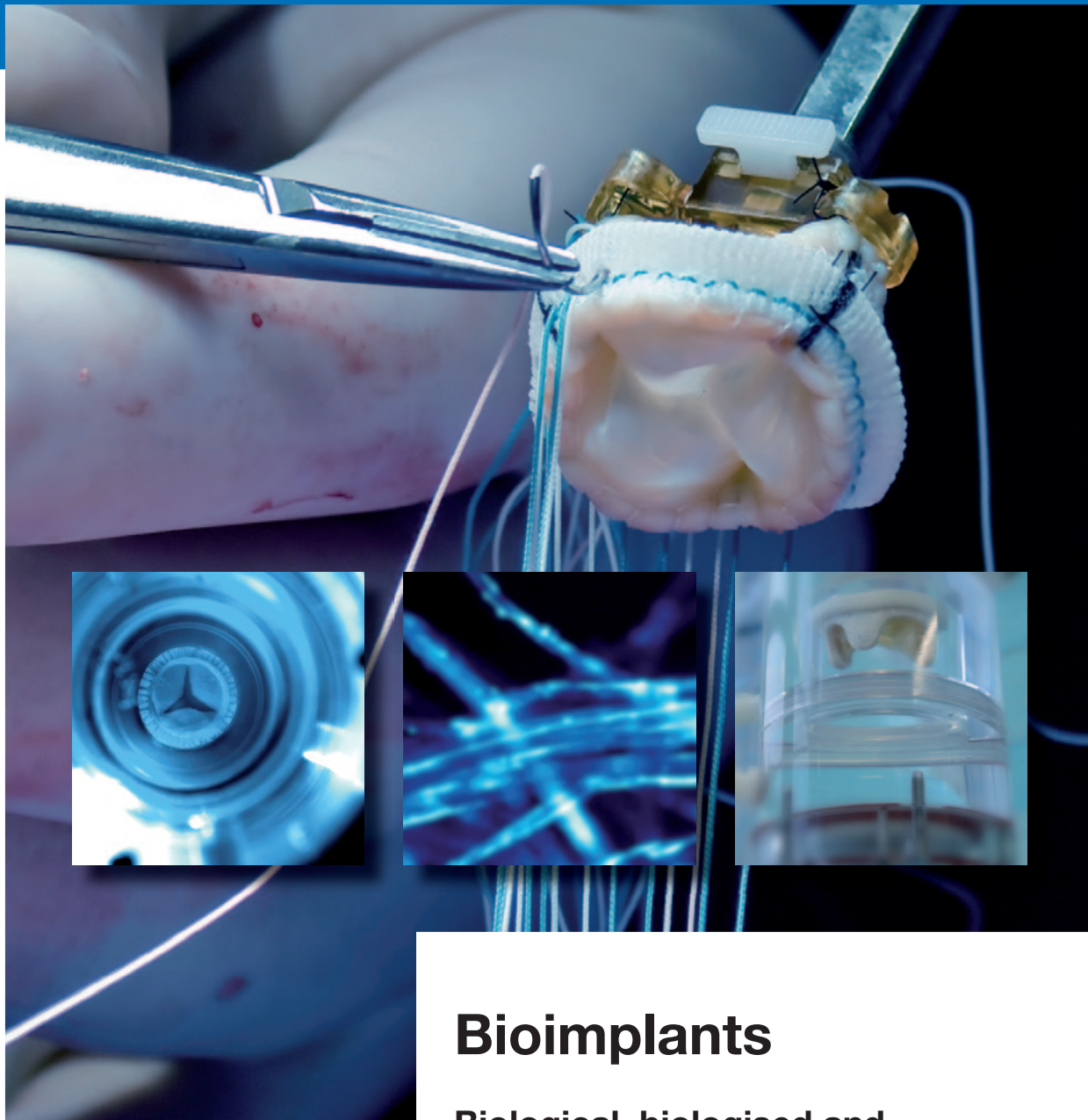


Position Paper



Bioimplants

Biological, biologised and
biofunctionalised implants

Imprint:

Position Paper

Bioimplants — biological, biologised and biofunctionalised implants

Identification of innovation obstacles and recommendations for future funding of research, development and innovation

A Joint Position Paper of

DGBMT (German Society for Biomedical Engineering) within VDE (Association for Electrical, Electronic and Information Technologies) and
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Abstract

Bioengineering used in medicine employs tissues or human living cells with the assistance of active agents and/or synthetic constructs in order to reproduce certain physical functions or treat the causes and not only the symptoms of diseases. A majority of research institutes as well as a series of predominantly small- and medium-sized businesses is also involved in the subject of bioengineering. As a whole, it concerns a field, which is characterised by a particularly high innovative force.

From the viewpoint of a medico-clinical user, most bioengineering products are implants since they are usually more or less implanted entirely in the patient's body. This position paper is concerned with such bioimplants. In this paper, three categories are taken into consideration from a technological viewpoint, irrespective of their regulatory treatment: biological, biologised and biofunctionalised implants. These are distinguished by the proportion of technical or biological components in the entire construct.

A considerable market growth for the bioimplant sector is expected in the next few years. The demand for vital tissues and organs for transplantations — following congenital deformities, disease-related malfunctions, after an accident or due to old-age degeneration — is increasing continuously. A crucial reason for this is the demographic transition and the increasing life expectancy of the populations in Western industrial nations.

According to the Bundesverband Medizintechnologie e.V. (German Medical Technology Association), approximately 100,000 cardiac pacemakers, 160,000 knee joints, 200,000 hip joints as well as 600,000 crystalline lenses are employed per year in Germany. In addition, there are approximately 1 million dental implants per year. However, on account of loss of function, for example due to infection or release of tension, it can lead to a greater number of operations involving implant replacement after a certain period. Studies conducted by the Institute for Quality and Patient Safety and comparable figures in the cardiovascular medicine sector show that a higher long-term function of the respective implants matches a significant savings potential in health expenditure at a magnitude of up to one billion euros per year. The development of technical biofunctionalised implants with matching surface coatings should prolong their shelf life and lifetime.

However, there are structural issues in the present value-added chain, which endanger the sustainable development of innovative (therapeutic) procedures and products. In particular, there is a significant translation bottleneck during the transfer of scientific knowledge in innovative products. Against this background, on May 3, 2011, the German Society for Biomedical Engineering (DGBMT) within Association for Electrical, Electronic and Information Technologies (VDE) and acatech - National Academy of Science and Engineering - organised a workshop in Munich with participants from science, industry and policy. Its goal was to identify the significant innovation hurdles from the viewpoint of the participants and to formulate respective requirements to overcome them.

The participants in the workshops came to the conclusion that despite the intensively funded research in the bioimplant field during the past few years, there is still a high demand for basic research in various sectors. Therefore, basic research should still be increasingly funded and at the same time it should be consequently worked towards the clinical applicability of bioimplants.

Topics to be increasingly funded in the future innovation programmes are:

- Biological interface engineering
- Standardisation to improve reproducibility
- Improved manufacturing conditions and automation
- Sterilisability and storability
- Development and consenting of adequate animal models for approval
- Development of non-invasive, non-destructive methods of in vivo diagnostics and quality assurance
- Definition of safety and efficiency

To improve the evaluation of the results, more focus is made on a consequent, value-added-chain-orientated joint funding with elements of the concomitant research as well as of the professional innovation management.

The interdisciplinarity of the subject area of bioimplants requires increased support for the collaboration between classical medical technology, biotechnology and pharmaceutical disciplines. With regard to the specialists required, the boundaries between the disciplines must be overcome in the training. The same must also apply to the design of funding programmes as well as in the evaluation of funding projects.

In Germany, the approval of bioimplants is regulated by a large number of laws. A separate act for the manufacturing and application of bioimplants is to be created to clarify the legal framework.

Different offices and authorities are often responsible for the different steps involved in the approval and reimbursement process. It is, therefore, recommended that a central office of coordinating the approval and reimbursing bioimplants is founded. The already existing offers, such as the innovation office at Paul Ehrlich Institute, are to be bolstered.

The high costs of clinical trials often constitute an innovation hurdle since an expense reimbursement at the time of approving a bioimplant is uncertain. Therefore, it is recommended to check the options of an official co-financing of clinical trials, if necessary, in the form of a “model similar to the Federal Education and Training Assistance Act” with the participation of the pertinent businesses.

In addition, the establishment of innovation centres is recommended for the sector of medical technology and bioimplants. Among other things, these innovation centres could in close coordination with the relevant authorities develop criteria for the verification of medical usefulness of innovative medical products which are accepted by all participants. Furthermore, they have at their disposal resources for initial clinical trials for temporary approval of innovative products.

1. Introduction

Bioengineering is generally comprehended as the application of methods and technologies from engineering, physics and mathematics in biological systems and organisms. As a rule, the goal is to develop medical applications to support healing processes, including products for the complete substitution of organ functions. Bioengineering used in medicine employs tissues or human living cells with the assistance of active agents and/or synthetic constructs in order to reproduce certain physical functions or to treat the causes of a disease more specifically. Most bioengineering products used in medico-clinical applications can be described as implants since they are usually more or less implanted entirely in the patient's body. From a technological viewpoint, this position paper is concerned with three types of implants and, irrespective of their regulatory treatment, takes into consideration:

- biological implants
- biologised implants
- biofunctionalised implants

All three groups cover implants with a biological component, but its proportion in the entire construction is differing. Therefore, the generic term “bioimplant” is employed in this case.

In particular, research and development knowledge in the field of tissue engineering in biological and biologised implants receives special significance since — to some extent — large parts of contiguous human tissue are used.

This position paper covers both scientific, regulatory and legal aspects associated with it. Therefore, it is indicated that the terms “organs” and “tissues” are scientifically and legally different in their use. According to § 1a of the German Transplantation Law and Tissue Regulation (TPG), organs indicate “all genuine parts consisting of different tissues in the human body, which — in relation to the structure, blood supply and capacity to implement physiological functions — form a functional unit, including organ parts and individual tissues of an organ, which can be used for the same purpose as the entire organ in the human body”.

In contrast, according to section § 1a of the German Transplantation Law and Tissue Regulation (TPG), tissues are “all genuine components consisting of cells in the human body, which are not organs, including individual human cells”.

In the field of tissue engineering, the terms of bioartificial tissue or bioartificial organ are used for distinction since a product in this technology can never be a tissue or an organ within the meaning of the above-mentioned definition. Within the context of the German Transplantation Law and Tissue Regulation act, all cells manufactured in vitro and cell combinations do not apply as tissues or organs. In the eyes of the law, tissue engineering products are thus always pharmaceutical products (if they include cells) or combination products of the risk category 3 of the medical products.

A comprehensive international benchmarking has not hitherto been conceived especially for the bioimplant field. However, a series of publications is concerned with the role of Germany in an international context on different subjects bordering the field of bioimplants. Among other things, these include two studies conducted under the order of the Federal Ministry of Education and Research (BMBF). The 2007 study entitled as “Regeneration Technologies for Medicine and Biology” [1] also reaches the conclusion that Germany occupies a lead-

ing global role in the area of regenerative medicine, particularly in science. On account of their wide spectrum, the study published two years previously on the situation of medical technology in Germany in the international comparison [2] covers a range of fields, in which there are overlaps with the bioimplant area. In the cell and tissue engineering domain, the study reaches the conclusion that Germany enjoys an outstanding global reputation. Another study [3] indicates that the medical technology branch identifies biotechnology as the most important cooperation partner in the future. Therefore, the goal is required to “invigorate and promote collaboration between both branches.” All three studies reached a similar conclusion — what the commitment of businesses in this field arrives at. The field is definitively characterised by a range of predominantly small- and medium-sized businesses, which, however, often lack capital and commercialisation structures.

Bioimplants cover a field, which is characterised by a particularly high innovative force and for which a significant market growth is expected for the next few years. The demand for vital tissues and organs for trans-plantations — following congenital deformities, disease-related malfunctions, after an accident or due to old-age degeneration — is increasing continuously. A crucial reason for this is the demographic transition and the increasing life expectancy of the populations in Western industrial nations. In fact, the “production” of entire organs with complete organ functions, if possible, stops at the limits of feasibility. However, nowadays, it is already possible to produce simple and organised tissues located outside the body in complex bioartificial tissue structures and implant these in patients, for example cartilage. Such simple and organised tissues are, for example, implanted to support diseased tissues or employed to support the organ function in biofunctionalised organ support systems until an organ suitable for transplantation is available.

In addition, the development of technical biofunctionalised implants with matching surface coatings prolongs their shelf life and lifetime. According to the Bundesverband Medizintechnologie e.V. (German Medical Technology Association), approximately 100,000 cardiac pacemakers, 160,000 knee joints, 200,000 hip joints as well as 600,000 crystalline lenses are employed per year in Germany. In addition, there are approximately 1 million dental implants per year. However, on account of the loss of function, for example due to infection or loosening, it can lead to a greater number of operations involving implant replacement after a certain period. Studies conducted by the Institute for Quality and Patient Safety and comparable figures in the cardiovascular medicine sector show that a higher long-term function of the respective implants matches a significant savings potential in health expenditure at a magnitude of up to one billion euros per year.

However, there are structural issues in the present value-added chain, which endanger the sustainable development of innovative therapy. In particular, there is a significant translation bottleneck during the transfer of scientific knowledge in innovative products. During the past few years, different institutions called for attention, for example the Forschungsunion Wissenschaft - Wirtschaft (Science Association Economy - Research) [6]. Against this background, the Deutsche Gesellschaft für Biomedizinische Technik (German Society for Biomedical Engineering) within Association for Electrical, Electronic and Information Technologies (VDE) and acatech - National Academy of Science and Engineering - organised a joint workshop on the topic of “Bioengineering - Biological, Biologised and Biofunctionalised Implants” on May 3, 2011 at the 128th Annual Congress of the German Society of Surgery in Munich. With the participation of representatives from science, industry and policy, the workshop pursued

the goal of identifying the innovation hurdles in the bioimplant field and formulating respective requirements to overcome these hurdles from the viewpoint of different participants.

The terms employed here for the three categories of bioimplants as well as the background and individual examples of applications are first defined as follows. Subsequently, the conclusions of the workshop are presented and matching recommendations for the promotion of innovative bioimplants are deduced.

2. Explanation of Terms and Applications

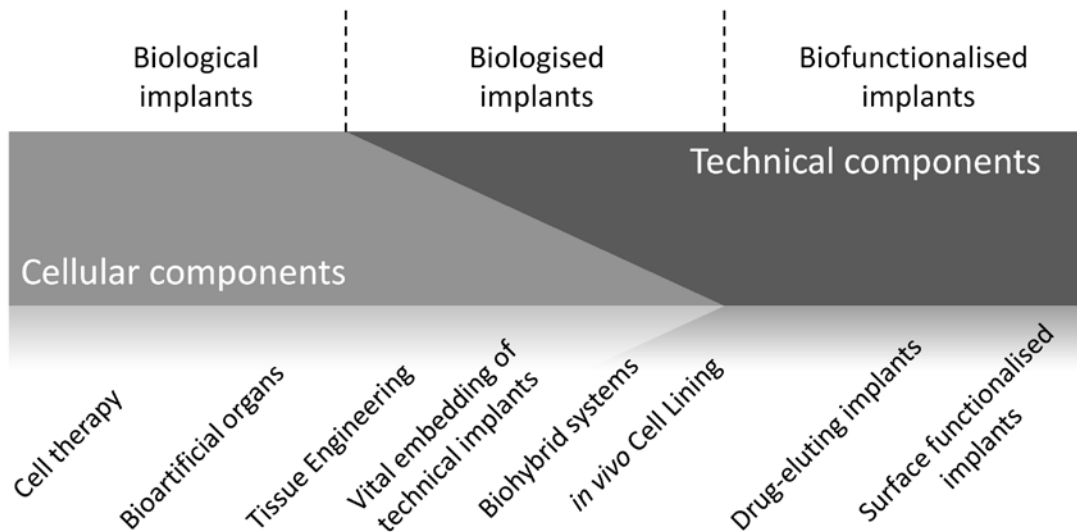


Fig. 1: Range of bioimplants

2.1 Biological implants

Bioimplants can be manufactured from living cells using tissue engineering methods. These bioimplants — and unlike donor organs — ideally consist of cells produced naturally in the body (i.e. autologous cells) so that the risk of rejection is minimised and the self-healing ability of the body as well as the effective mechanisms are involved. The term “regenerative medicine” expresses this concept appropriately. The tissue-specific function and integration of the bioartificial tissue is a basic prerequisite for the long-term replacement or support for the damaged organ. The cellular alignment in the matrix before implantation, leading structures of uncolonised matrix components and the vascularisation of bioartificial tissues before and after implantation play a decisive role in the mechanisms of cellular interactions. The three essential components for the in vitro production of bioartificial tissues and organs are produced using these basic cell biology pre-requisites: (1) functional tissue-specific cells, (2) carrier structures (matrices, scaffolds), which predetermine a three-dimensional (3D) form, encompass the cellular components and/or support them in their function, and (3) biochemical reactors (bioreactors), in which the cells are brought to the matrix and the bioartificial tissues can mature in vitro.

These may be reproduced in vitro following enzymatic isolation of tissue-specific cells that are made of biopsy material. Therefore, the cells are usually reproduced in a two-dimensional manner on synthetic surfaces without having any contact with proteins of the extracellular matrix (ECM). One challenge is the fact that signal transduction mechanisms can be activated, which lead to modifications in the expression of surfaces or cytoskeletal proteins and, therefore, dedifferentiation processes, that are associated with the loss of function, are triggered. These intracellular signal chains can, however, revert back to the physiological process after the matrix structures are colonised or after implantation of bioartificial tissues. However, the reliability of this redifferentiation is always represented again as a major challenge.

Extensive skin injuries that arise due to burns, chemical burns or severe forms of diabetes mellitus are, for example, applications of autologous (produced naturally in the body) transplants for tissue engineering. In order to form bioartificial skin tissue, cells are isolated from a skin biopsy approximately as large as a stamp or mature cells from follicles grown from “plucked” hair roots of the patients are reproduced in vitro. The epidermal progenitor cells of the keratinocytes are important for the reproduction process. Progenitor cells differentiate in keratinocytes under organotypic culture conditions and form a multilayer epithelium. This bioartificial tissue is the equivalent of the human epidermis, but has no dermis, hairs, sweat glands or pigment cells. The bioartificial skin has at most another texture and resembles scar tissue. Despite of the initial clinical success, it is worthwhile to improve the current results.

A problem, that remains unsolved in the case of cell-based implants, is the so-called terminally differentiated cells. Examples of this are nerve cells (post-mitotic neurons) or cardiac cells (cardiomyocytes). These cells can, in fact, be cultivated as primary cultures, but not further reproduced. Frequently, no sufficient cell quantity is available for the colonisation of carrier structures and no biological implant can be produced. The use of adult stem or precursor (progenitor) cells, embryonic stem cells as well as induced pluripotent stem cells (iPS) is considered as alternatives. The use of embryonic stem cells for therapeutic purposes bears ethical concerns and in Germany, due to legal reasons, it is not possible so that these are not discussed in further detail.

To produce the iPS cells, cells, which are mostly fibroblasts of the adult organism, are modified using viral infections or molecular techniques with the use of essential genes from embryonic development, such that they possess the pivotal properties of the embryonic cells. These cells can then multiply and be differentiated in the most diverse cell types. In the future, in vitro autologous nerve or cardiac cells could be available for regenerative therapy.

An application of cell therapy with adult stem cells is the transplantation of bone marrow, or precisely bone marrow stem cells, following chemotherapy of cancer diseases. Since the mid-1980s, there has been some success in genetic engineering to use manufactured haematopoietic growth factors for the mobilisation and reproduction of stem cells and, thus, introduce the stem cell therapy of the haematopoietic system in the clinic. In 2010, 2,730 autologous and 2,615 allogeneous stem cell transplantations were performed in Germany [7]. Multicentre studies are currently carried out to investigate the effectiveness of adult mesenchymal stem cell transplantations for the regeneration of cardiac muscle tissue in patients after a myocardial infarction.

There are also applications, which show an intersection of the biological and biologised implants, the decellularised or acellularised implants. For example, among these are the decellularised heart valves obtained from pigs or deceased humans. During the manufacturing process, all cells are first removed via a physicochemical process, namely, the donor tissue is decellularised and is now cell-free (acellular). The reduced devitalised, cell-free extracellular matrix of the heart valve on its pure material property is the result of decellularisation. Following implantation of the decellularised heart valve, this matrix must be integrated by colonisation of the autologous cells of the recipient organ. On the contrary, in such a case, this is described as guided tissue regeneration in tissue engineering. As is described in the section, this process occurs particularly frequently in the biologised implants.

The rejection of decellularised heart valves in the recipient organ or, more specifically, a graft-versus-host reaction was not described in either allogeneous applications in animals nor in

human treatment., According to current knowledge, no blood coagulation is induced by the implantation of a decellularised heart valved as opposed to the application of a conventional artificial heart valve, Namely, the consumption of lifelong medication with anticoagulants to prevent thrombus formation would be dispensable.

2.2 Biologised implants

The production of a complete biological implant according to the tissue engineering principle represents a highly technical challenge and is associated with a costly, time-consuming and labour-intensive in vitro pre-cultivation phase. Biologised implants, on the other hand, consist of a combination of cellular components and permanent biomaterial. The permanent biomaterial shows the actual, mechanical stable basic structure involved in the process. Only a cellular colonisation or implantation of the foreign material takes place, in which optimised biocompatibility can be achieved more rapidly. This may lead to significant savings in the manufacturing expenses of an individualised implant.

The biologised implants occupy an intermediate position between the biological and the biofunctionalised implants (see Fig. 1). They are distinguished from the biological implants due to the permanent, non-biodegradable carrier structure so that no completely autologous implant with a growth potential can exist in the biologised implants. Furthermore, they are limited by the biofunctionalised implants due to the cellular components, leading to a permanent coating of the implant. The in vivo induced cellular colonisation (e.g., the targeted anchoring of endothelial progenitor cells following stent implantation), in this case, represents a borderline case between both areas.

The area of biologised implants covers a wide range of problem-solving approaches from bioengineering and, among other things, includes:

- the (textile-)reinforced tissue engineering with non-biodegradable material
- embedding of technical implants in vital tissues (for example, stents)
- the development of biohybrid systems for temporary or permanent organ support
- the in vitro targeted, or in ideal cases in vivo cell colonisation of foreign surfaces.

The biologised implants are particularly distinguished by the relationship between technical and biological components. The non-biodegradable, reinforced tissue varieties rather target a histological reconstruction of the target tissue.

In addition to the purely biomechanical reinforcement, the technical structure can fulfil other functions, such as in a cell-colonised stent prosthesis. The stent fulfils its conventional function of stabilising the arteriosclerotic plaques, whereas complete integration of the stent structure in a vital blood vessel with a functionally active endothelial cell layer provides optimised haemocompatibility and exclusion of the plaques from the bloodstream.

Another example of the application for the combination of technical and biological components are classical biohybrid systems. These, in particular, fulfil the function of a temporary organ substitute. In this case, technical systems, which ensure the survival of the patient within the context of bridging the time to transplantation (bridging to transplant) or convalescence (bridging to recovery), are mainly involved. Examples are allogeneous or xenogeneous hepatocytes in liver hybrid systems separated by means of a technical membrane from the patient and replace the function of the diseased liver. Similar developments are also sought

after in renal replacement therapy, in which, in addition to the pure dialysis, the lacking synthetic function of the kidneys must be compensated for by using suitable cellular sources.

The surface lining of technical implants and systems (as a singular cell coating) with suitable epithelia is intensively promoted in many areas of medicine, such as the cardiovascular field (artificial heart, heart valve and vascular graft), gastroenterology (oesophagus and bile duct replacement) as well as urology (artificial urinary bladder and ureteral replacement). Adequate surface modification of the biomaterials is generally necessary for optimised and permanent adhesion to the cells. A form of the implant biofunctionalisation already mentioned is the coupling of ligands that are suitable and specific to target cells in ideal cases. The actual cell colonisation can either occur beforehand in vitro, directly intraoperatively or by replacing a purely technical biofunctionalised implant, which is epithelialised/endothelialised in vivo via suitable ligands with localised or circulating (progenitor) cells.

2.3 Biofunctionalised implants

Since the successful market introduction of drug-eluting stents, a clear trend for the so-called combination products, that use pharmacological, biotechnological and cellular components, has been recognised. The market development accompanies various technological developments together with advanced aspects of miniaturisation, molecularisation and computerisation of medicinal products [2]

However, advances in molecularisation of medicinal products require a comprehensive understanding of molecular interactions between technical materials and biological tissues. The term of biofunctionalisation of medicinal products is frequently related to this concept. In general, the term 'biofunctionalisation' is comprehended as a field of surface treatment with the purpose to optimally use the surface for life science applications [8]. On this basis, all technical systems with structured or bioactive surfaces, which interact with the biological environment after implantation, are described as biofunctionalised implants as follows. The purpose of a study in this field is the development and application of customised properties of material surfaces, for example, corrosion resistance, biostability, biocompatibility and bioinductivity, without the loss of mechanical, electrical and optical properties of the base materials required.

The surgical professional associations as well as the dentistry branch constantly highlight the need for biofunctional coatings. Moreover, methods of biofunctional coatings in in vitro diagnostics are of increasing significance. Likewise, in the product groups of implants, therapeutic systems, dental materials, surgical auxiliary devices as well as in regeneration medicine, biofunctionalised products of significantly higher efficiency as compared to the conventional products are in demand. When treating older patients, future biofunctionalised materials will play an important role (for example in geriatric traumatology or geriatric surgery). It is expected that patient use is significantly improved, on the one hand, by the combination of materials and medicinal products and, on the other hand, by the cost efficiency of the treatment.

The purported use of biofunctional coatings is very diverse. However, the general consensus is that biofunctionalisation, on the one hand, serves to improve the functionality of materials and, on the other hand, improves the long-term stability of products and also optimises haemocompatibility and biocompatibility.

Hyperplastic tissue reaction and scar formations must be suppressed by coatings containing antiproliferative, cytostatic or antiinflammatory materials. The most important market in this application is drug-eluting stents, which suppress the renewed obturation of blood vessels

following a successful balloon dilatation by means of their pharmacological components. The focus of new developments is directed at another functionalisation of stent surfaces (“healing stents“, “biodegradable scaffolds“) to significantly reduce the hitherto necessary long-term treatment using anticoagulants. In addition, there is a great demand for antibacterial coated products for surgery and interventional cardiology. Coatings with antibacterial effective substances are required to prevent bacterial colonisation on implant surfaces since these complications, such as implant failure, sepsis and subsequent operations, are involved.

A coating of implants with growth and adhesion factors to stimulate tissue formation is of greatest economic and scientific significance in orthopaedics and trauma surgery as well as in dentistry. In particular, older patients are distinguished by a significant demand for products to improve bone regeneration and osseointegration of the implants. A significant improvement in clinical long-term results using the coating of implants with osteoinductive growth factors and cellular binding domains is expected in revision endoprosthetics.

Medicinal products, which come in contact with blood, may benefit from haemocompatible coatings. The interactions of cellular and acellular blood components with material surfaces are very complex. Catheters, cannulae, syringes, vascular prostheses, heart valves, stents, etc., are of particular interest. Repulsive, anti-adhesive coatings are usually used to date. In contrast, concepts, which aim at a rapid coating of the implants with an enclosed endothelial layer, are pursued in long-term implants to achieve permanent functionality.

Another application of biofunctionalised implants is the improvement of repaired growth and tissue regeneration using appropriate surface coatings. Tissue regeneration essentially consists of three cellular reactions: cell proliferation, cell differentiation and structural formation. While cell proliferation and cell differentiation can be achieved by administering material components, such as growth and differentiation factors, structural formation is mostly induced by mechanical application of force or structural substrates. Examples are nerve guides, which are used to control regenerating peripheral nerve fibres or textile implants, which exhibit inductive properties due to their inherent structure.

Examples of a new class of materials are regenerative biomaterials, the purpose of which is to initiate tissue regeneration in order to be replaced by de novo synthesised extracellular matrix components during the regeneration process. These materials usually consist of cross-linked biomolecules, for example collagen, hyaluronic acid, albumin and chitosan as single components or mixtures containing minerals and growth factors. They are degraded by tissue proteases without harmful components during the remodelling process. The most frequent application hitherto is regenerative biomaterials in bone and cartilage as well as skin augmentation and matrix-assisted cartilage transplantation.

Against this background, an increasing demand for biofunctional coatings and surfaces in virtually all growth-intensive product groups of medical technology (implant, diagnostics, therapeutic systems) and regenerative medicine looms ahead. For example, the massive increase in the market volume of biofunctional stents can be assessed as its index. Since 2003, as a whole, drug-eluting stents were marketed for over 4 billion US dollars [9]. This market success is traced back to biofunctional coatings. However, due to increased complication rates caused by stent thrombosis at an advanced stage, further research in this field is also necessary.

3. Workshop Results

3.1 Activity requirements in the bioimplant sector

Several areas with increased demand in research and development for all three bioimplant categories were identified comprehensively at the workshop. In particular, the following fields are listed:

Biological interface engineering

Analytical techniques with resolution at the molecular level to study interfaces or, more specifically, boundary layers between the biological environment and material/biomaterial are developed. A need for new procedures that combine bioanalytical methods with material science methods exists in this case to structurally and chemically characterise the boundary layers between the material and biological system located at a molecular level.

For example, the analysis of the distance from the cell to the biofunctional surface and their influence of intracellular signalling cascades is a prerequisite for a basic understanding of the interactions between the biological environment and the respective material.

In addition, there is a significant need for coating and sedimentation technologies of biomolecules that are suitable for production, for example by using self-assembled and self-healing coatings. A problem-solving approach could be found in the use of biomimetic principles in targeted drug release, such as switchable pores in coatings, which can release drugs in accordance with the functional principle of channel proteins.

Furthermore, microbiology and nanotechnology procedures, that are suitable for production, must be developed for the structural and chemical modification of surfaces with complex geometries. Moreover, the development of basic understanding is required to evaluate the safety and efficacy in the drug release at surfaces.

Standardisation

In particular, with a view to approve bioimplants, the standardisation of manufacturing conditions and processes is highly significant. In addition, the establishment of relevant efficacy criteria for the essential applications and diseases or, more specifically, medicinal indications, an adequate risk management as well as a most extensive quality assurance is necessary. In order to carry out the latter, the development of suitable analytical techniques of mechanical test methods to measure (bio-)chemical parameters is required.

Automation

In order to be able to produce bioimplants in a cost-effective manner and of the same constant quality, optimisation and, in particular, automation of the production processes are required. In this process, the identification and establishment of suitable subprocesses can also be involved. Moreover, in general, a significant demand for production technologies exists for cost-effective manufacturing, scalability and reproducibility of functional layers.

Sterilisability and storability

The currently available technologies and procedures for sterilisation and storage of biological, biologised and biofunctionalised materials, surfaces and implants must be developed further. A great burden for biomolecules is the sterilisation that uses steam, gamma radiation or ethylene oxide treatment. All three procedures adversely affect the efficacy and chemical integrity of biomolecules or pharmaceutical substances. However, in pharmacology, there are approaches, which, for example, protect the therapeutical biomolecules during sterilisation and improve storability. These concepts are until now hardly introduced in medical technology.

Validated and characterised animal models

Different issues (e.g. inflammation, haemocompatibility, endothelialisation) must be drawn on the development and testing of products from the field of bioimplants in major animal models. However, there is still no consensus concerning the suitability of certain animal models and their clinical relevance among the professional associations as well as among regulatory authorities.

Non-invasive in vivo diagnostics

There is little knowledge of the factors and processes affecting the process of tissue regeneration in terms of time and space. Therefore, the development of non-invasive — in particular, non-destructive and in vivo investigative methods, such as imaging procedures, is considered as important. These should facilitate a detailed monitoring and documentation of the in vitro culture conditions of biological implants during the expansion and 3D culture and, therefore, improvement of the efficiency of animal experimental studies. Therefore, the number of animals used in experimentation can be reduced, the information content per experiment is increased and the time response is shown.

Education and junior recruits

In the entire bioimplant area, there is a particularly close connection of the most diverse disciplines. In order to be able to meet the need for professionals in the future, it is necessary to overcome the cross-disciplinary boundaries in education. Moreover, the model representation of the steps required along the value-added chain within the context of individualised medicine, starting from research and development via implementation, approval and market induction to marketing of a product sample from the bioimplant, could make the required knowledge more readily available and, therefore, it is effective as a driving force of innovation.

Specific requirements in the areas of research, development and legal parameters are explained in the following sections.

3.2 Biological implants

Among biological implants, the workshop focused on cell therapy and matrix-based implants. Therapies using haematopoietic, mesenchymal and induced-pluripotent stem cells were summarised among the former. Such bioimplants, which largely establish themselves on components in the extracellular matrix, are understood as matrix-based implants.

Cell therapy

In cell therapy, the discussion concentrated on regenerative therapeutic approaches using adult stem cell transplants as well as adult differentiated cells. In the domain of therapy using haematopoietic stem cells (HSC), there are, in particular, activity needs in the optimisation of cell culture conditions and in new procedures, which investigate the sterility and risk of transfer of infections at any time during the manufacturing process.

In particular, the need for activity in developing methods and technologies is viewed for therapy using human mesenchymal stem cells (MSC) as well as for the use of adult differentiated cells, facilitating predictions of the determined quality criteria of the product.

In general, it applies for all areas of stem cells mentioned that there is a lack of comprehensive understanding of the mechanism of action, effectiveness and the persistent clinical use of these biological implants.

In the area of induced pluripotent stem cells, in the meantime, virtually all tissue- and organ-specific cells, including the cells of the haematopoietic system can, in fact, be differentiated. However, the entire field focuses on basic research throughout the world. Therefore, the list of fields, in which the need for treatment is considered, is longest here. In particular, it involves optimised manufacturing and reproduction, standardisation of culture conditions as well as comprehensive animal experiments to exclude the carcinogenic potential following implantation of undifferentiated and differentiated transplants. Moreover, efficient in vitro differentiation protocols and systems, proof of the stable differentiation as well as comprehensive surrogate parameters for cellular functions and differentiation stages play a role. In addition, the definitions lack adequate animal models, non-invasive tracing and characterisation methods as well as the establishment of safety and efficiency of separate methods in the entire value-added chain.

Matrix-based implants

In this case, there are already preclinical or clinical studies for different applications, for example a number of new, matrix-associated autologous chondrocyte-transplants (MACTs). Different biomaterials, such as collagen and autologous chondrocytes are combined in these regenerative therapies to generate in vitro three-dimensional cartilage transplants. Significant progress in evaluating the efficacy of this "pharmaceutical" was the establishment of morphological and biochemical magnetic resonance tomography (MRT) to show the ultrastructure of these cartilage matrices. A feasibility study ("MOCART") was conducted for this purpose. In the study, a morphological scoring (Brittberg score) and a biochemical T2 mapping are experimentally used to distinguish non-invasively the cartilage replacement tissue in the knee joint after two different MACT procedures. This feasibility study is the first in vivo test that differentiates the efficacy or, more specifically, the superiority of two different matrices for cartilage replacement [10]. Further efficacy studies of this type are necessary to use biological implants or, more specifically, regenerative therapies effectively and promptly in a clinical application, which is, in turn, a fundamental prerequisite to back up the know-how acquired in Germany and the spin-off companies supported by public resources.

3.3 Biologised implants

Successful translation of biologised implants in the clinic depends highly on whether a cost-effective production and simple approval of the products can be achieved. The cell shows the minimally standardised and, hence, most uncertain components of the approval. This not only concerns the implants, which are precolonised *in vitro* but at the same extent biofunctionalised implants, which mature *in vivo* to biologised implants by means of ligand-mediated cell tracking (e.g. endothelial progenitor cells to endothelialisation of vascular prostheses). There are large interindividual fluctuations in the quality and quantity of autologous cells, which also depend on age, gender, different preceding diseases as well as the current hormonal balance. A large proportion of these factors is not susceptible and, therefore, will lead to different matching individual implant qualities.

	Remodelling	Self-Repair	Immunogenicity/ Inflammation	Reproducibility	Storability	Production expenses	Logistic expenses
Biological implants	+	+	+	(-)	(-)	↑↑	↑↑
Biohybrid systems	-	-	(+)	(+)	(-)	↑	↑
Reinforced implants	(+)	+	(+)	(+)	(+)	↑↑	↑
Vital embedding	(+)	+	(+)	(+)	(+)	↑↑	↑
<i>in vitro</i> Cell Coating	-	-	(+)	(+)	(+)	↑	↑
<i>in vivo</i> Cell Coating	-	-	(+)	+	+	↓	↓
Biofunctionalised implants	-	-	(-)	+	++	↓	↓

Tab. 1: Weighing-up criteria for a patient-optimised implant (+ = positive, - = negative properties, ↓ = low, or ↑ = high expense)

Therefore, it is generally required to reduce the biological or cellular portion of the implant as far as possible and construct them accordingly on standardised, medical technology components. The extent of biologisation is finally defined by the requirements for the implant and, therefore, in individual cases, can require a purely biological solution, for example if a growth potential is required. In this case, it is worthwhile to bring into accordance the desirable biological properties (capacity for the implant to fit / remodelling, mechanisms of autorepair, complete immunological integrity) with the technical requirements of production (reproducibility and storability of the implant, general production expense, logistic requirement for compressive expansion) (cf. Tab. 1).

A cost reduction in the sector of biological components should be taken into consideration during the developmental phase and will early lead to a change of manual and, therefore, labour-intensive processes in an automated system. Moreover, it is expected that the automated cell cultivation effects a reduction of contamination rates and, furthermore, allows a simplified documentation as well as standardisation of cell culture processes.

Therefore, from a production-technical viewpoint, the in vivo or, more specifically, directly intraoperative colonised implant represents the ideal solution process. It allows the standardised manufacturing of a medicinal product, if necessary, that is associated with a bio-functionalised surface (coupling of specific ligands). In particular, however, it is problematic to define a suitable animal model for the preclinical studies for these implants. Based on the high cell- or, more specifically, to some extent, species-specific adherence of the target cells to the ligands, this may be even impossible under some circumstances and only initial clinical studies can be evaluated.

As a whole, it must be adhered that despite intensive research endeavours and many promising preclinical successes, a significant translation bottleneck also exists. Strong restriction of the industry is established in the process. This is based both on the situation that regulatory aspects are unclear in many cases as well as on the issues associated with many uncertainties of the health economic proof of benefits and the remuneration based on the proof. Even if the high innovation potential of the biologised implants is obvious, many companies baulk at the expenses incurred at the initial approval. There is a lack of financial support during the early clinical pilot stage. In particular, in the biologised as well as in biological implants, on account of the high cell-specific function, the animal experimentation study with a significant limited validity is taken into consideration. The initial clinical studies, therefore, represent extended feasibility studies.

In summary, on behalf of both the representatives of the industry and the academic discussion partners, the field of biologised implants was recognised as future-oriented technology. A close connection of industry and academic research is necessary, not least to fill the still existing distance between the medical technology branch and regenerative medicine that is frequently dominated by biosciences. In addition to the still limited automation and standardisation of biological processing steps, the apparent bottleneck in the translation lies in the lack of funding of initial clinical studies. A comparable funding programme of the Federal Ministry of Education and Research (Innovative Therapeutic Procedure on Molecular and Cellular Basis, announced on 11.06.2010) could be used as an example here.

3.4 Biofunctionalised implants

The applications of biofunctionalised coatings are, as mentioned in the beginning, very comprehensive. The essential purported uses of coatings lie in their antibacterial, anti-proliferative, anti-inflammatory, osteoinductive, haemocompatible, conductive (conductor rails) and regenerative effects.

Overall, a strong increase of publications on implant-imparted, monitored drug release is identified. This concept helps to control cell growth, cell differentiation and, therefore, tissue regeneration.

The status of the technology varies significantly in various clinical application fields. Therefore, a different research and development requirement also exists, depending on the purported use of the implant.

Thus, there is a wide knowledge available in dentistry, stomatology and orthodontics as well as of materials and surface structures to optimise osseointegration and the adhesion of mucosal epithelia. In general surgery, in contrast, the use of antibacterial and antiadhesive coatings to prevent scar formation is in the fore-front. Special attention is focused on the effect of coatings on the biological tissues surrounding them.

For these so-called intelligent implants, i.e. highly complex systems, that bind sensors, actuators and signal processing with one another to a varying measure, [11], by contrast, the effect of the biological tissue on the materials and material surfaces is of extremely great significance. It is because their long-term function decisively depends on this. Biofunctionalisation concepts until now have been playing a subordinate role in this process. In contrast, it is focused on encapsulation technologies.

Despite the large range of applications, there is a common bracket for all forms of biofunctional coatings. The superior goal is to achieve a modification of artificial or, more specifically, technical surfaces so that these can be used optimally for medical applications.

3.5 Innovation framework requirements

The innovation parameters of medical technology are identified by a high degree of technology intensity, interdisciplinarity, regulation and competition as well as a comparable complex network of stakeholders. For the bioimplant field, this applies to a particular extent since a pronounced interface exists in the biosciences. Factors result from this complexity, hindering innovations and, therefore, can lead to negative economic effects. In unfavourable cases, the patients gain no access to new technologies with high medical advantages.

The innovation parameters of medical technology were addressed in a range of studies and projects [1, 2, 12-14]. In particular, in the study commissioned on behalf of the Federal Ministry of Education and Research, which is entitled as “Identification of Innovation Hurdles in Medical Technology” [12], a systematic analysis was undertaken for the first time. By means of the study, which is also commissioned on behalf of the Federal Ministry of Education and Research and entitled as “Regeneration Technologies for Medicine and Biology — Contributions for a Strategic Grant Concept” [1], a study of the innovation parameters is also available with a view on regenerative medicine. A study on the innovation parameters with explicit focus on bioimplants has not hitherto been published.

Overall, the parameters in Germany for research, development and commercialisation of innovative medicinal products are evaluated as good. In the May 3, 2011 strategy workshop, the discussion focuses only on the respective innovation parameters, which can have an obstructive effect on the bioimplants. These are divided into six groups and the corresponding discussion results are summarised. The six groups shown below are partially connected strongly with one another in content.

Knowledge transfer and interdisciplinary skills

The interdisciplinary interactions of different fields and professional groups are a firm component of research and development in medical technology. Medical technology innovation exists through close cooperation, in particular, between engineers, natural scientists, computer scientists and medical scientists associated with deep market competence. Both research facilities and companies can look back to a long and successful cooperation. However, the organisation of interdisciplinary knowledge transfer still represents a major challenge and must always be redeveloped anew. In addition to the collaboration of professional groups in the scientific-technical-clinical area, this also leads to an intensified interaction with professional groups from the regulatory environment.

The interdisciplinary triangular collaboration of engineering, biotechnology and medicine is in need of improvement in view of the bioimplants. The “technical distance” of medical technol-

ogy for cell and molecular biology as well as for the clinical application and patient care is significantly greater than, for example, for computer science and communication technology or, for instance, microsystems technology. The structural difference is identified from a technical respect, on the one hand, by engineering and equipment technology and, on the other hand, by biology, biochemistry, medicine and clinical care. The technical areas of interest are coined by different scientific, technical and clinical careers of the players, different working languages, networks and approaches to overcoming challenges as well as various incentive systems. University education generally covers the corresponding areas in separate study courses at different faculties, which are slightly linked to one another. Research is primarily conducted in the respective specialist fields of the universities as well as being published in the corresponding technical journals. The differences are partially resumed at the entrepreneurial levels, in which individual product groups and clinical applications are focused on against the background of market and risk evaluation. In general, this pronounced structural separation always represents an innovation barrier for the development of biological, biologised and biofunctionalised implants since relevant stakeholders of the “interdisciplinary value-added chain” are not even or at least not sufficiently incorporated at an early stage.

Clinical research

In many cases, bioimplants comparatively target small patient groups and often represent a form of personalised medicine based on biomedical technology. The consequence of this is that the identification of a suitable clinical partner for clinical research of an innovative implant can represent a challenge. Since the ideal partner must have a suitable skill profile associated with a suitable patient population and sufficient number of cases. In general, a lack of suitable clinical research partners is assumed.

This aspect is intensified by the fact that from a methodical hindsight, many issues of clinical testing of bioimplants are open. In particular, this applies for the definition of suitable clinical final points with a view to a proof of benefits to obtain cost refund from the Legally Required Health Insurance (GKV) (see in the same section below). In addition, the complexity of medical technology clinical research has been significantly increased by amending the Medical Devices Act (MPG) and the introduction of the Advanced Therapy Medicinal Products (ATMP). In particular, problems of demarcation exist in biological, biologised and biofunctionalised implants as well as with respect to the Medical Devices Act (MPG). Against the background of rapidly changing and increasing regulations, the required interaction between university clinics, study centres, medical technology manufacturers and authorities is established too narrowly, too few and too slowly. The cooperation between university clinics and industry is also formed in a difficult manner, especially with respect to contract processing and patent negotiations.

Furthermore, medical technology clinical research is, thus far, not established and systematised both on behalf of the clinics as well as on behalf of the manufacturer of medicinal products, as is the case in clinical research in the pharmaceutical sector. Therefore, each expertise is expandable on both parties. In the case of clinics, a comparatively low interest in doctors adds to the medical technology and clinical research as the complicating factor. During the past few years, the overall situation has, in fact, improved. However, the comparatively low impact factors of medical technology technical journals always prove to be the major obstacle. Medical technology, in general, is also less of a centrepiece of interest to many physicians that are active in clinical research. This is not in the least traced back to a character of medi-

cal study, which focuses more on biological molecular medicine and hardly on the technical research content.

Patenting

Patenting of research and development results plays an important role in medical technology innovation process. Inventions are protected against prohibited use by third parties so that refinancing of the expenses for research and development is supported by a temporary monopoly. Active use is made in a gratifying manner by this possibility: medical technology with 10,500 patent applications (2010) reaches the peak at the European Patent Office [15].

However, patenting is not only fraught with difficulties when considering bioimplants. The entire process is expensive and costly and, in particular, for such stakeholders, who only find it difficult to cope with, when they have no systematic or, more specifically professional innovation management. A great amount of expertise is required to select patents with realistic prospects of commercial applicability. Even small and young businesses in this position run the risk of collapsing. Patenting in medical technology is also identified by a general non-patentability of purely medical procedures and an associated demarcation problem. An innovation must be associated with a novel structural configuration of a device, an instrument or a component in order to be able to receive a patent. The aspect of “biological patents” is added to bioimplants. In this case, there are numerous legal determining factors with respect to the patenting of genes, (stem) cells or living organisms, which are also frequently altered.

Also, if the maximum number of patents is registered in the medical technology area, it must be assumed that the “patent effect” is more weakly pronounced as compared to the pharmaceutical sector. The speed of technological progress is very high in medical technology so that medical products — regardless of their patent protection — can be rapidly replaced by other new solutions. From an economic viewpoint, the specific characteristics of the medicinal product markets also play a role. In comparison to the segments in the pharmaceutical area, it mostly concerns a smaller number of items with a different margin structure. The typical “blockbuster” business model of the pharmaceutical industry is lacking. This aspect further gains meaning due to the concept of “personalised medical technology”, which plays an important role in bioimplants.

Legal parameters and product approval

In Germany, the acquisition and application of human cells and tissues as well as the materials, equipment and appliances required are subject to different laws and ordinances. For example, among these are the German Pharmaceuticals Act (AMG), the German Transplantation Law (TPG), the relevant Ordinance for the Production of Medicinal Products and Active Substances (AMWHV) and the German Transplantation Law and Tissue Regulation (TPG-GewV) as well as the Medical Devices Act (MPG). A legal pharmaceutical manufacturing permit of the relevant federal state authority is basically required to produce autologous or allogeneous cell and tissue products. The federal authority, Paul Ehrlich Institute (PEI), only exercises a consulting function in establishing the conditions during the manufacturing process. However, the recommendations prepared by PEI usually represent the basis of the production guidelines of the manufacturing permit. The German Pharmaceuticals Act also regulates the elementary process steps in the application of biological therapeutic procedures in order to prevent undesirable adverse reactions for all European patients, such as the trans-

fer of infections. To achieve a high extent of patient safety in the entire European legal space, the 2004/23/EC directive, the so-called EC-tissue directive was issued by the European Parliament and European Council. Two other directives were adopted by the European Commission for their implementation: The 2006/17/EC directive contains technical directives for the donation, procurement and testing of human tissues and cells, the 2006/86/EC directive contains requirements for the traceability, obligation to report, coding, processing, preservation, storage, testing and distribution. The Tissue Act is the execution of this EU directive in German legislation. Despite of the corresponding recommendations at the Federal Parliament and numerous technical societies, the Federal government abandons the development of a separate body of laws, but rather executed the EU directives as an omnibus law by changing the German Pharmaceuticals Act (AMG), the German Transplantation Law (TPG) and the German Transfusion Act (TFG) and other legal guidelines.

In summary, it must be established that the marginal conditions for approval of bioimplants are unsatisfactory. In particular, it is not clearly ruled when the approval directives for medicinal products and when those for pharmaceuticals apply. The responsibilities of the Federal Institute for Drugs and Medical Devices (BfArM), on one hand, and PEI, on the other hand, are also occasionally difficult to comprehend in this connection. Moreover, the approval condition is in a constant modification process, in which the degree of complexity increases further.

Another legal aspect is the recently arising issue of liability. This, for example, is the result of intraoperative cell colonisation. In such a case, the (medicinal) product delivered by the industry is merely an intermediate product. The additional “value addition” is executed intraoperatively by surgeons. Both a transfer of liability to the surgeons or to the clinic as the manufacturer is a result of this. However, it may not be forgotten that an increased value addition is also produced for the clinic, at which the industrial supplier is only a participant under some conditions. A potential solution to this problem could lie in special clinics, which are operated by primary manufacturing companies. Comparable approaches are recognised from the sector of dialysis centres, at which the dialyser manufacturer is also the supporter of the dialysis centre at the same time.

Recompensation by means of the legally required health insurance

It is decisive for the successful commercialisation of a bioimplant in Germany whether expense refund is carried out by the Legally Required Health Insurance. In this process, the determining factors of the expense refund are distinguished in the ambulatory and stationary care. In the ambulatory sector, according to §135 Social Security Code (Fifth Book (SGB V)), the “Prohibition with Reservation of Authorisation”, namely, in self-administration in health care, the Federal Joint Committee makes decisions concerning the acceptance of an innovation in standard care. A test is carried out to check whether the innovation for a sufficient, appropriate and economical provision of the insured party is suitable. The concrete reimbursement terms, including the price assessment, are distinguished with respect to the rating of the innovation as a pharmaceutical, ATMP or medicinal product. A new regulation was only recently introduced to early benefit the evaluation of the pharmaceutical using the Law on Realignment of the Pharmaceutical Market in Germany (AMNOG).

In contrast to the ambulatory sector, the “Permit with Reservation of Prohibition” applies in the stationary sector, i.e. innovations can be reimbursed while subject to the Diagnostic Related Groups (DRG)), unless the Federal Joint Committee opposes this permissibility. If the innova-

tion can be reproduced economically in an existing DRG, it can be used, as a consequence, directly in the stationary care. Otherwise, there is the possibility of applying for the implementation of a “New Study and Treatment” (NUB). If the Institute for the Hospital Remuneration System (InEK) evaluates the application as positive, the requesting hospitals may process the NUB remuneration of a flat-rate payment with the payer.

In addition to both “major passages” depicted above in the reimbursement, there are still other possibilities, for example modelling projects or contracts of integrated care (IV contracts).

Generally, the legally required health insurance for the reimbursement of biological, biologised and biofunctionalised implants is fraught with obstacles. Overall, the margin conditions for the reimbursement are very complex and non-transparent.

The transfer of an innovation in reimbursing the expenses in a legally required health insurance is often tedious with respect to the probability of success, which is difficult to assess and generally associated with high costs. From an entrepreneurial viewpoint, the parameters are, furthermore, subject to continuous modifications, which increase the economic risk. The aggravating fact is that on the side of the industry, no applications to undertake an innovation in reimbursing the costs can be made and even no direct industrial participation is provided in the decision-making process.

The issue of proving the benefits of the innovations proved to be a central problem. In this case, many methodical issues, in particular, with respect to a long-term proof of benefits, are not defined or not clearly provided. Even smaller businesses often have no adequate expertise in order to refund expenses to the innovations. The expenses are mostly not representable. Moreover, the basic issues of counterfinancing the bioimplants are shown as strongly individualised therapeutic forms by the legally required health insurance and, therefore, also by the supportive community.

Complex problems of cost reimbursement for biological, biologised and biofunctionalised implants can only be touched on at the workshop. In particular, with a view on method development, a deepening involvement with the topic is required for proof of benefits and for the Health Technology Assessment (HTA).

Commercialisation

On account of their marketing access to hospitals, in particular to surgery and intensive medicine, medical technology businesses are in the best position to successfully commercialise biological, biologised and biofunctionalised implants. However, they usually lack both experience in dealing with biological fluid systems and the respective technical expertise. The willingness to take risks to deal with bioimplants is comparatively low. In contrast, biotechnology and to some extent, pharmaceutical companies have the appropriate technical expertise. However, the marketing methods focus less on the clinical sectors at the hospitals, where implants are used.

Biological, biologised and biofunctionalised implants represent strongly individualised medicinal products, which place special requirements for manufacturing and storage and for which specific medicinal biological competence of the companies is required for their development and manufacturing. This currently contrasts with the medicinal products available on the market, which are standardised to a high extent and often use many indications and different clinical applications for great patient groups. In particular, the integration of “biologicals“

(pharmaceuticals, which are manufactured by means of biotechnology in genetically modified organisms) is a challenge, which requires a stronger combination with pharmaceutical companies. There is also the fact obstructing the innovations that, currently, there are no adequate action guidelines. Bioimplants, therefore, support new business models from the companies. The example already mentioned of the dialysis equipment made by the manufacturers operated at the dialysis centres exhibits in a potential direction for such business model innovation. It is, however, generally also due to the complex marginal conditions that a comparatively low risk-taking is observed on the part of the companies.

Overall, at present, there is no pioneer in the market, who could act as an initiator for the entire branch. The situation is, therefore, aggravated by the fact that there are currently only few significant and resilient market potential estimations.

4. Recommendations for Action

1. Research funding

During the past few years, research was funded intensively in the field of bioimplants. However, there is still a high demand for basic research in various sectors. This basic research forms the indispensable prerequisite for the potentially complete use of the value-added potential of bioimplants and, therefore, should also receive appropriate funding in the future. However, intensified value should be placed on combining basic research with applied research. Furthermore, there is a need for consequential focus on the clinical application of bioimplants in order to intensify translation and technology transfer.

A range of topics for the three bioimplant categories could be identified comprehensively, in which a substantial need for research funding exists. These are:

- Biological interface engineering
- Standardisation to improve reproducibility
- Improvement of manufacturing conditions and automation of (partial) processes
- Sterilisability and storability
- Development and consenting of adequate animal models for approval
- Development of non-invasive, non-destructive method of in vivo diagnostics and quality assurance
- Definition of safety and efficiency

It is, therefore, recommended that special weight is laid on these topics to justify the funding programmes in the bioimplant field in the future. In topics, such as „interface engineering“, basic engineering remains the centrepiece; in other topics, as in the issue of suitable animal models, it is, by contrast, finding the consensus between the participants from science, industry and the regulatory authorities.

2. Forms of research funding

Support for interdisciplinary joint projects

In addition to funding to the above-mentioned topic areas, for which a high demand on research and development is viewed, it is recommended to check the forms of research funding.

In general, focus is made on funding for manageable, large, interdisciplinary composite joint research and development projects. The research and development groups should incorporate project partners from clinics and industry to an adequate extent in order to intensify the translation and technology transfer. In the selection of joint projects, the aspects of translation, technology transfer and commercial applicability of research and development results must be weighed in a more intensive manner or, if necessary, a corresponding project qualification should be performed in the forefront of funding. In larger funding programmes, in which several joint projects receive funding, the facility of an accompanying research project also proved successful. The goal of the accompanying research is to minimise innovative hurdles that apply for all participants. For example, this can involve the development of a specific pool of knowledge related to the subject, the project anchorage in the medical user community,

the development of method proposals in clinical research, research-accompanying standardisation or the development of risk management concepts.

Support from an innovation manager

In order to further enhance the prospect of commercial applicability of the research and development results, it would also seem appropriate to provide support for the grant project from an „innovation manager“. The „innovation manager“ is an expert, who provides individual advice in each project, consolidates the possibilities of different scientific knowledge as well as projects on the potential market and „paves the way“ for results evaluation in this manner at an early stage. The focus of the activities carried out by an „innovation manager“, therefore, existed in the targeted identification and coordination of utilisation potentials of an association, the identification and the address of suitable partners, the development of utilisation strategies and connection facilities, the contention with all aspects of patenting and product approval as well as the reimbursement and associated marginal conditions, which should be taken into consideration at an early stage in a research and development project. The development of new business models, which take into consideration special conditions in the field of bioimplants, should also be part of the task of the „innovation manager“. At the Workshop 5, „Well Positioned in Unison — Cooperative and Business Models for Innovative Medicinal Products“ made by attending experts of the 2011 future conference in medical technology, the need was consistently addressed to such an attendant of research and development projects with a view on funded research and development projects in the medical technology. Since it generally concerns medical technology and especially bioimplants in a very complex, multidisciplinary and highly regulated innovative environment, there is an especially pronounced need for a targeted support for result evaluation.

Cofinancing clinical studies

Furthermore, among other things, the phase of clinical studies was identified as obstructive to innovations in the area of approving innovative bioimplants. The prevailing reason for this is the cost associated with the clinical studies, which frequently refuses market access for small- and medium-sized businesses. Except for a few exceptions, as in the example of the grant of the innovative therapeutic procedure (Federal Ministry of Education and Research, announced on 11.06.2010), clinical studies are, however, not eligible for grants. Different models of cofinancing clinical studies from public funds were discussed at the workshop. In addition to financial security, the goal of such a promotion is to include companies in the development phase of bioimplants at an early stage. Science and industry can, by this means, best benefit from one another and together contribute to a targeted development process. It would be conceivable that, depending on the involvement of third parties, the public sector would fund the initial clinical studies. In the case of a market success, the incentives could be reimbursed („Model similar to the Federal Education and Training Assistance Act“).

3. Interdisciplinarity

Companies and institutions from the field of classical, mainly technically coined medical technology and, to some extent, from biotechnology are predominantly active in research and development of bioimplants. Work on bioimplants, however, requires increasingly more biological and medical experience. Pharmaceutical companies and research facilities, in turn, have these. It is, therefore, recommended to expand the collaboration between classical medical technology, biotechnology and pharmaceutical disciplines and to provide more funding in order to, for example, acquire better basic understanding of the specific effects, similarly to the pharmaceutical disciplines. Also listed among these are drug profiles and release kinetics of layers (dosage, kinetics, safety and efficacy, etc.) as well as the exchange of experience with regard to storability, logistics and market access.

The high extent in interdisciplinarity also requires specialists with both technical as well as biological and medical know-how.

Therefore, it is recommended to overcome the cross-disciplinary boundaries in education as well as to integrate more biological and medical content in technical disciplines as well as more technical content in the biological and medical disciplines.

However, not only the education of future specialists for research and development as well as the application of bioimplants should be shaped in an interdisciplinary manner. This also applies to the interdisciplinary aspects in the determination of grant projects.

In addition, a greater connection between knowledge and industry is aimed at in order to achieve a stronger orientation in the approval conditions in the beginning of research and development projects.

4. Central office of coordinating approval

In Germany, the approval of bioimplants is regulated by a large number of laws. It is not always clear to decide whether the Pharmaceutical or the Medical Device Act is effective in the current bioimplant product. Moreover, different offices and authorities are often responsible for the different steps involved in the approval and reimbursement processes. It is therefore recommended to form a central office to coordinate the approval and reimbursement of bioimplants, which could, for example, satisfy a type of pilot function when the manufacturing permit is enquired. The innovation office of Paul Ehrlich Institute is an initial step to support ATMP manufacturers in the regulatory field in the classification of their products and in potential approval alternatives. Moreover, such a central coordinating office could inform of the necessary step along the value-added chain within the context of individualised medicine, starting from research and development through implementation, approval and market introduction to commercialisation. Based on a bioimplant product example, they can make the knowledge required more readily available and, hence, promote the existence of innovative products.

5. Legislation for bioimplants — clarification and simplification of the legal situation

As already described above, the regulatory parameters for the production and approval of bioimplants in Germany are very comprehensive. It is recommended to aim at clarification and standardisation of the legal situation. Therefore, a separate law could be made, which regulates the production and application of bioimplants.

6. Clinical innovation centres for medical devices and bioimplants

The emergence of innovative products in the bioimplant field is frequently broken since before the approval process starts, no assessment of the cost reimbursement from the sponsor of any kind is possible. On the other hand, the relevant instance (Federal Joint Committee) can only provide such a commitment if a corresponding proof of the medical benefit was produced. For this reason, clinical studies are required in return, which, however, are usually associated with high costs and many manufacturers baulk at the backdrop of an unclear cost refund. In addition, to provide such a proof of benefits, it is necessary, to identify evidence-oriented and simultaneously practical criteria. An essential problem lies in the discrepancy between the theoretical criteria required to establish the evidence, as is common in pharmacological studies, and the applicability of criteria in a clinical study with medical products and bioimplants. The criteria employed hitherto in the studies were often not accepted by the Federal Joint Committee and by the Institute for Quality and Efficiency in Healthcare (IQWiG). There is also the fact that the patient cohorts for highly specialist products become smaller and the numbers of cases required are only available in specialised medical centres.

Therefore, it is recommended to establish clinical innovation centres for medical products and bioimplants, which develop the criteria for proof of medical benefit in close coordination with the Federal Joint Committee and the Institute for Quality and Efficiency in Healthcare. Moreover, the centres should have the appropriate resources in order to implement initial clinical studies for temporary approval of innovative products. In addition, such centres could work in close coordination with the regulatory authorities to develop new, more efficient and clinically relevant physical, biochemical and animal experimental test procedures for efficacy and efficiency evidence. It would also be imaginable — as described before — that the equipment at special clinics, which is operated by primary manufacturing companies, is practised similarly to that already used, for example in dialysis. However, this requires a manufacturer with corresponding financial power.

In association with the clinical proof of benefits of medical products, the Federal Joint Committee should apparently receive a new instrument for the testing of „study and treatment methods that are not related to drugs“ [16]. In the draft bill of the Relief Act, section II.2.5 „Innovative Treatment Methods“, according to the *Deutsch Ärzteblatt*, a chronologically limited test procedure is described, which can be requested by the method provider. Furthermore, an appropriate participation of the expert group of interest is guaranteed as well as a proportionate financing of a system surcharge according to § 139 c German Social Code V with the participation of the manufacturer. Such an approach is welcomed as a step in the right direction.

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6. List of Abbreviations

AMG	Arzneimittelgesetz - German Pharmaceuticals Act
AMNOG	Arzneimittelmarktneuordnungsgesetz - Law on Realignment of the Pharmaceutical Market in Germany
AMWHV	Arzneimittelwirkstoffherstellungsverordnung - Ordinance for the Production of Medicinal Products and Active Substances
ATMP	Advanced Therapy Medicinal Product
BAföG	Bundesausbildungsförderungsgesetz - Federal Education and Training Assistance Act
BfArM	Bundesinstitut für Arzneimittel und Medizinprodukte - Federal Institute for Drugs and Medical Devices
BMBF	Bundesministerium für Bildung und Forschung - Federal Ministry of Education and Research
BQS	Bundesgeschäftsstelle Qualitätssicherung - National Institute for Quality, Institute for Quality and Patient Safety
DGBMT	Deutsche Gesellschaft für Biomedizinische Technik im VDE - German Society for Biomedical Engineering within VDE
DRG	Diagnostic-related case group
ECM	Extracellular matrix
EC	European Community
EU	European Union
G-BA	Gemeinsamer Bundesausschuss - Federal Joint Committee
GKV	Gesetzliche Krankenversicherung - Legally required health insurance
HSC	Haematopoietic stem cell
HTA	Health Technology Assessment
InEK	Institut für das Entgeltsystem im Krankenhaus - Institute for the Hospital Remuneration System
iPS	Induced pluripotent stem cell
IQWiG	Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen - Institute for Quality and Efficiency in Healthcare
IV	Integrierte Versorgung - integrated care
KMU	Kleine und mittlere Unternehmen - small- and medium-sized businesses
MACT	Matrix-associated autologous chondrocyte transplant
MOCART	Magnetic Resonance Observation of Cartilage Repair Tissue
MPG	Medizinproduktegesetz - Medical Devices Act
MRT	Magnetic resonance tomography
MSC	Mesenchymal stem cell
NUB	Neue Untersuchungs- und Behandlungsmethode (new examination and treatment method)
PEI	Paul Ehrlich Institute
PharmBetrV	Pharmabetriebsverordnung - Pharmaceutical Operation Ordinance
SGB V	Sozialgesetzbuch - Social Security Code, Fifth Volume
TFG	Transfusionsgesetz - German Transfusion Act
TPG	Transplantationsgesetz - German Transplantation Law
TPG-GewV	Gewebeverordnung - Tissue Regulation
VDE	Verband der Elektrotechnik Elektronik Informationstechnik e.V. - Association for Electrical, Electronic and Information Technologies



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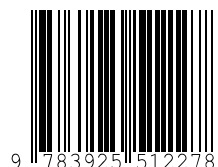


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