For example, the California Institute for Regenerative Medicine (CIRM) has a budget of 3 billion US Dollars for the promotion of stem cell research at Californian universities and research facilities. German scientists who are funded in the context of a BMBF project can participate in these CIRM funding initiatives by participation in German-Californian cooperation projects, as confirmed by the first tender invitation for a BMBF-CIRM cooperation in late 2009. In particular innovative and prom-

ising companies may also receive grants from international organisations like e.g. the Juvenile Diabetes Research Foundation or more broadly oriented biomedicine support organisations like the Wellcome Trust. Companies who wish to benefit from these funds must always provide equity co-financing.

Other funding options

In addition to funding assistance for R&D expenditures, the investment banks of Berlin and Brandenburg provide further funding options, e.g. in the form of subsidies for business consulting, patent applications and product marketing.

Equity from financial investors

The conditions for equity financing of RegMed projects are similar in Germany and internationally: The approval and refund of RegMed products are still often less predictable than for other life sciences technologies, which impacts negatively on follow-on financing and can therefore already limit the chances of early phase financing.

The German High-Tech Founder Fund (HTGF) successfully occupied the previously difficult early phase segment in recent years, partly in cooperation with the investment funds of the state banks such as IBB-Beteiligungsgesellschaft or Brandenburg Capital. Despite the innovation performance of companies and research organisations in the RegMed field, the HTGF portfolio so far includes only few RegMed companies. Apart from the development and market risks always inherent in life science projects, unclear refund and approval strategies additionally limit the possible scenarios for follow-on financing or an exit in RegMed projects, probably also from the perspective of the HTGF. These problems are especially evident in the field of stem cell based therapies. In Brandenburg, the regional early phase fund now being prepared – an instrument already established in other German states – will form a good supplement to the HTGF. However, this new fund is unlikely to provide significantly better financing opportunities for projects with unpredictable refund or approval situations.

In the current financial market environment, competition for scarce German and European venture capital for later financing cycles has also intensified further. Existing investors now play a far greater role in many follow-on financings than they did only a few years ago.

With the two new funds, Charité Biomedical Fund for companies close to the Charité and the Humboldt Fund for spin-offs from Humboldt University, the opportunities should at least improve for the most promising projects.

Attracting equity at the stock exchange by an IPO is currently unrealistic, not only for German RegMed companies. The last IPO in Berlin-Brandenburg in the RegMed sector was launched in 2001 by the company Co.don AG.

Project-related joint ventures with an investor are an interesting but less common financing instrument in the life sciences sector. In certain circumstances, this form of financing can be attractive for financing clinical trials from Phase II onwards.

Equity from strategic investors and partners

Many RegMed projects entail long and expensive development periods often substantially defined by regulatory requirements, and target products whose health insurance refunding must yet be secured. Here, business models which already involve experienced partners in early clinical development, in the planning for obtaining health insurer refunding and, in particular, in commercialisation, can be very valuable. The possible instruments for RegMed project equity financing include corporate ventures, R&D cooperation projects, out-licensing or M&A. Many of the big strategic partners suited for these strategies are US companies which often have more extensive regulatory, refund and commercialisation experience and may also possess more equity.

Conclusion

The funding conditions for RegMed projects in Berlin-Brandenburg are very attractive, especially also due to the BCRT. Equity co-financing, however, remains THE main challenge every company has to confront in global competition for scarce capital. Possible investors are usually well versed and therefore highly selective. Extensive support in the regulatory and approval strategy, e.g. by the BCRT, the development of a refund strategy and cooperation with the best strategic partners are essential to optimise the prospects for successful solicitation of equity capital.

Business Models in the Regenerative Medicine Industry

Ina Krüger

Rising life expectancy is creating greater demand for therapies to treat age-related illnesses. Among younger people, too, the incidence of new popular diseases like joint and back pain, osteoporosis, diabetes and obesity is rising, due among other things to lack of exercise and bad dietary habits. The majority of these diseases can still not be healed, but their symptoms can be relieved by chemical or biological medicines. Regenerative Medicine (RegMed) and Tissue Engineering (TE) hold out the hope of healing many of the diseases mentioned permanently.^[1,2] The commercialisation of Regenerative Medicine has only just begun, however. The first start-ups in the field of TE/RegMed

in Germany date from the early 1990s. The founder wave reached its peak with 15 new companies founded in 2000. As in biotechnology more generally, a first consolidation then began.^[3]

Stem cell research has made tremendous progress in recent years. So far, however, medical scientists have only rarely succeeded in healing defined diseases with the aid of stem cells. One pioneer is blood cell transplantation. This procedure was first tested successfully on a patient in Heidelberg 25 years ago. In the meantime it has become standard in the treatment of acute leukaemia^[4] and is also established at the Charité in Berlin.

As is the case in all high-tech sectors, a large proportion of RegMed innovations have until now come from university or research institutes. German academic RegMed research occupies a leading position internationally. It should be noted that, despite comparatively unfavourable conditions, Germany is the number 2 after America in terms of the number of companies in the field of Tissue Engineering.^[5]

Table 1 shows the number of companies listed in the MedTRACK database (www.medtrack.com) in summer 2010 under the respective search terms. The database of Business Insights Limited (www.business-insights.com) states for 2006 that 106 stem cell companies existed worldwide. After combining and evaluating these data and removing repeat listings of the same companies the figures show that some 860 companies worldwide are engaged in Regenerative Medicine in the broadest sense of the term, of which app. 53 companies can be described more specifically as Tissue Engineering companies. In 2007, Capgemini counted 29 RegMed companies in Germany.^[6] In Berlin-Brandenburg, app. 15 SMEs are currently affiliated with the Regenerative Medicine Initiative Berlin-Brandenburg (excl. consulting firms).

TABLE 1

Number of companies in online databases (www.medtrack.com and www.business-insights.com) listed under the cited search terms for the countries/regions specified

Search terms	USA	EU	Germany	Other	World
Biomaterials and tissue regeneration	203	124	24	89	416
Stem cells	100	54	10	54	208
Cell based therapies	45	35	5	21	101
Transplants	14	4	0	3	21
Tissue Engineering	86	48	12	58	192

At the start of 2010, the international database for clinical studies (<http://clinicaltrials.gov>) listed 107 studies on the use of mesenchymal stem cells (MSC) alone. Four companies, Osiris Inc. in the USA, Cellerix S.A. in Spain, FBC Pharmicell Co. Ltd. in South Korea and Miltenyi Biotec GmbH in Germany are already conducting MSC phase II studies. Researchers at the Berlin-Brandenburg Centre for Regenerative Medicine (BCRT) are also involved in the German study. Many patent fam-

ities which cover the applications of stem cells for regeneration in different indications (e.g. Osiris) or protect the principle of Tissue Engineering, for example, already exist. Here, it is important that researchers are aware of the fundamental importance of patents and their timely registration as the precondition and foundation for business models and license sales. In addition, the creativity of scientists in detecting new aspects and innovations over the prior art is vital.

“Successful German biomedical research continuously opens up new application areas. Tissue Engineering already provides patients with many products, e.g. heart valves and vessels, bones, discs and many others. Breakthroughs have also been achieved in treating extensive skin injuries and cartilage damage. Germany has the opportunity to translate the results of cutting-edge research into benefits for patients, economic success and new jobs.”^[8]

Companies engaged in Regenerative Medicine compete with providers of substitutes, e.g. orthopaedic implants. Medical engineering and pharmaceutical manufacturers, which have primarily developed and marketed substitutes until now, are increasingly also turning to Regenerative Medicine. The business consultancy Capgemini still sees major problems in the development of marketable RegMed products, including remaining gaps in the understanding of cell-biological processes, lack of evidence of the safety of the products and processes and the lack of standardisation causing excessively high production costs. There is, in particular, considerable optimisation potential in the field of innovative logistics solutions. The internationally very diverse approval and reimbursement regulations impede expansion to foreign markets. Nonetheless, the range of products is increasing and the pipelines are full. The dominant technologies used are autologous cells, adult stem cells and growth factors, partly combined with biopolymers.^[7,8] The growth factors are attracting interest among pharmaceutical manufacturers since they can be produced and marketed in the classical pharmaceuticals value chain.

Table 2 presents and compares the existing RegMed business models. It looks only at the models in operation or scheduled to start operation following approval in Berlin-Brandenburg and/or Germany.

The companies fill their product pipelines from their own R&D departments or on the basis of R&D cooperation with university or other research working groups. The intellectual property (IP) of the companies often consists of their own patents and/or exclusive or non-exclusive licenses. In some areas (autologous cell therapy agents, cell or tissue banks, cell-based test systems, R&D materials), there partly exists ‘freedom to operate’. This means that the methods, technologies or materials used there are either not patentable, already prior known (state of the art) or that the patents have expired. Especially in the field of cell and tissue banks attempts are therefore being made to acquire patents or licenses for freezing or decellularisation technologies.

The cells and tissues used in the different business models come from different sources. The cells and tissues for autologous applications (the patient receives his own cells/tissue back) are exclusively obtained by medical intervention in an operating theatre/room (OR). In the ATMP producing business models these autologous cells are then still processed in the OR or external GMP laboratories and returned to the patient in a further operation. This business model therefore corresponds more to a service than a typical production process like those practiced in the pharmaceutical or medical engineering industry.

Banks obtain their cells or tissues from living (OR) or deceased donors (pathology) under strict ethical and legal regulations. This leads to allogeneic cell or tissue sources, i.e. allocation of the donor to a particular receiving patient is no longer necessary. A 'raw material warehouse' can be established and the materials processed using classical production processes. These cell and tissue banks can become suppliers for enterprises engaged in the other business segments ('R&D services', 'Cell-based test systems', 'R&D materials' and 'ATMP devices and materials') listed in Table 2.

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Business Segment	Companies	Production	Product Approval	Market	Sales Channel	Reimbursement
Tissue engineering (ATMP)	Mainly SME	Under GMP, in own system or outsourced	Under AMG	Patients with defined indications	Hospitals, doctors in practices	health insurers, self-payers
Autologous cell therapy products (ATMP)	SME and hospitals	Under GMP, in own system, outsourced or directly in hospital OR	Under AMG or as experimental therapy	Patients with defined indications	Hospitals, doctors in practices	Health insurers, self-payers
Cell banks (e.g. stem cells from umbilical blood)	(non-profit) SME, university hospitals	Cell isolation under GMP, storage	Ethical decision and depending on market, under tissue law	R&D facilities, TE-SME, hospitals, doctors' practices, mothers giving birth	B2B or hospitals and doctors in practices	Direct, self-payers
Tissue banks (e.g. bones, heart valves)	(non-profit) SME, university hospitals	Decellularisation under GMP, in own system	Ethical decision and depending on market, under tissue law, medicinal product law	R&D facilities, TE-SME, hospitals, doctors' practices	B2B or hospitals and doctors in practices	Direct or health insurers
Medical engineering (e.g. coated stents)	SME, big industrial companies	(Own) clean room production	Medicinal product law	Hospitals, patients with defined indications	Hospitals	Direct or health insurers
R&D services	SME	Laboratory and/or office	free	R&D facilities, (TE-)SME, hospitals, big industrial pharma and med-tech companies	B2B	Direct payment by customers
Cell-based test systems	SME, R&D facilities	Laboratory	free	R&D facilities, (TE-)SME, hospitals, pharmaceutical industry	B2B	Direct payment by customers
R&D devices and materials (e.g. serums, bioreactors)	SME, big industrial companies	Laboratory, poss. clean room	free, poss. CE or TÜV	R&D facilities, hospitals, big industrial pharma and med-tech companies	B2B	Direct payment by customers
ATMP devices and materials	SME, big industrial companies	Poss. own clean room production	free, poss. under medicinal product law, CE or TÜV	R&D facilities, (TE-)SME, hospitals, doctors' practices	B2B	Direct or health insurers

TABLE 2

Comparison of different business models in Regenerative Medicine

(ATMP = Advanced Therapy Medicinal Product, B2B = business to business, CE code = freely marketable industrial products in the European Union, R&D = research and development, GMP = Good Manufacturing Practice, SME = small and mid-sized enterprises, TE = Tissue Engineering, TÜV = the German Technical Service Corporation)



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