Novel biomedical products: Conventional biologics or ATMPs?

Wissenschaftliche Prüfungsarbeit

zur Erlangung des Titels

“Master of Drug Regulatory Affairs”

der Mathematisch-Naturwissenschaftlichen Fakultät
der Rheinischen Friedich-Wilhelm-Universität Bonn

vorgelegt von

Dr. Gabriele Noffz

aus Braunschweig

Bonn 2011

Betreuer und erster Referent: Prof. Dr. Christa Schröder
Zweiter Referent: Prof. Dr. Barbara Sickmüller

Table of Contents

1. Introduction / Objectives 6

2. Biologics, Biotechnological products, Advanced therapy medicinal products – a short outline

2.1 Peculiarities of biological medicinal products 7

2.2 Biologicals as medical products 7

2.3 History of biotechnological products 8

2.4 Benchmarks in biotechnology 9

2.5 Development of regulatory legislatives 9

2.6 Development of the ATMP regulation 11

2.7 Advanced therapy medicinal products 11

3. Legal framework in the European Union

3.1 Definitions

3.1.1 Biological medicinal products 12

3.1.2 Immunological medicinal products 14

3.1.3 Blood and blood products / Plasma and plasma-derived products 14

3.1.4 Advanced therapy medicinal products (ATMPs) 15

3.1.5 Other biological products 16

3.1.6 Biopharmaceuticals 16

3.1.7 Conventional biologics 17

3.2 Regulations 3.2.1 Regulation (EC) 1394/2007 – the legal framework for ATMPs 17

3.2.2 Regulations for other biological medicinal products 18

3.3 Classification of ATMPs 3.3.1 CAT (Committee for Advanced Therapy) 19

3.3.2 Procedure of the Classification 19

3.3.3 Classification criteria 22

3.3.4 Classification criteria for medical devices and combined ATMPs 25

4. Examples 26

Example 1: 29

Example 2: 30

Example 3: 31

Example 4: 32

Example 5: 32

Example 6: 33
Example 7: 34
Example 8: 35
5. Consequences of the new framework on the demarcation 35
5.1 Regulatory requirements of marketing authorisation applications 36
5.1.1 Dossier requirements: Quality 36
5.1.2 Dossier requirements: Non-clinical data 36
5.1.3 Dossier requirements: Clinical data 38
5.2 Requirements on medical devices 38
5.3 Requirements on SPC/Labelling and package leaflets
5.3.1 Summary of Product Characteristics (SmPC) 38
5.3.2 Labelling of outer/immediate packaging 39
5.3.3 Package leaflet 39
5.4 Marketing authorisation procedures 39
5.5 Safety requirements 5.5.1 Risk management system 40
5.5.2 Environmental risk assessment 40
5.5.3 Risk analysis 41
5.6 Post-authorisation requirements 5.6.1 Traceability 41
5.6.2 Periodic safety update reports (PSUR) / additoninal monitoring /safety and efficiency follow up / post-authorisation safety studies (PASS) 41
5.6.3 Variations 42
5.6.4 Scientific requirements 42
5.6.5 Fees / Incentives 42
5.7 Requirements on GCP / GMP and GLP 42
5.7.1 GCP 42
5.7.2 GMP 43
5.7.3 GLP 43
5.8 Pharmacovigilance 43
5.9 Clinical trials 44
5.10 Ethic concerns 44
6. Discussion 44
6.1 Are the classification criteria clear and suitable to distinguish ATMPs from other medicinal products? 45
6.2 Does it make sense to limit the ATMP to these three classification groups? 48

6.3 Justify the differences in ATMPs and conventional biological medicinal products also a stronger regulation for ATMPs? 48
6.4 Which impact has the demarcation in the view of health protection and health market 49
7. Conclusion and Outlook 49
8. Summary 50

List of Abbreviations 51
Literature 53

1. Introduction / Objectives

Biotechnology has brought a considerable input into the development of human healthcare. About 25 years ago biological products used for treating diseases were mostly obtained by extraction from human or animal tissue. For example, insulin extracted from cattle or pigs has been used to treat diabetic patients for decades before recombinant human insulin was introduced [1]. The use of biotechnological products such as recombinant proteins overcomes the problems of extracting sufficient amounts from natural sources as well as possible intolerances to animal proteins. Furthermore, concerns regarding contaminants such as the bovine spongiform encephalopathy, commonly known as mad cow disease, increased the demand for recombinant products in order to replace available extracted products [1]. Another important example of biotechnological products are monoclonal antibodies. Due to their selective binding to unique antigens they are widely used for protein purification but also for therapeutic purposes [1].

Biotechnology has evolved a broad variety of divergent medicinal products including hormones and blood factors as well as vaccines and monoclonal antibodies for chronic, acute and rare diseases, such as some cancers, especially breast cancer, hepatitis C, chronic renal failure, haemophilia, diabetes, growth deficiency, multiple sclerosis, rheumatoid arthritis and Crohn's disease [2]. Within the pharmaceutical market the biopharmaceutical sector is significantly growing. In 2007 biologics accounted for 94 billion US$ representing around 15% of all sales within the pharmaceutical sector [2]. At least 500 potential biopharmaceuticals are currently being evaluated in clinical trials. Vaccines and monoclonal antibody-based products represent the two largest product categories [1].

Thus, biotechnology has been recognised as a key technology of the 21st century in many sectors and human health can be regarded as one of the main application area [3]. The European Commission adopted in 2002 a strategy containing a 30 point action plan in which the European member states were requested to foster innovation of biotechnology in the pharmaceutical sector. Similarly, a focus was set on better regulation and risk communication [3].

Emerging fields of biotechnology are therapies based on gene therapy, somatic cell therapy or tissue engineering [4]. Such innovative therapeutics are summarised under the term advanced therapy medicinal products (ATMP). ATMPs offer new opportunities for treatment of rare or previously untreated diseases or early detection of dysfunctions of the human body or others, e.g. skin replacement products [5].

In 2007 a regulation for ATMPs has been adopted to overcome the lack of a clear and coherent legal framework and to boost research in this field [6]. The intention was to harmonise the regulation of these therapies and to adapt technical specificities to ATMP products. The regulation involves a classification procedure to facilitate the classification of these products. This is important for the companies when the classification of the case is ambiguous as the application of ATMP requires a lot more data regarding quality and safety compared to other biological products.

The aim of the present master thesis is to give an overview of the classification and demarcation of ATMPs as compared to other biological medicinal products. Despite of classification criteria in the legal framework for ATMP the delimitation to other biotechnological products is not simple and clear. The differences in the regulation of ATMPs and other biological medicinal products will be illustrated. Furthermore, the significance and the limitation of such a classification will be discussed.
The thesis describes the status as of March 2011.

2. Biologics, Biotechnological products, Advanced therapy medicinal products – a short outline

2.1 Peculiarities of biological medicinal products

The term “biologic” comprises a quite heterogenous group of substances used for medicinal products encompassing peptides or proteins, nucleic acids (DNA, RNA), cells or tissues. Generally, biologics differ from their chemical counterparts in their complexity with regard to structure, size, mechanism of action and sensitivity to various degradation pathways [7].

For biological medicinal products the quality is defined by the manufacturing process [8]. Even minor changes in the process may affect the quality, functionality and / or stability of the drug substance in the product. The functionality of the medicinal product is determined by the biological activity. For example, the biological activity of proteins is determined by the three-dimensional and conformational structure of the molecule [1]. Changes in the manufacturing process as the use of a different manufacturing system may lead to alterations in the specific structure. Post-translational modifications such as glycosylation or phosphorylation or the lack of them may cause a change in activity, stability or trafficking of the protein [1]. The impurity profile depends on the manufacturing process as well. Biologics can be derived from any living source such as animals, humans, bacteria, plants, or even viruses. During the manufacturing process a multitude of special analytical methods is applied in order to measure each step in quality, stability and potency or functionality of the drug substance. Those are unique for a biological medicinal product as the parameters of a product are not identical [1].

Many of the biological medicinal products are immunogenic [8]. The term immunogenicity describes the property of a molecule to provoke an immune response upon contact with cells of the immune system of the treated patient. If this immune response is unspecific a large number of cytokines and chemokines may be secreted by activated cells leading to unwanted inflammatory reactions. Thus, the risk of immunogenic adverse reactions must be minimised and addressed in a risk-based approach. Adequate screening and assays have to be developed, validated and standardised [8].

2.2 Biologicals as medical products

The use of biologicals as medical products started already around 300 years ago as in

1701 Giacomo Pylarini, a Venetian physician, inoculated a mild strain of smallpox on children for prevention of a serious smallpox disease [9]. Almost a century later in 1798 the British physician Edward Jenner improved that procedure by the use of cowpox as a vaccine to induce resistance to smallpox and thereby established the modern vaccination against smallpox [10]. However, the responsible mechanisms of the immunology behind this were still not yet understood. In mid-19th century more knowledge regarding nature and the human body were obtained. Nevertheless, it took another century since the development of the cowpox vaccine, until a further important step in the progression of medicinal products were made. Louis Pasteur used attenuated micro-organisms as vaccines against fowl cholera, anthrax and rabies [9]. The discovery of antibodies as the carrier of the passive immunity followed a few years later by Emil von Behring [9]. Shortly before the beginning of the next century, in 1897, Paul Ehrlich proposed that antibodies are responsible for immunity. He developed together with Emil von Behring the diphteria antitoxin as a first success of the modern immunotherapy [9].

In between, in 1871, DNA was isolated for the first time from the sperm of trout [9]. But it took until 1935 that DNA was further examined [9]. In 1938 proteins and DNA were studied in various labs with X ray crystallography. The term “molecular biology” was born. The developments in biology boosted the innovation in the pharmaceutical industry. Insulin, firstly isolated in 1916, was already produced in large scale less than 10 years later. In 1928 Oskar Wintersteiner identified its proteineous character [9].

2.3 History of biotechnological products

The research on nucleic acids and proteins as biomedicine continued. New scientific findings in the 1940s and 1950s formed the basis of biotechnology. DNA was first determined as hereditary material by Oswald Avery, Colin MacLeod and Maclyn McCarty in 1944 [9]. One year later Max Delbrück and Alfred Hershey could show examples of genetic recombination on viruses and in 1952 Joshua Lederberg demonstrated the transduction of genes, the exchange of genes from bacteria [9]. Furthermore, he discovered extrachromosomal genetic material in bacteria, which he called plasmid [9]. Today plasmids are an important tool in the molecular biology. One year later, Francis Crick and James Watson proposed their double-stranded, helical model for the DNA [9]. The discovery of the DNA structure resulted in a boost of research in the molecular biology field but the breakthrough of the modern biotechnology was the development of the recombinant DNA technology in 1972 / 1973 [9]. A recombinant DNA is an engineered artificial nucleic acid by the use of chemical or enzymatic synthesis techniques. In 1978 researchers used this technique to produce human insulin with recombinant DNA in bacteria [9].

In 1975 Georges Köhler and César Milstein developed the monoclonal antibody technology allowing the manufacture of large amounts of pure antibodies as well as their characterisation [9]. The conventional technique until now of collecting antibodies from blood serum of immunised animals resulted in polyclonal antibodies which were usually poorly characterised and more difficult to purify.

Kary Mullis developed one of the key tools in the molecular biology, the polymerase chain reaction (PCR), in 1983 [9]. These tools were essential for the development of macromolecules into therapeutic products and mark the birth of the modern biotechnology era.

2.4 Benchmarks in biotechnology

In 1982 the first recombinant biotechnological product, insulin, was approved by the FDA. The following years between 1986 and 1991 were a period of a massive increase of the number of biotechnology products. Approvals of the first recombinant enzymes and growth factors were obtained. In 1986 the FDA granted approval for the first recombinant vaccine, a vaccine against hepatitis [9]. Also in 1986 the first monoclonal antibody for therapeutic use, muromonab-CD3, was approved. Muromonab-CD3 is a murine monoclonal antibody against the CD3 receptor, a cell surface protein of T lymphocytes [9].. A few years later, in 1990, the first gene therapy trial was set up. It was used on a four-year-old girl with an adenosin desaminase (ADA) deficiency, an immune system disorder. Even though the therapy appeared to work it provoked a discussion on ethics both in academia and the media [9]. In the following years, medicinal products based on gene therapy, immune system modulation and genetically engineered antibodies against cancer entered the clinic [9]. In 1997 the development of a new technique combining PCR, DNA chips and computer programming for DNA mapping without sequencing provided a tool for diagnosis of disease causing genes [9]. A second therapeutic antibody-related product, abciximab, was approved in 1994. Abciximab, an antibody fragment, is chimeric, with the constant, non-binding regions having human instead of murine sequences [9]. In 1997, the first whole chimeric antibody, rituximab, and the first humanised antibody, daclizuman, were approved. These gentically engineered modifications reduce the amount of immunogenic non-human sequences within monoclonal antibodies. Thus, they facilitate chronic therapeutic use of antibodies [9].

2.5 Development of regulatory legislatives

In parallel, regulatory legislatives developed in the USA as well as in Europe. The need to include this new technology into a regulative legislative and the need to respond to the variable market demand pushed the development [9].

In December 1986 the first directive was established which included medicinal products derived by biotechnology (Council Directive 87/22/EEC) thereby establishing a first definition of high technology products [12]. In the next years, several directives came into force including immunological medicinal products such as vaccines, toxins, serums and allergens (Council Directive 89/342/EEC) and products derived from human blood and human plasma (Council Directive 89/381/EEC) [13, 14]. Those products were not covered in the Council Directive 87/22/EEC. Both directives amended the Directive 65/65/EEC, the main directive for all medicinal products which was established as a reaction to the Thalidomide tragedy. Developments in the genetic sector have raised many issues and led to further regulatory initiatives. In 1990 two directives regarding genetically modified organisms (GMO) were established, focussing on the deliberate release of genetically

modified organisms into the environment (Council Directive 90/220/EEC) and on the contained use of GMO (Directive 90/219/EC) [15, 16]. In the latter one, the biosafety level of GMO were classified. In 1993 the Council Regulation (EEC) No. 2309/93 came into force introducing the concept of a new agency, the EMEA, and a standardisation of the regulatory process in a centralised procedure [17]. It replaced the Council Directive 87/22/EEC. In annex A of this Regulation the following products derived from biotechnological processes were included:
recombinant DNA technology
controlled expression of genes coding for biologically active proteins in prokaryotes and eukaryotes including transformed mammalian cells
hybridoma and monoclonal antibody methods.
Furthermore, as mentioned in part B of the same Regulation, medicinal products produced by other biotechnological process and new medicinal products derived from human blood or human plasma were also included in this Regulation. The harmonisation of the regulation of those products was a great success as medicinal products produced by biotechnological process in the EU before 1980 were regulated on a national basis.

Further directives and guidances including biological or biotechnological derived products were created in the following years. Many of them are consolidated in the Directive 2001/83/EC for human use which replaced the Directive 65/65/EEC in 2001 [18]. A further important directive was laid down in the same year, the clinical trial Directive 2001/20/EC establishing specific provisions regarding the conduct of clinical trials and protecting clinical trial subjects by defining quality, safety and ethical criteria to be observed [19]. This Directive led to harmonisation of the procedures in clinical trials within the EU member states and is also valid for biological products.

Cells, especially derivatives of human blood cells and human plasma were already included in the Council Directive 89/381/EEC and adopted by the Directive 2001/83/EC. In 2003 the Directive was amended by the Directive 2002/98/EC focussing on setting standards regarding quality and safety for the collection, testing, processing, storage and distribution of human blood and blood components for extended therapeutic use [20]. This legislative should overcome the lack of any Community binding legislation to include quality, safety and efficacy requirements of medicinal products containing whole blood, plasma and blood cells of human origin. Furthermore, a system to ensure traceability of blood and blood components was established. Similarly, in 2004 Directive 2004/23/EC laid down standards on quality and safety for the donation, procurement and testing of all human tissues and cells intended for human use [21]. Included are also products derived from human tissues and cells, haematopoietic progenitor cells and stem cells but not blood and blood constituents as already regulated by Directive 2002/98/EC. A directive for the use of other cells than blood cells and their derivatives was not established before Directive 2003/63/EC in 2003 [22].

Before 2003 a variety of guidelines were adopted compensating the lack of a binding legislative. The guideline *Points to consider on the manufacture and quality control of human somatic cell therapy medicinal products* adopted in May 2001 set out rules for the characterisation and quality control of living human somatic cells including modified cells intended for administration as a medicinal product [23]. However, the use of xenogeneic

cells was excluded, meaning material originating from another species. Such cells were considered in a new guideline adapted in December 2004 dealing with the manufacture and quality criteria but also with implications on non-clinical testing and pharmacovigilance [24]. Both guidelines are now revised. Other guidelines regarding the use of biological products as DNA vaccine, cells or for gene transfer were revised or newly created within the last few years [25, 26].

2.6 Development of the ATMP regulation

The progression of innovative medical products using biological substances continued as well as the number of clinical trials. It became obvious that those innovative medicinal products could not be sufficiently regulated through the existing regulations and directives. Thus, appropriate regulatory standards had to be developed to regulate these novel biological medicinal products. In 2002, the European Community started an action plan for the development of biotechnology in Europe. This plan proposed the implementation of a Community regulation of new technology products with the goal of a better regulation regarding transparency and communication, especially in regard to safety, quality and efficacy aspects as well as a legislation for GMO including traceability, labelling and deliberate release [3]. In 2003, amendments to the existing main directive for medicinal products, Directive 2001/83/EC, added definitions and requirements for the market authorisation application for gene therapy medical products and medical products containing cells or cell products [4]. Later it was recognised that this amendment was not sufficient as for example tissue engineering as a product of an emerging biotechnology sector was not included [27]. The lack of any Community legislative on tissue engineering products led to divergent approaches. Tissue engineered products were either regulated as a medicinal product or as medical device and some countries differentiate this on a case-by-case basis. To overcome this problem the European committee decided on the development of a new regulation which entered into force in 2007 [28].

2.7 Advanced therapy medicinal products

Most common products for somatic cell therapies containing manipulated cells as active substance are cancer vaccines [2]. The first therapeutic cell-based product, Dendreon®, approved by the FDA in 2010, is a cellular vaccine directed against metastatic prostate cancer [2]. The vaccine contains patient-derived blood cells, stimulated *in vitro* with a recombinant prostatic acid phosphatase-granulocyte-macrophage colony-stimulating factor (PAP-GM-CSF) fusion protein, and enriched with the marker protein CD52. After stimulation the cells are returned to the patient. The idea behind this is that the monocytes in the blood will differentiate into stimulated dendritic cells after exposure to the fusion protein. These cells act as antigen-presenting cells which are causing activation of T cells by presenting processed prostate cancer antigens. This way activated T cells are able to initiate a specific immune response against the prostate cancer.The recombinant prostatic acid phosphatase acts as an antigen, the cytokine GM-CSF effects the differentiation of monocytes into dendritic cells [2, 29].

Tissue engineered products are used for the repair, replacement or regeneration of

tissues or organ defects as for treatment of ulcers and cartilage damage in early arthritis [30]. The first licensed tissue engineered product in the EU, ChondroCelect®, contains patient-derived cartilage-forming cells for the regeneration of cartilage. The cells are harvested during diagnostic knee arthroscopy, proliferated *in vitro* and re-implanted under open knee surgery using a collagen membrane to cover the defect [31]. This ATMP are described in more detail in the chapter 4.

Nucleic acid-based products are most commonly used to cure cancer but also for monogenetic disorders, diseases caused by single gene defects, or cardiovascular diseases [2]. Despite of more than 1000 clinical trials in over 20 years no product has yet been approved in the EU or US [2]. An example is Glybera® which is currently under evaluation by the EMA [2]. This product comprises an adenoviral vector system engineered to express the human lipoprotein lipase (LPL) for the treatment of LPL deficiency, a monogenetic disorder. The disease is caused by a mutation in the LPL gene resulting in an inactive protein. LPL catalyses the hydrolysis of the triglycerides which are present in the very low density lipoproteins (LDL). A deficiency of the gene results in an elevated level of triglycerides and LDL in the blood stream of the patient and may lead to type 2 diabetes and obesity. The gene encoding for LDL is mainly expressed in skeletal muscle, heart muscle and adipose tissue. The gene therapy medicinal product is delivered to the skeletal muscle where it replaces the mutated gene for an intact gene and thus, restores the enzyme activity [32].

3. Legal framework in the European Union

3.1 Definitions

3.1.1 Biological medicinal products

Although biologics are widely used for a long time a definition for “biologics” or other frequently used terms as “biologics”, “biological products” or “biotechnological products” was missing in the European Union until 2003 [33]. Not even guidelines intended for the use of biological or biotechnology products really defined the term “biologics” indicating the problem of characterisation of such complex products. In the ICH guideline *Q5C Quality of Biotechnological Products: Stability Testing of Biotechnological/Biological Products* biological products are stated as *products typically consisting of proteins or polypeptides with biological activity, isolated from tissues, body fluids and cell cultures or produced by recombinant DNA technology* [34]. This definition limits biological product solely to the product class of proteins but excludes the process by which the biologic is manufactured or isolated. The biological activity is also not explained in detail.

In the US, in 1902 a Biologics Control Act was adopted where regulatory requirements to a variety of biological products, namely *any virus, serum, toxin, antitoxin, therapeutic serum, vaccine, blood, blood component or derivative, allergenic product, or analogous products*, were established. Only in 1944 the Public Health Service Act incorporated the Biologics Control Act as a legal basis for regulation of “biologics”. Today the US Food and Drug Administration (FDA) defines a biological product as *any virus, therapeutic serum,*

toxin, antitoxin, or analogous product applicable to the prevention, treatment or cure of diseases or injuries of man (21 CFR 600 Biological Products General, Subpart A – General Provisions, Sec.600.3 Definitions). The definition of the product is now stated by its source and / or the process. On the CBER (Center for Biologics Evaluation and Research) website of the FDA this definition of biological products is highly expanded including *a wide range of products such as vaccines, blood and blood components, allergenics, somatic cells, gene therapy, tissues, and recombinant therapeutic proteins. Biologics can be composed of sugars, proteins, or nucleic acids or complex combinations of these substances, or may be living entities such as cells and tissues. Biologics are isolated from a variety of natural sources – human, animal, or micro-organism – may be produced by biotechnology methods and other cutting-edge technologies...* (Questions and Answers: What are "Biologics"). However, the definition remains stipulated by source and process of the products [33].

In the EU the term "biological product" was first published in Directive 2003/63/EC, amending Annex I of Directive 2001/83/EC. The term is similarly defined as in the regulation of the FDA, by its source or by the process involved but not through its function: *A biological product is a product, the active substance of which is a biological substance. A biological substance is a substance that is produced by or extracted from a biological source and that needs for its characterisation and the determination of its quality a combination of physico-chemical-biological testing, together with the production process and its control.* The description of the biological source mentioned in the Directive includes a broad range of references and is amended as follows: *any substances of biological origin such as micro-organisms, organs and tissues of either plant or animal origin, cells or fluids (including blood and plasma) of human or animal origin, and biotechnological cell constructs (cell substrates, whether they are recombinant or not, including primary cells).*

Furthermore, in the same Directive all products which fall in the category of biological products are precisely listed:
The following shall be considered as biological medicinal products:
Immunological medical products
Medicinal products derived from human blood and human plasma as defined, respectively, in paragraph (4) and (10) of Article 1
Medicinal products falling within the scope of Part A of the Annex to Regulation (EEC) No. 2309/93
Advanced therapy medicinal products as defined in Part IV of this Annex
The kind of biological products mentioned complies with the biological products stated on the website of the FDA [33].

Interestingly, the definition of a biological product differs from the definition of classical, non-biological, medicinal product in a way that the latter one is defined by its action: *Any substance or combination of substances presented as having properties for treating or preventing disease in human beings; or any substance or combination of substances which may be used in or administered to human beings either with a view to restoring, correcting or modifying physiological functions by exerting a pharmacological, immunological or metabolic action, or to making a medical diagnosis* (Article 1 of Directive 2001/83/EC (consolidated)).

A further definition regarding biological medical products is stated in the current Good Manufacturing Practice (GMP) Guideline Annex 2 (Manufacturer of Biological medical Products for Human Use): *.... Biological medical products can be defined therefore largely by reference to their methods of manufacture* [35]. This definition refers only to the process involved in the manufacturing of biological products. Included are manufacturing processes such as microbial cultures excluding those resulting from recombinant DNA techniques, microbial and cell cultures including those resulting from recombinant DNA or hybridoma techniques, extraction from biological tissues and propagation of live agents in embryos or animals. In the draft version of the GMP guideline from April 2010 the definition of biological products has been revised to include new developments in legislation as the ATMP regulation. An illustrative table included in this guideline gives a non-exhaustive overview to biological products. For details please look at annex I.

Also the CMDh (Co-ordination Group for Mutual Recognition and Decentralised Procedures - Human) addresses on their Website in the Question & Answer part to "Biologicals" the question to the definition of "biological medicinal products" [36]. The CMD(h) follows the definition given in Part I of Annex I of Directive 2001/83/EC (as amended by Directive 2003/63/EC). In "Question No.2: How is the definition applied?" further products are included which are not explicitly mentioned in the Directive above but fulfil the criteria of the biological origin and complexity. A non-exhaustive list of those biological products is published on the website.

In the following some of the biological products, mainly those which are mentioned in the Annex I of the Directive 2003/63/EC, are illustrated.

3.1.2 Immunological medicinal products

Immunological medical products are defined in the Directive 2001/83/EC, Article 1(4). This group of products includes any products which consist of vaccines, toxins and serums which are either able to generate active or passive immunity against certain diseases as listed in the Directive or to diagnose the state of immunity. Included in this group are allergen products which are as well able to identify or induce a specific alteration in the immunological response to a sensitising allergen. This subgroup of biological medicinal products is defined mainly through its function rather than by its source. A more precise definition can be found in the German pharmacopoeia (AMG), §4 AMG, for the biological products serum, vaccine and allergenic agents. Serums are defined as medicinal products containing antibodies, antibody fragments or fusion proteins with an antibody as functional part as active substance and which are used in view of their activity (§4(3) AMG). In §4(4) AMG vaccines are stated as medicinal products containing antigens or recombinant nucleic acids which are used for the induction of specific immunity in humans or animals and which are intended for prophylactic use for treatment of infectious diseases.

3.1.3 Blood and blood products / Plasma and plasma-derived products

Medicinal products derived from human blood or human plasma, as stated in the Directive

2001/83/EC in Article 1 (19) are medicinal products based on blood components which are prepared industrially by public or private establishments, *… including, in particular, albumin, coagulating factors and immunoglobulins of human origin*. The term "industrial" is not further defined and allows interpretation. Blood, blood products and blood components are defined in Directive 2002/98/EG (Art. 3) as well: *"Blood" shall mean whole blood collected from a donor and processed either for transfusion or for further manufacturing*. *"Blood component" shall mean a therapeutic constituent of blood (red cells, white cells, platelets, plasma) that can be prepared by various methods*. *"Blood product" shall mean any therapeutic product derived from human blood or plasma* [20].

Blood and blood-derived products are classically defined by their source. A similar definition for blood products is stated in the German pharmacopoeia in §4 AMG. Additionally, the components of the source from which the blood products are prepared are defined as the active substance.

3.1.4 Advanced therapy medicinal products (ATMPs)

The definition of the advanced therapy medicinal products is published in Directive 2001/83/EG, Annex 1, part IV, 2 as well as in Art. 2 of Regulation (EC) 1394/2007. In the Directive the definition of two categories (Gene Therapy Medicinal Products (GTMP) and Somatic Cell Therapy Medicinal Products (CTMP)) are stated, in the Regulation the definition of the third category, tissue engineered products (TEP), was added. As the definition of those three categories will be described in more detail in the section "Classification" only a short overview of the definitions is given here.

Gene therapy medicinal products are defined as biological products containing a recombinant nucleic acid as an active substance for the treatment of humans, for therapeutic, prophylactic or diagnostic reasons. The active substance shall act in regulating, repairing or replacing of the genetic information or can be used for adding or deleting of a genetic sequence.

Somatic cell medicinal products are defined as a biological product containing or consisting of cells or tissues which have been either manipulated in that manner that the biological, physiological or structural characteristics intended for the clinical use have been altered, or alternatively, are defined as biological product which essential function is different in the recipient and the donor. Furthermore, those manipulated cells or tissues need to act pharmacologically, immunologically or metabolically and are used for therapeutic, prophylactic or diagnostic reasons.

Tissue engineered products are defined as a product containing or consisting of engineered cells or tissues used for regenerating, repairing or replacing a human tissue. The viability of the cells or tissues does not play a role.

All three classes of the ATMP products are mainly defined by their functions.

3.1.5 Other biological products

The third group of products mentioned in the list in Annex I of Directive 2001/83/EC are products manufactured by a biotechnological process as described in the Council Regulation (EEC) No. 2309/93, Annex, Part A [17]. Involved are biotechnological processes such as recombinant DNA technologies, hybridoma and monoclonal antibody technologies and the controlled expression of genes coding for biologically active proteins in prokaryotes and eukaryotes including transformed mammalian cells. This class of products is defined by its (biotechnological) process.

The Regulation has been expanded in April 2006 by the Commission Communication 98/C/229/03 [37]. Medicinal products manufactured by the use of a monoclonal antibody method are now defined as *any medicinal product for which a monoclonal antibody is used at any stage in the manufacturing process*. Furthermore, products containing a protein as a part of them and are obtained by a recombinant DNA technology belong to the definition of the Council Regulation, even if the protein component is not an active substance.

3.1.6 Biopharmaceuticals

A further term which is widely used is the term “biopharmaceuticals”. The website www.ebe-biopharma.org defines biopharmaceuticals as *pharmaceuticals manufactured by biotechnology methods* containing *products having biological sources, usually involving live organisms or their active components* [38]. Such products include biological products derived from hybridoma technology or genetic engineering, the most common biotechnologies. Other sources exclusively understand recombinant proteins as a “biopharmaceutical” [39].

According to the definition of the EMA “biopharmaceuticals” are medicinal products manufactured with one or more of the following biotechnological techniques: recombinant DNA techniques, controlled gene expression and antibody methods [39]. In this definition the part of the “live organism or their active component” is missing but includes as well as the other definition above the manufacturing process via biotechnological methods. According to the EMA definition, biological products, which have not been modified, are not “biopharmaceuticals” which implicates the idea that unmodified, pure biologics are not medical products at all. Serums, hormones and similar products derived from human or animal sources extracted or purified from its source consequently would not belong to them. On the other hand, many of such protein-based substances, polypeptide hormones, vaccines or enzymes are now produced by recombinant DNA technology and the source, either produced using recombinant DNA technology, or obtained by purification from natural sources, does not necessarily results in differences of the product.

Taking all these definitions into consideration the term “biopharmaceutical” should be avoided due to its unclear and inconsistent meaning.

3.1.7 Conventional biologics

All biological products according to the definition of biological medicinal products mentioned in the Annex I of Directive 2001/83/EC, amended by the Directive 2003/63/EC, with the exception of the advanced therapy medicinal products are considered as conventional biological products in the present master thesis whereas ATMPs are defined separately.

3.2 Regulations

3.2.1 Regulation (EC) 1394/2007 – the legal framework for ATMPs

The main legislative document for Advanced Therapy Medicinal Products is Regulation (EC) No. 1394/2007 published in November 2007 amending the Regulation (EC) 726/2004 and the Directive 2001/83/EC [28, 40, 18]. The choice of a Regulation instead of a Directive should ensure a uniform and more timely application of the new rules. A Directive needs to be implemented via a member state legislation and can be adapted to their special requirement. The Regulation comprises the complex therapeutic products gene therapy products, somatic cell therapy products and tissue engineering products. Whereas in the Annex I of the Directive 2003/63/EC amending 2001/83/EC gene therapy and somatic cell therapy products are already defined, the legal definition of tissue engineering products is laid down in Regulation (EC) No. 1394/2007. The decision of the Committee to include the tissue engineered products into the Regulation should overcome the lack of a clear regulatory framework and harmonise the definition and classification of tissue-engineered products within the national authorities in Europe. Previously, in some European countries tissue engineered products were registered as medical device, in others as conventional biologics. Included in the Regulation are also borderline products as combination products, medical devices or active implantable medical devices which are combined with cellular or tissue components. The definitions and conditions for such products are given.

Further key points of the provision are the regulation of the ATMPs through the centralised authorisation procedure as mandatory for other biotechnology medicinal products and the establishment of a new expert committee, CAT. The establishment of the Centralised Procedure results in harmonisation of the evaluation of the products and access to the whole European market for ATMPs [6, 41]. The authorisation tools as full, conditional or marketing authorisation under exceptional circumstances will apply to the ATMPs as well as to other medicinal products regulated by the centralised procedure. The formation of a new scientific committee, the Committee for Advanced Therapy (CAT) should cope with the specific expertise required for this new field in biotechnology. The CAT is responsible for all scientific questions regarding ATMPs. Coordination and cooperation between CAT and other committees shall ensure scientific consistence and efficiency of the system. More details on the role and responsibilities of the CAT are described below.

As a consequence of the establishment of a new regulation concerning advanced therapies the requirements in regard to scientific evaluation, clinical and non-clinical aspects as well as GMP and GCP were adapted or supplemented. Other legal texts

containing principles or standards and other requirements as laid down in Directive 2001/20/EC, Directive 2005/28/EC, 2004/23/EC or 2003/94/EC remain valid [19, 42, 21, 43]. Post-marketing monitoring such as traceability and mechanisms for reporting and documenting adverse reactions and issues with regard to efficacy of ATMP were included in the regulation. A management system for documenting risks related to ATMPs represents one key point. This is especially essential for ATMPs designed to remain in the human body for an indefinite period of time. Establishment and maintenance of the traceability must follow rules which are set out in Directive 2004/23/EC and Directive 2002/98/EC. To boost the development of ATMPs an incentive of a considerably reduced fee is offered especially to small- and medium-sized enterprises (SMEs). Furthermore, as particularly SMEs perform studies for demonstrating non-clinical and quality safety, the new Regulation offers a certification procedure as an incentive. This certification is an independent procedure but may facilitate future applications for clinical trials based on those data. Furthermore, a classification procedure to clarify the appropriate category is proposed for all applicants. The procedure is described in the chapter classification.

Not included in the Regulation are issues which may evoke social debates such as the use of embryos. This issue will be regulated through national legislation. The Regulation also does not cover ATMPs produced in the clinic on a non-routine basis for individual patients. Again, this issue will be regulated through national legislation. The transitional period during which already legally authorised products need to be re-registered for complying with the provision expires for gene therapy and cell therapeutic products on 30 December 2011, for tissue-engineered products on 30 December 2012.

3.2.2 Regulations for other biological medicinal products

For the last three decades the European Community has adopted a number of directives and regulations covering biological medical products. Many of them are consolidated in Directive 2001/83/EC. This Directive is the principal Directive for common medicinal products containing chemical substances as active substance but also for many biological products including blood, plasma and their derivatives. In order to comply with the special requirements of biological products additional legislatives such as Directive 2002/98/EC comprising the standards of quality and safety for collection, testing, processing, storage and distribution of human blood and blood components and Directive 2004/23/EC containing requirements for donation, procurement and testing of human tissues and cells are laid down [20, 21]. Further missing requirements are fulfilled by special guidelines to specific types of biological products, mainly to vaccines [44]. Another main legislative for biological medicinal products is the Regulation (EC) 726/2004, the principal framework for medicinal products regulated via the Centralised Procedure [40]. In this legislative, mainly products manufactured using a biotechnological process are authorised, especially processes such as recombinant DNA technologies, hybridoma and monoclonal antibody technologies and techniques involving controlled expression of genes. Furthermore, certain diseases such as cancer, neurodegenerative disorders, diabetes, AIDS and others are covered by the same Regulation as well. National legislatives concerning biological medicinal products do no longer play an important role. Most of the Directives are already implemented into the national legal framework. Nevertheless, some aspects will still be

regulated nationally as the use of embryonic stem cells.

3.3 Classification of ATMPs

3.3.1 CAT (Committee for Advanced Therapy)

A major point to the Regulation (EC) No. 1394/2007 on advanced therapy medical products is the establishment of the Committee for Advanced Therapy (CAT). The CAT is a scientific, multidisciplinary expert committee which is composed of members nominated by the EU member states, the Committee for Human Medical Products (CHMP) and the European Commission. All members of the CAT are qualified for at least one of the scientific areas relevant to advanced therapy including medical devices, tissue engineering, gene therapy, cell therapy, biotechnology, surgery, pharmacovigilance, risk management and ethics. Such a composition of experts is unique within the EMA. The decision to establish the CAT represents the realisation that there is not sufficient expertise in CHMP for reviewing ATMPs. The exact composition of the CAT includes five members and five alternates of the CHMP, one member and one alternate designated by each EU member state which is not represented by the members and alternates appointed by the CHMP and each two members and two alternates to represent clinicians and patient associations appointed by the European Commission. The members are designated for a term of three years. The CAT meets once a month [6, 41].

The main task of the CAT is to review the quality, safety and efficacy of ATMPs according to standards established by regulatory authorities as well as the evaluation of the marketing authorisation applications by providing a draft opinion. The final adoption will be done by the CHMP as the CAT has an advisory function only. The CAT is an independent, non decision-making body. The CAT is also responsible for scientific recommendations regarding classification and certification procedures, provides scientific expertise and scientific advice for ATMPs and the develops scientific guidelines, reflection papers, regulatory procedures and scientific articles.

3.3.2 Procedure of the Classification

The application for a scientific recommendation on classification of Advanced Therapy Medical Products is optional for the applicant. The purpose of the recommendation is to clarify whether a product meets the criteria of an ATMP already at an early time point in order to give the applicant the possibility to react accordingly. The legal basis of the classification procedure is Article 17 of Regulation (EC) No. 1394/2007 and is to be considered only for products based on genes, cells or tissues. Involved in the procedure are the CAT, the European Commission (EC) and the Innovation Task Force (ITF). Within the CAT, the CAT coordinator appointed by the CAT members is responsible for the preparation of a draft recommendation report and its amendment. The CAT coordinator discusses issues and comments concerning the request with the Committee. The CAT secretariat coordinates the ATMP classification within the Committee and consults the European Commission whereas the Innovation Task Force (ITF) nominates an EMA coordinator which is responsible for proving the validity of the request, the support of the

CAT coordinator and the contact to the applicant. Further responsibilities of the Innovation Task Force (ITF) are supporting background information to the CAT coordinator and discussion of all issues arisen during the entire classification procedure. The EC gives recommendations and comments on all up-coming requests and issues. Other Scientific Committees and Working Parties can be involved in the classification procedure if needed. The classification is performed according to the classification procedure described below [45]. An illustrative overview on the classification procedure is provided in Figure 1.

The procedure starts monthly on the date published on the EMA website and usually takes 40 to 60 days. Before the start of the procedure the applicant sends the request for ATMP classification to the CAT secretariat (day -15). The request should contain information on the product and the status of the development of the product as well as a statement regarding their own position on the classification of their product. A letter of intent shall be dispatched at least 1 month before the request. After receipt of the application a validation period follows during which all information provided by the applicant is checked for completeness.
At day 1 of the procedure the CAT coordinator will be nominated and the time schedule adopted. Within 15 days the CAT coordinator prepares a draft of the scientific recommendation supported by the EMA coordinator and sends the draft to the CAT and the ITF which have 7 days for comments. By day 27 the CAT coordinator amends the draft recommendation, if needed, for discussion at the CAT meeting, decides if further information from the applicant is necessary and sends a draft list of question to the CAT secretariat. For those tasks he will be supported by the EMA. The CAT meeting is held at day 30. During the meeting the draft version of the scientific recommendation as well as the requirement of further information from the applicant are discussed.

If no additional information is required the CAT adopts the draft version at day 30 and the CAT secretariat sends the scientific recommendation to the European Commission. The EC has 10 days for comments. Without comments the applicant receives the final scientific recommendation at day 40 and the summary of the scientific recommendation published on the EMA website will be updated. If comments are received from the EC the final scientific recommendation is adopted by the CAT considering the comments of the EC and dispatched to the applicant at day 60. The summary of the scientific recommendation published on the EMA website will be updated.

If additional information is required the EMA coordinator serving as the contact person for the applicant discusses the open questions arisen during the CAT meeting with the applicant. At that step a meeting with the applicant in order to provide oral explanation might be useful and will be organised by the CAT. Furthermore, a clock stop is possible for 30 days if the applicant agrees. Within this time, discussion and final adoption must be finalised. If the consultation of another Committee or Working Party is required this should be done within the time frame set. If more time is necessary the applicant must agree to an additional clock stop. After the clock stop at day 31, either restarted by submission of additional information by the applicant or by the end of the agreed clock stop, the CAT coordinator updates the draft of the scientific recommendation with support of the EMA coordinator. The CAT adopts the draft recommendation and the CAT secretariat sends

the scientific recommendation to the EC for further comments. The EC has to write their comments on the draft within 10 days. Without further comments the applicant receives the final scientific recommendation on day 41. If further comments are received from the EC, the CAT coordinator prepares the final recommendation considering the comments of the EC which will be adopted by the CAT at day 60. The final recommendation is dispatched to the applicant. The summary of the scientific recommendation published on the EMA website will be updated.

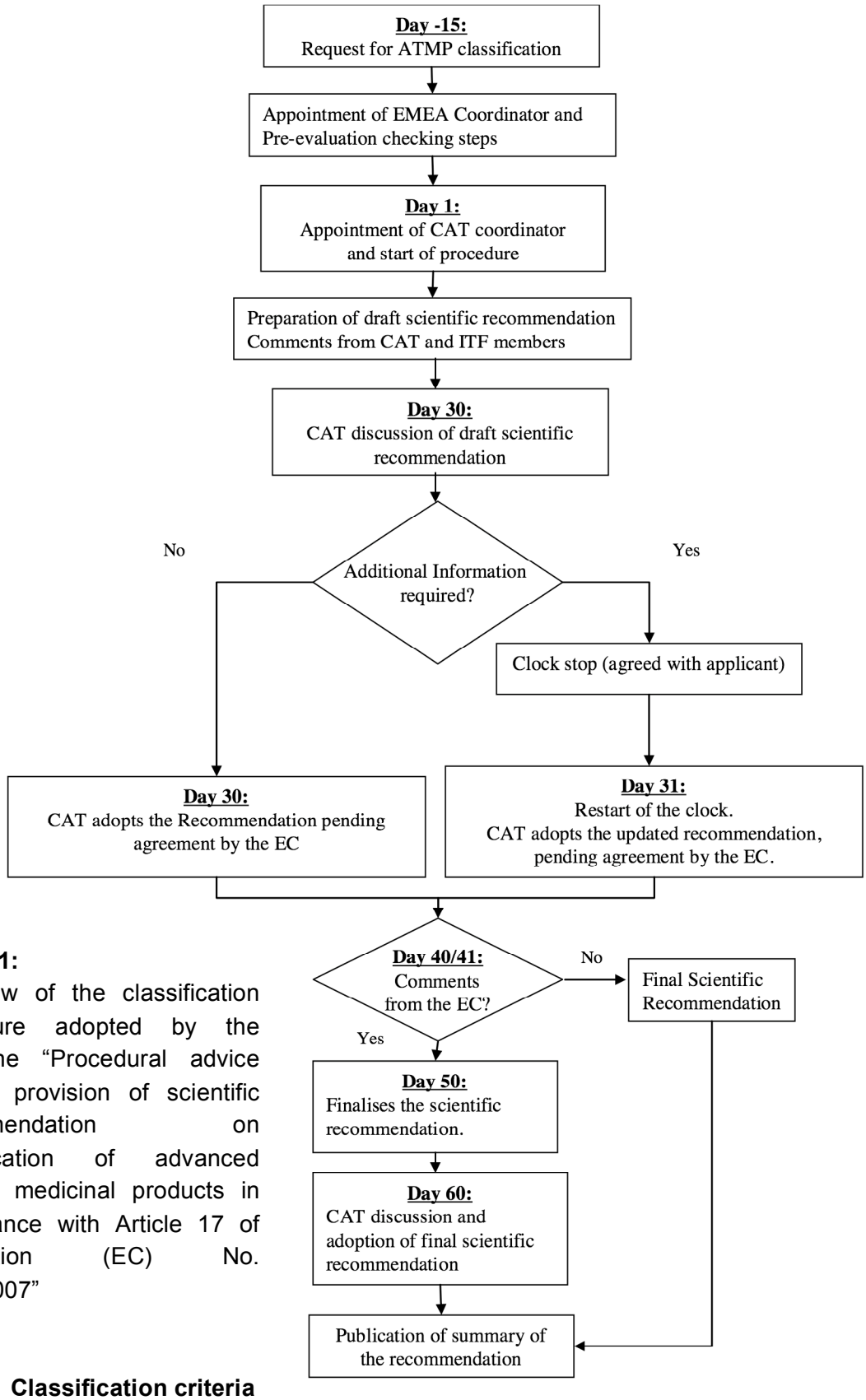

Figure 1:
Overview of the classification procedure adopted by the Guideline "Procedural advice on the provision of scientific recommendation on classification of advanced therapy medicinal products in accordance with Article 17 of Regulation (EC) No. 1394/2007"

3.3.3 Classification criteria

The criteria classifying a medicinal product as an ATMP are mainly laid down in Part IV of Annex I of Directive 2001/83/EC for gene therapy medical product or somatic cell medical products and in Article 2 of the Regulation (EC) 1394/2007 for tissue-engineered products. An overview of the classification criteria is illustrated in the decision tree below (Figure 2).

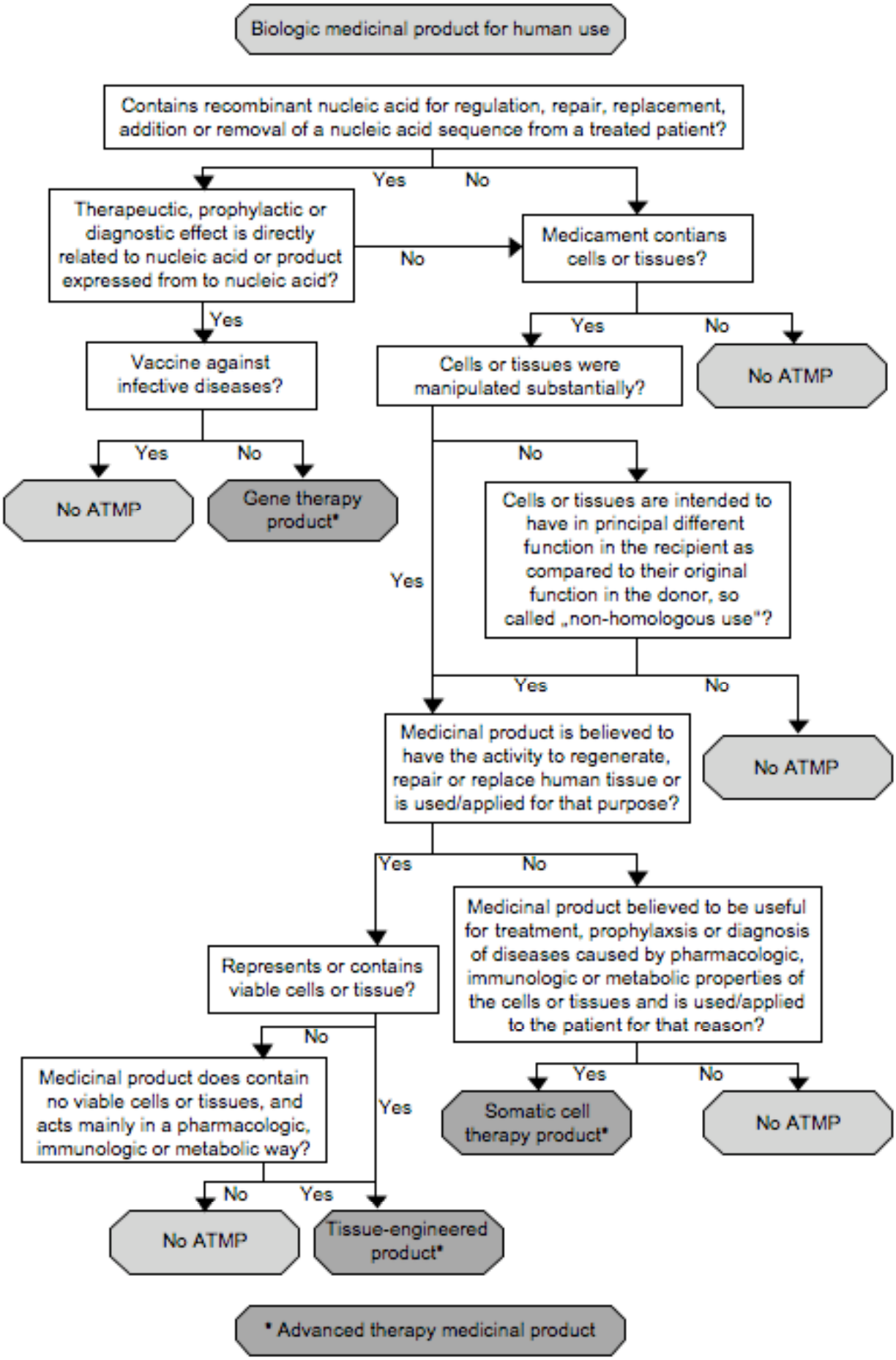

Figure 2: Decision tree (adapted from the website www.pei.de)

Annex I of Directive 2001/83/EC defines the gene therapy product as a product with an active substance *which contains or consists of a recombinant nucleic acid* as well as its specific function *...with a view to regulating, repairing, replacing, adding or deleting a genetic sequence* and the intended use *... used in or administered to human beings*. Furthermore, gene therapy products can be used for therapeutic, prophylactic or diagnostic purpose with effect relating *directly to the recombinant nucleic acid sequence it contains, or to the product of genetic expression of this sequence*. Excluded from the definitions of gene therapy medicinal products are vaccines against infectious diseases.

In the same Annex of this Directive somatic cell products are defined as a product with an active substance which *contains or consists of cells or tissues* but are manipulated in that way *that biological characteristics, physiological functions or structural properties relevant for the intended clinical use have been altered*. Alternatively, cells or tissues remain unchanged but must not work in the identical essential manner in the donor and the recipient. Similar to gene therapy products the cells or tissues are intended for the use in or the administration to humans only for the purpose of *treating, preventing or diagnosing a disease through the pharmacological, immunological or metabolic action of its cells or tissues*.

The definition for the tissue engineered products given in the Regulation (EC) No. 1394/2007, Art. 2 describes them as a product which *contains or consists of engineered cells or tissues*, for the treatment of humans and its specific function for *regenerating, repairing or replacing a human tissue*. The definition does not stipulate the origin of tissues or cells (human, animal or both) or the viability of cells or tissues but cells or tissues which contain or consist exclusively of non-viable cells or tissues *and which do not act principally by pharmacological, immunological or metabolic action* are excluded from the definition. Furthermore, the containment of additional substances, explicitly mentioned cellular products, biomolecules, biomaterials, chemical substances, scaffolds or matrices is admissible in tissue engineered products.

Regarding the term “engineering” a clear definition is given as follows [28]:
Cells or tissues shall be considered “engineered” if they fulfil at least one of the following conditions:
cells or tissues have been subject to substantial manipulation, so that biological characteristics, physiological functions or structural properties relevant for the intended regeneration, repair or replacement are achieved. The manipulations listed in annex I, in particular, shall not be considered as substantial manipulations,
the cells or tissues are not intended to be used for the same essential function or functions in the recipient as in the donor.
The second condition complies completely with the condition for the somatic cells used for cell therapy. Even the first condition is similar to the conditions described for somatic cells in view of changes in the biological characteristics, the physiological functions and/or structural properties. Non-substantial manipulations as stated in Annex I of Regulation (EC) No. 1394/2007 are:

Cutting	Cell separation, concentration or purification
Grinding	Soaking in antibiotic or antimicrobial solutions
Shaping	Filtering
Centrifugation	Freezing
Lyophilization	Cryopreservation
Sterilization	Vitrification

In Directive 2001/83/EC, Annex Part IV, 3 “Specific requirements for all advanced therapy medicinal products” the definitions for gene therapy products are slightly extended, stating that gene therapy products can contain genetically modified micro-organisms or viruses as an active substances as well. A combination with medical devices is admissible. This was previously defined for somatic cell therapy products and tissue engineered products only.

Furthermore, the Regulation contains criteria for a hierarchical classification applicable if a medicinal product fulfils the definition of a gene therapy product, a cell therapy product or a tissue engineered product. It describes two possible cases:
Case 1 applies if the product can be defined as CTMP or as TEP. In this case the medicinal product shall be considered as a tissue engineered product.
Case 2 applies if the product can be defined as a CTMP, TEP or as GTMP. Then the product shall be considered as a gene therapy medicinal product.

3.3.4 Classification criteria for medical devices and combined ATMPs

As mentioned above, ATMPs do also comprise medical devices or active implantable medical devices and together they form the class of combined ATMPs. Medical devices are covered by the principal Medical Device Directive 93/42/EEC, and two associated Directives, Directive 90/385/EEC for active implantable medical devices and Directive 98/79/EEC for *in vitro* diagnostic medical devices [46,47, 48].

The definition for medical devices as outlined in the Directive 93/42/EEC states medical devices as *any instrument, apparatus, applicance, software, materials or other articles, whether used alone or in combination.* Their intended use includes prevention, treatment, monitoring, diagnosing, replacement or modification of the anatomy or of a physiological process. A medical device should never *achieve its principal mode of action in or on the human body by pharmacological, immunological or metabolic means but may be assisted in its function by such means*. If a product acts primary pharmacological, immunological or metabolic in or on the human body, it is classified as medicinal product. The combination of cells or tissues with an incorporated device as an integral part is permitted but only cells and tissues which are derived from human blood, plasma or transplants, or from tissues and cells of animal origin if they are non-viable. Those products can be used separately (Directive 2000/70/EC) [49]. Transplants or tissues human origin or cells other than those mentioned above are explicitly excluded (Art 1 (5f) and Art 4a).

The definition of the combined ATMPs is laid down in Regulation (EC) No. 1394/2007 Art. 2. It states that a medical devices or an active implantable medical devices need to form

an integral part with a cell therapy medicinal product or a TEP. Cells or tissues used in combination with medical devices may be viable or non-viable but in the latter case cells or tissues must act within the human body in a pharmaceutical, immunological or metabolic way in order to consider it as the principal mode of action and to classify them as combined ATMP.

4. Examples

The table below shows a summary of CAT scientific recommendations on ATMP classification.

Product Description	Therapeutic Area	Classification
Layer of autologous corneal epithelium containing stem cells	Corneal lesions	Tissue engineered product – not combined
Lentiviral vector expressing the naturally occurring human anti-angiogenic proteins endostatin and angiostatin	Age-related macular degeneration	Gene therapy medicinal product
Allogeneic human aortic endothelial cells cultured in a porcine gelatin matrix	Vascular injury	Somatic cell therapy medicinal product – not combined
Non-integrative vector including a gene coding for an anti-HSV-1 Meganuclease for the ex-vivo transduction of human cornea	Prevention of infectious diseases in cornea grafted patients	Gene therapy medicinal product
Adult skeletal muscle derived cells	Female stress urinary incontinence	Tissue engineered product – not combined
Allogeneic human placenta-derived, culture-expanded, mesenchymal-like cell population	Chronic inflammatory diseases such as Crohn's disease, multiple sclerosis, rheumatoid arthritis and for ischemic stroke	Somatic cell therapy product
Autologous bone marrow-derived progenitor cells	patients with failed left ventricular recovery despite successful reperfusion therapy post acute myocardial infarction, chronic ischemic heart disease, peripheral vascular diseases and Buerger's disease	Tissue engineered product
Allogeneic mesenchymal precursor	Cardiovascular disease	Tissue engineered

cells		product
Umbilical cord blood cells expanded ex vivo using allogeneic mesenchymal precursor cells	Haematology-oncology therapeutic area	Tissue engineered product
Frozen, cultured allogeneic keratinocytes on a silicone dressing material	Acute burn wounds	Tissue engineered product – not combined
Autologous human keratinocytes	Superficial, partial and full thickness burns	Tissue engineered product – not combined
Hollow fiber cartridges populated with the C3A cells to be used with ancillary support equipment	Acute on Chronic Hepatitis	Somatic cell therapy medicinal product – combined
Autologous *ex-vivo* pulsed dendritic cells	Ovarian cancer	Somatic cell therapy medicinal product
Mixture of porcine beta cell and their accompanying endocrine cell populations embedded in an alginate matrix	Endocrinology: Diabetes	Somatic cell therapy medicinal product – not combined
Genetically modified Lactococcus lactis secreting human interleukin-10	Inflammatory bowel disease	Gene Therapy Medicinal Product
DNA plasmid encoding for the human fibroblast growth factor type 1 (FGF 1)	Critical limb ischemia (CLI)	Gene Therapy Medicinal Product
Allogeneic T cells encoding an exogenous TK gene	Adjunct treatment in haematopoietic stem cell transplantation	Somatic cell therapy medicinal product
Allogeneic human dermal fibroblasts	Dystrophic epidermolysis bullosa	Tissue Engineered Product
Lentiviral vector expressing the truncated form of human tyrosine hydroxylase (TH), human aromatic L-amino-acid decarboxylase (AADC), human GTP-cyclohydrolase 1 (CH1)	Parkinson's disease	Gene Therapy Medicinal Product
Autologous osteoprogenitor cells, isolated from bone marrow and expanded in vitro, incorporated, as an integral part, with 3D biodegradable scaffold	Repairing, regenerating and replacing of bone defects in Odonto Stomatology and Maxillo-Facial surgery	Tissue engineered product - combined
Salmonella typhi strain genetically modified to secrete a fusion protein of the prostate specific antigen (PSA) and a protein leading to an increased antigenicity	Oncology: Prostate cancer	Gene Therapy Medicinal Product

Product consisting of naturally occurring antigen-specific CD8+ donor lymphocytes isolated with Streptamers	Infectious diseases	Not an advanced therapy medicinal product
Mesenchymal stem cell-derived microvesicles (containing receptors, proteins, lipids, mRNA and microRNA).	Renal diseases	Not an advanced therapy medicinal product
Lentiviral vector expressing the human MYO7A gene.	Retinitis pigmentosa	Gene therapy medicinal product
Lentiviral vector expressing the ABCA4 gene, packaged into infectious VS virus envelope.	Retinal disorders	Gene therapy medicinal product
Buffy coat of centrifuged autologous bone marrow containing hematopoietic and mesenchymal stem cells.	Incomplete and complete chronic traumatic spinal cord injury	Advanced therapy medicinal product
Autologous cultured chondrocytes integrated in a scaffold.	Repair of symptomatic cartilage defects in joints such as the knee and ankle	Tissue engineered medicinal product - combined
Adenovirus encoding vascular endothelial growth factor C (VEGF-C).	Secondary lymphoedema associated with treatment of breast cancer	Gene therapy medicinal product
Autologous cell therapy product.	Crohn's disease	Somatic cell therapy medicinal product
Allogeneic natural killer cells activated with a lysate from a cell line which is established from a patient with acute monoblastic leukaemia.	Acute myeloid leukaemia	Somatic cell therapy medicinal product
Allogeneic cultured corneal epithelial cell sheet in amniotic membrane scaffold.	Ocular diseases	Tissue engineered product
Adeno-Associated Virus (AAV) vector containing a gene coding for N-sulfoglucosamine sulfohydrolase	Congenital, hereditary, or neonatal diseases and abnormalities	Gene therapy medicinal product
Fresh and freeze-dried thrombocytes isolated from autologous or allogeneic blood	Wound healing in orthopedic and dental surgery	Not an advanced therapy medicinal product
Autologous tolerogenic dendritic cells derived from peripheral blood monocytes	Rheumatoid arthritis	Somatic cell therapy medicinal product. Not combined
A combination of lysates of tumor cells (autologous and allogenic) and	Oncology: Glioblastoma	Somatic cell therapy medicinal

living cells of a glioblastoma cell line		product
Haploidentical donor T lymphocytes genetically modified to express HSV-Tk gene	Oncology: adjunctive treatment post bone marrow transplantation in patients with high risk acute leukemia	Somatic cell therapy medicinal product
Suspension of expanded autologous skeletal muscle derived cells (myoblasts)	Urology/Gynecology: Regeneration of the external urethral sphincter muscle (rhabdosphincter) in stress urinary incontinence patients	Tissue engineered product. Not combined
Immunotherapeutic medicinal product composed of autologous tumour cells	Oncology: Colon cancer	Somatic cell therapy medicinal product.
Advanced therapy medicinal product containing substantially modified cytotoxic T-cells of human origin	Oncology: Ovarian cancer	Somatic cell therapy medicinal product.
Advanced Therapy Medicinal Product composed of substantially modified human allogeneic fibroblasts and keratinocytes administered in conjunction with fibrin as structural component	Dermatology: Chronic venous leg ulcers	Somatic cell therapy medicinal product.

Table modified from www.ema.europa.eu

Example 1:

Layer of autologous corneal epithelium containing stem cells

Therapeutic use	Treatment of extended corneal lesions
Classification	ATMP – Tissue engineered product – not combined
Source	Autologous cells
Active substance	Autologous corneal epithelium containing stem cells
Mode of action	Regeneration (Forming of corneal tissue)
Medical device	No
Engineered	Yes, epithelium has been manipulated to contain stem cells

Example 1 deals with a tissue engineered product. Its active substance is a layer of corneal epithelium tissue derived from the same person for which it will be used. It is manufactured for regeneration of the patient tissue. The corneal epithelium, the anterior of the five layers of the corona, is a thin epithelial tissue layer usually kept humid by tear liquid. Lesion of the cornea disrupts the smoothness of the air-tear film interface which leads to a reduction of the visual acuity.

The classification criteria for a tissue engineered product include all kind of tissues independent of its source and thus accept the use of autologous cells. The intended purpose of the regeneration of corneal tissue fulfils the requirement of TEPs regarding a therapeutic use including regenerating, repairing or replacing a human tissue. Responsible for this action of the tissue are the stem cells which are included in the tissue as a result of a not further described manipulation. Stem cells are cells able to differentiate into specialised cell types and therefore are suitable as a repair or regeneration system. There are two broad types of stem cells, embryonic stem cells and adult stem cells. Embryonic stem cells are isolated from blastocytes, whereas adult stem cells are recovered from various tissues. The use of embryonic stem cells is not covered in the Regulation of ATMPs. In the example above, adult stem cells are used. As also the last criterion for tissue engineered products, the term “engineered”, has to be fulfilled, the tissues or cells have to be either substantially manipulated for their intended use or have to be used in a complete different function in the recipient as compared to their function in the donor. The manipulation of the tissue with stem cells complies with the requirement “engineered” whereas the function of the tissue is still the same as before. As medical devices are not involved the product can be classified as a non-combined tissue engineered product.

Example 2:

Salmonella typhii strain genetically modified to secrete a fusion protein consisting of the prostate specific antigen (PSA) and a protein leading to an increased antigenicity

Therapeutic use	Treatment of prostate cancer
Classification	ATMP – gene therapy product
Source	Salmonella typhii strain, genetically modified
Active substance	Gene coding for a fusion protein of the prostate specific antigen (PSA) and a protein which is not closer defined
Mode of action	Increase of the antigenicity
Medical device	No
Engineered	Genetic modification of a Salmonella typhii strain
Vaccine against infectious disease	No

Example 2 is classified as a gene therapy product. The active substance is a gene coding for a protein of the prostate specific antigen (PSA) fused to a protein which is not closer defined. PSA is considered as a marker protein in prostate cancer. Although already present in serum of healthy people, its serum level increases in most patient with prostate cancer [51].

The gene is expressed in a well-known bacteria strain, Salmonella typhii. The modified bacteria cells in this product can be defined as “genetically modified organisms” as stated in the definition of Directive 2001/18/EC, Article 2 and Council Directive 90/220/EEC, Annex IA, Part 1 and 2 because the genetic material of the bacterial cells has not been changed by naturally occurring mating or recombination processes. Gene therapy products, either the nucleic acid sequence itself or the genetic expression product (protein), shall be used for therapeutic, prophylactic or diagnostic reasons and not as a vaccine against infectious diseases. The purpose of this product is an increase of the antigenicity of the PSA-containing prostate cancer cells by stimulating an immune reaction of the patient towards PSA. Thus, all classification criteria for a gene therapy product are fulfilled.

Example 3:

Fresh and freeze–dried thrombocytes isolated from autologous or allogeneic blood

Therapeutic use	Wound healing in orthopedic and dental surgery
Classification	No ATMP
Source	Thrombocytes isolated from autologous or allogeneic blood
Active substance	Fresh and freeze–dried thrombocytes
Mode of action	Regeneration (Wound healing)
Medical device	No
Engineered	No

This product is an example of a product which is not classified as an ATMP. The active substance is dried thrombocytes of autologous or allogeneic origin. In terms of the source of the thrombocytes used the criteria for somatic cell therapy products are fulfilled. The thrombocytes are involved in the wound healing of tissue and thus, comply for the classification criterion of tissue engineered products regarding the intended use of regeneration, repair or replacement but not the criterion for somatic cell therapy medicinal products which shall be used for treating, preventing or diagnosing a disease. Even if this example does not fulfil the exclusion criterion of the product as an ATMP it depicts the problem of the classification of cells which are intended for the use of regeneration or repair. Furthermore, according to the classification criteria of somatic cell therapy products, the cells shall be either altered in their biologic characteristics, physiological function or structural properties or, if unaltered, work in a different way in the donor as compared to the recipient. In this case the active substance is used in the identical way of their usual function and is unaltered. Freezing of the cells is not regarded as “substantial manipulation” as outlined in Directive 1394/2007, Annex I. Thus, the criteria for the classification as an ATMP are not met.

Example 4:

Product consisting of naturally occurring antigen-specific CD8+ donor lymphocytes isolated with Streptamers

Therapeutic use	Treatment of infectious diseases
Company	STAGE Cell Therapeutics GmbH, Göttingen, Germany
Classification	No ATMP
Source	Allogeneic or autologous cells
Active substance	Naturally occurring antigen-specific CD8+ donor lymphocytes
Mode of action	Lymphocyte-mediated destruction of micro-organisms
Medical device	No
Engineered	No

Example 4 is a product containing antigen-specific CD8+ lymphocytes as an active substance. Those cells are used unaltered ("naturally occurred") and are of allogeneic or autologous origin. CD8+ lymphocytes are cells which express the CD8+ protein on their surface and are involved in the cell-mediated immunity. In this medicinal product these cells are intended to be used against infectious diseases meaning that they act principally in the identical manner in the donor as well as the recipient. As mentioned in the last example if the product should be classified as an ATMP the cells must be manipulated substantially by a method which is not provided in the list in Regulation (EC) No. 1394/2007 Annex I. In this case the active substances, the lymphocytes, are isolated by a method called Streptamers®. This method represents a specific purification process for the cells and does not manipulate cells itselves [52]. Thus, also this example does not meet the criteria for the ATMP classification.

Example 5:

Autologous cultured chondrocytes integrated in a scaffold

Therapeutic use	Repair of symptomatic cartilage defects in joints such as knee and ankle
Company	TiGenix N.V., Leuven, Belgium
Classification	ATMP – Tissue engineered product – combined
Source	Autologous cells
Active substance	Autologous cultured chondrocytes integrated in a scaffold
Mode of action	Repair of symptomatic cartilage defects in joints such as knee and ankle
Medical device	Yes (scaffold)
Engineered	No

The product of example 5 is classified as a combined tissue engineered product and uses autologous chondrocytes as active substance. Chondrocytes are cartilage forming cells and in this product are intended for the repair of symptomatic cartilage defects in joints such as knee and ankle. The chondrocytes are harvested from a cartilage biopsy and expanded *ex vivo* prior to their medicinal use [31, 53].

The cells in this product are intended to be used for the same essential function in the donor and the recipient. However, culturing the cells changes the cells and partially leads to their dedifferentiation [30]. Even if that effect is not intended and the cells have to be controlled by marker analysis, these cells can be considered as manipulated. Furthermore, the chondrocytes are integrated in a scaffold forming an integral part of it. According to the classification criteria the combination of cells or tissue with medical devices or other substances is permitted. The purpose of this product is the repair of body tissue within the patient which complies with the criteria for tissue engineered products. Thus, this product can be classified as combined tissue engineered product.

Example 6:

Mixture of porcine beta cells and their accompanying endocrine cell populations embedded in an alginate matrix

Therapeutic use	Treatment of diabetes
Classification	ATMP – Somatic cell therapy product - non-combined
Source	Xenogeneic cells
Active substance	Mixture of porcine beta cells and their accompanying endocrine cell populations
Mode of action	Replacement of non-functional cells
Medical device	No
Engineered	Cells are embedded in an alginate matrix

In example 6 a mixture of xenogeneic cells, porcine pancreatic beta cells and their accompanying endocrine cell populations, are the active substance of this ATMP product. It is classified as a somatic cell therapy product. Beta cells are a cell type in the pancreas responsible for the production and release of the hormone insulin controlling the level of glucose in the blood.

The essential function of the cells intended for the use in the patient are identical to that of the donor and replaces the original cells of the patient which all meet the criteria of the definition. The cell mixture is embedded in an alginate matrix which can be used according to the classification criteria and counts as substantial manipulation according to Annex I of Regulation (EC) No. 1394/2007. The matrix used consists of alginate, a polysaccharide, formed by brown algae. That means that this matrix is of biological origin and therefore, does not belong to the group of medical device (see Definition of the

Medical Device Directive 93/42/EEC, Art. 1 (2a): ... *medical devices means any instrument, apparatus, applicance, software, materials or other articles, whether used alone or in combination.*) Thus, this ATMP is a non-combined somatic cell therapy product.

Example 7:

Hollow fibre cartridges populated with C3A cells to be used with ancillary support equipment

Therapeutic use	Treatment of Acute on Chronic Hepatitis
Company	Vital Therapies, Inc,. San Diego, US
Classification	ATMP – Somatic cell therapy product – combined
Source	Source unclear
Active substance	Hollow fibre cartridges populated with C3A cells
Mode of action	Repair
Medical device	Yes (Hollow fibre cartridges; and further support equipment)
engineered	No

Example 7 is a product consisting of hollow fibre cartridges which contain C3A cells. C3A cells are an immortalised human hepatocyte cell line which still performs most of the metabolic functions of normal liver cells. The cells grow in the hollow fibre cartridges. The principle of this biological medicinal product is the treatment of hepatitis by a system which is similar to the dialysis technique. The cartridges are part of an extra corporeal blood pumping system and separate plasma from the cellular components of the blood. The plasma circulates through the cartridges and reaches the cells feeding them with nutrients and oxygen. On the other hand, the cells remove toxins from the plasma and release liver cell metabolites into the plasma. After passage of the cartridges the cellular component and the plasma are recombined and returned to the patient [54].

The combination of a medical device with a biological medicinal products such as cells has to be examined carefully, as such a product might be categorised as a medical device, a combined ATMP or even a conventional biological medicinal product. The biological medicinal product component in this case is the C3A cell line. Cells which are propagated in vitro usually change their physiological properties during culturing. Thus, the cell line can be considered as substantially manipulated and be classified as ATMP. If a biological medicinal product is classified as a combined ATMP, the ATMP component must act primary upon the human body. The condition of a primary action is the ability of the cells or tissues to act pharmacological, immunological or metabolic according to Regulation (EC) No. 1394/2007 which is already fulfilled if the cells or tissues are viable. In this example the cells are viable and therefore, the product mentioned can be considered as combined somatic cell therapy product.

Example 8:

Non-integrative vector including a gene coding for an anti-HSV-1 mega nuclease for the *ex vivo* transduction of human cornea

Therapeutic use	Prevention of infectious diseases transmitted by cornea transplants
Company	Cellectis, Romainville, France
Classification	ATMP – gene therapy product
Source	Non-integrative vector
Active substance	Gene encoding for an anti-HSV-1 Mega nuclease
Mode of action	Providing a gene coding for an enzyme which destroys viruses in cornea transplants
Medical device	No
Engineered	No
Vaccine against infectious disease	No

The product in example 8 uses a nucleic acid encoding for an anti-HSV-1 (anti-Herpes simplex virus-1) mega nuclease as active substance for the prevention of an infectious disease in cornea grafted patients.
The anti-HSV-1 mega nuclease is a HSV-1 sequence-specific endonuclease which binds to and cuts the viral HSV-1 DNA at a single site leading to an *in vitro* destruction of the virus in cornea transplants. This prevents infection of a patient with HSV-1 contaminated cornea transplants [55]. The gene of the anti-HSV-1 mega nuclease is provided within a non-integrative, not further defined vector. The use of non-integrative plasmids as a carrier for a therapeutic gene complies with the definition for “Gene therapy medicinal products” in annex I, part IV of Directive 2001/82/EC. Furthermore, a gene therapy product must fulfil the criteria for the purpose used. This includes therapeutic, prophylactic or diagnostic reasons. Additionally, it does not have to work against infectious diseases. This ATMP is created for the elimination of HSV-1 in cornea transplants prior to their transplantation into patients. Thus, all criteria of a gene therapy product are fulfilled.

5. Consequences of the new framework on the demarcation

The classification criteria for ATMPs as laid down in the Regulation (EC) No. 1394/2007 demarcate ATMPs from conventional biological products. This demarcation causes further consequences on regulatory requirements. In the following some aspects are described in more detail.

5.1 Regulatory requirements of marketing authorisation applications

The regulatory requirements of marketing authorisation applications for ATMPs regarding data concerning quality, non-clinical and clinical data are outlined in Regulation (EC) No. 1394/2007 as well as in Annex I, part IV of Directive 2001/83/EC, amended [28, 18].

5.1.1 Dossier requirements: Quality

The quality part of the marketing authorisation documentation contains information on the active substance of medicinal products, data on the manufacturing processes, the analytical and validation methods as well as information on excipients, reference standards used and the stability of the product.

The special dossier requirements concerning quality data for ATMPs described in Part IV of Annex I of Directive 2001/83/EC are almost limited to information on starting materials of the products. This includes detailed information on processes used and controls on the starting material such as information on viruses and plasmids used including nucleic acid sequence determination of the material, the attenuation of virulence and the tropism for specific tissues and cell types. Similar information is required for the biological substance in conventional biological medicinal products as described in Part I of Annex I in the same Directive. Moreover, the documentation for ATMPs focuses also on risk factor information and risk evaluation. Such an evaluation is not explicitly required for conventional biological products. An exception regarding documentation requirements represent biological products such as vaccines and plasma-derived products. For these products a special documentation, so-called stand-alone documentation, is suggested: for vaccines the VAMF (Vaccine Master File) and for plasma derived products the PMF (Plasma Master file). These documentations are quite detailed containing, amongst others, information on cell banks, characteristics of infectious agents for bacterial and viral vaccines and data on stability of the attenuation characteristics for live vaccines. For the characterisation and examination of the ATMPs as well as for other biological products a large amount of analytical methods are required. Details are not mentioned in the Directive but recommended in several specific guidelines. These guidelines are usually applied for conventional biologic products as well as for ATMPs.

5.1.2 Dossier requirements: Non-clinical data

The dossier requirements regarding the non-clinical study reports are described in module 4 of the authorisation documentation. It should contain reports concerning pharmacology, pharmacokinetics, toxicology and other toxicity studies. Toxicological data contain among others data on genotoxicity, carcinogenicity and reproductive toxicity. Pharmacological studies contain data on efficacy and safety of a drug substance and investigate potential undesirable pharmacodynamic effects of a substance on physiological functions. Pharmacokinetic studies describe the effect of the body on the drug substance and its metabolites through a time-dependent concentration profile of the substance and comprise data on absorption, metabolism, distribution and excretion.

Due to the diversity of their nature and their dependence on the environment, advanced therapy medicinal products require quite specific pharmacological and toxicological data. In order to consider the specificity of the medicinal products non-clinical testing needs to be modified. Requirements and some considerations are mentioned in Annex I of Directive 2001/83/EC. Standard toxicological programmes in general are inappropriate as the medicinal products are not able to cross the nuclear membrane and interact with DNA [4]. In the case that a medicinal product has proliferative activity, for example engineered tissue products, alternative approaches such as cellular proliferation assays are needed to get information on the mitotic characteristics of the medicinal product on normal as well as on cancer cells [18]. Similarly, the proof of conventional pharmacokinetic parameters such as absorption, metabolism or excretion might be less informative in the case of cell-based therapeutic products. Parameters such as viability, longevity, distribution, growth, differentiation and migration are more appropriate because cells or tissues are usually implanted to remain at the new site for a long time [4]. On the contrary, for gene therapeutic products biodistribution studies such as persistence, clearance, mobilisation and the risk of germline transmission should be analysed. Further critical points are the risks of release of viral particles (viral shedding) and of transmission to healthy individuals which should be evaluated in the examination as well. A proof of concept should be demonstrated for all products. This means for example for gene therapy products that it should be demonstrated that the nucleic acid sequence reaches its intended target and provides its intended function [18]. Cell therapy products should be tested for the desired interaction with the surrounding tissue in order to enable a potential physiological effect. Questions to the effective dose, frequency of dosing and the duration of function should be answered as well. For all immunological products requiring repeated administration it is suggested to test for unwanted generation of antibodies. In all cases the choice of suitable models and animal species is one of the most challenging parts. The biological product may be of limited activity or may not show any activity in the animals or it may provoke immunogenicity issues [4]. Furthermore, studies on the reproductive function, embryonal/foetal and pernatal toxicity, the mutagenic and carcinogenic potential should always be examined [18]. For combined ATMP, a proof of suitability, safety and biocompatibility of all structural components/additional substances should be demonstrated as well [18].

There are no special requirements for conventional biological products in the Directive 2001/83/EC. Most of the mechanisms described for ATMPs apply for other biological products as well. However, some guidelines include considerations regarding non-clinical aspects of various biological products such as *Note for Guidance on the Quality, Preclinical and Clinical Aspects of Gene Transfer Medicinal Products* or *Note for Guidance on Human cell-based medicinal products* or *Note for Guidance on Preclinical Pharmaceutical and Toxicological Testing of Vaccines* [56, 25, 57]. Those guidances can also be applied for ATMPs. Not applicable for ATMPs is the ICH Guideline *ICH Topic S6 Preclinical Safety Evaluation of Biotechnology-Derived* Pharmaceuticals [58]. This guidance represents a basic framework for the pre-clinical safety evaluation of biotechnological pharmaceuticals.

5.1.3 Dossier requirements: Clinical data

The dossier requirements regarding the clinical study reports are described in module 5 of the marketing authorisation documentation. This part should contain clinical study reports on biopharmaceutical studies, pharmacokinetic studies, pharmacodynamic studies, reports about efficacy and safety studies and to post-marketing experiences. Furthermore, it should include an evaluation of the safety of the product and a summary of clinical observations.

Any peculiarities in view of the clinical documentation for conventional biological products are not mentioned in the Directive 2001/83/EC except that all materials of animal or human origin have to be free of any infectious agents. In Annex I of the same Directive specific requirements for ATMPs are listed which should be addressed in the clinical studies. Similar to non-clinical studies, clinical studies need to be adapted with regard to the active substance and information obtained from the non-clinical studies and have to be justified on a case-by-case basis. Specialised guidances directed to certain biological products are applicable for conventional biological medicinal products as well as for ATMPs. Examples are the above mentioned guidelines *Note for Guidance on the Quality, Preclinical and Clinical Aspects of Gene Transfer Medicinal Products* or *Note for Guidance on Human cell-based medicinal products* for medicinal products based on genes and cells [56, 25].

5.2 Requirements on medical devices

Medical devices may be used in the form of a combination product with ATMPs or with other biological products.
The medical device part needs to conform to the requirements of the medical device Council Directive 93/42/EEC and in case of an active implantable medical device needs to conform to the Council Directive 90/385/EEC [46, 47]. This includes the evidence for conformity of the medical device. Furthermore, medical devices containing tissue of animal origin must be examined in order to exclude the risk of TSE/BSE infections to conform with the requirements of Directive 2003/32/EC for medical devices manufactured utilising tissues of animal origin [59]. These requirements apply to all biological components in medical devices.

5.3 Requirements on SPC/Labelling and package leaflets

5.3.1 Summary of Product Characteristics (SmPC)

The SmPC of conventional biological products follows the information for SmPC provided in Article 11 in Directive 2001/83/EC. It does not contain any additional requirements to biological products as compared to classical chemical medicinal products. However, the CHMP or former CPMP (Committee for Proprietary Medicinal Products) adopted a few guidelines on product information to adapt the SmPC in the Directive regarding special aspects relevant for certain biological products such as the *Pharmaceutical Aspects of the Product Information for Human Vaccines* published in November 2003 or the *Warning on*

transmissible agents in summary of product characteristics (SPCs) and package leaflets for plasma-derived medicinal products published in October 2003 [60, 61]. Others are still in preparation. As requested and adopted in Annex II of Regulation (EC) No 1394/2007 for Advanced Therapy Medical Products the information for SmPC contains updates and/or additional issues which have to be considered. The composition and the posology need to be described in more detail as well as special warnings and precautions, also for disposal of a used medicinal product. Name and pharmaceutical form follow other rules than those obligated for chemical medicinal products. The information on the name, pharmaceutical form and composition is in line with the requirements on vaccines described in the guideline mentioned.

5.3.2 Labelling of outer/immediate packaging

Similar to the SmPC, the information regarding the labelling requirements of the outer/immediate packaging of conventional biological products listed in Article 54 in Directive 2001/83/EC corresponds to those of the chemical medicinal products. Special aspects for biological products are not considered but are partly added by scientific guidelines adopted by the CHMP [60]. In Annex III of Regulation (EC) No 1394/2007 labelling requirements of the outer/immediate packaging for ATMPs are described. The changes in the requirements compared to conventional biological medicinal products are similar to the changes of the requirements for SmPCs: information on the name, pharmaceutical from and composition, a complete list of excipients including preservative systems, a labelling for products which are for autologous use only and donation and product codes for traceability.

5.3.3 Package leaflet

The instruction for the package leaflet for conventional biological medicinal products corresponds to the instruction of the chemical medicinal products. They are listed in Article 55 in Directive 2001/83/EC. Similar to the SmPC and the packaging labelling special aspects for biological products are not considered in the Directive but are partly added by scientific guidelines adopted by the CHMP. The information on the package leaflet for ATMPs is described in Annex IV of Regulation (EC) No 1394/2007. Again, changes in the requirements compared to conventional biological medicinal products are similar to the changes of the requirements for SmPCs. Exceptions are biological medicinal products such as vaccines. Corresponding guidelines to this group of biological medicinal product are adapted to the requirements of the package leaflet regarding name, dosage form and composition [60].

5.4 Marketing authorisation procedures

ATMPs are regulated according to the Centralised Procedure. Also most conventional biological medicinal products are regulated in the same way. In particular, these are products which are explicitly mentioned in the Annex of the Regulation 726/2004/EC such

as products developed by the use of recombinant DNA technology, products employing controlled expression of genes coding for biologically active proteins in prokaryotes or eukaryotes including mammalian cells, products prepared by hybridoma or monoclonal antibody methods or products for the treatment of special diseases such as for cancer and viral diseases. Thus, many vaccines directed against viral infectious diseases are regulated by the Centralised Procedure. In contrast, vaccines against bacterial infectious diseases may be regulated by a national or decentralised procedure if they are not produced by recombinant DNA technologies. Most molecular biology techniques fall in the competence of the Community whereas most of cell-based products which are not intended for the use in one of the disease mentioned in the Annex of the mentioned regulation are not authorised by the EMA. Until recently, tissue-based products had no clear defined regulatory basis and were regulated differently within the various member states of the EU.

5.5 Safety requirements

5.5.1 Risk management system

According to Directive 2010/84/EC risk management systems are *a set of pharmacovigilance activities and interventions designed to identify, characterise, prevent or minimise risks relating to a medicinal product, including the assessment of the effectiveness of those activities and interventions* [62]. This directive requires that the marketing authorisation holder (MAH) should plan pharmacovigilance studies for each medicinal product in the context of a risk management system considering that a risk management system is obligatory for all products once this Directive is transposed into national law. Currently, a risk management system is only required if appropriate. The wording “appropriate” is not further connected to any special group of medicinal products. For ATMPs a risk management system is obligatory. A safety and efficacy follow-up system has to be integrated in the marketing authorisation application as a part of a risk management system, for example details such as long-term safety issues. Risks regarding medical devices must be taken in consideration as well. An example for this is the *in vivo* durability of the associated medical device part. A guideline illustrating the requirements for a RMS has already been adopted [63].

5.5.2 Environmental risk assessment

Environmental risk assessment is required for all medicinal products identifying possible risks caused by the use or disposal of the medicinal product. Especially for medicinal products containing or consisting of genetically modified organisms (GMO) additional information are requested. Such information are methods for detection and identification of the GMO, information on the GMO itself, a post-market monitoring plan and other special particulars relevant to the GMO and the product [18]. For ATMPs an appropriate risk management strategy is needed for all types of medicinal products even if they do not contain genetically modified organisms [64].

5.5.3 Risk analysis

A risk analysis for the application of marketing authorisations is required for ATMPs due to the specific nature of the ATMPs [28]. Such analyses are not requested for other biological products. The risk analysis should cover the entire product development and include all risk factors which might be envisioned. Those are highly specific and depend on the biological characteristics of the active substance. A draft of a concept paper has been published which outlines risks for each ATMP class. Those risk factors should be considered in the risk-based approach [28].

5.6 Post-authorisation requirements

5.6.1 Traceability

Traceability is a requirement stipulated in Directive 2002/98/EC for human blood and blood components and in Directive 2004/23/EC applied for human tissues and cells including haematopoietic peripheral blood, umbilical-cord blood, bone marrow stem cells, reproductive cells such as eggs and sperm, foetal tissues and cells and adult as well as embryonic stem cells. Organs, tissues and animal cells as well as other conventional biological products are excluded. According to the Regulation (EC) No. 1394/2007 traceability is a requirement for all types of ATMPs, even for gene therapy products.

5.6.2 Periodic safety update reports (PSUR) / additoninal monitoring /safety and efficiency follow up / post-authorisation safety studies (PASS)

Other post-authorisation requirements than traceability might be considered. Post-authorisation studies regarding safety and efficacy may be imposed by the authority in order to collect more data. This possible requirement can be applied to all medicinal products.

A periodic safety update report (PSUR) is an obligation for all authorised medicinal products [18]. If a risk management is required for a product it has to be included in the PSUR.

The safety and efficacy follow up is a requirement for ATMPs only and is a part of the risk management system. For details please see the description above.

An additional monitoring for ATMPs has to be implemented as a post-authorisation requirement with regard to safety and efficacy. This requirement is laid down in the new Regulation (EC) No. 1235/2010 for pharmacovigilance which will get in force in July 2012. According to this new Directive 1235/2010 additional monitoring will be required for biological products in future, too. Currently, such a post-authorisation monitoring is not needed for biological medicinal products [65].

5.6.3 Variations

As ATMPs are regulated by a centralised procedure, variations to an ATMP follow the variation procedure laid down in the Commission Regulation (EC) No. 1234/2008 [66]. Variations on other biological products authorised by a centralised or decentralised procedure are assessed based on the same regulation. Still an exemption to this are biological products which are authorised nationally. Depending on the member state in which the medicinal product is registered either the new Regulation will be applied or the former variation regulation, the Commission Regulation (EC) No. 1084/2003 or an independent national regulation, for example the German Pharmacopeia (AMG) [67]. For the same reason, some products containing tissues and which in a few countries are still regulated as an medical device, those products will be regulated according to the Council Directive 93/42/EEC for medical devices [46]. A variation system for medical devices is not available.

5.6.4 Scientific requirements

Special guidances for biological medicinal products such as for vaccines, human cell-based medicinal products or gene transfer medicinal products are adopted by the CHMP. These guidelines overcome the lack of regulations for biological products. Most of the guidelines also cover ATMPs. There are only very few guidelines which are limited solely to ATMPs. Those guidances are the CAT/CHMP statement on Creutzfeldt-Jacob disease and a concept paper on the development of a guideline on the risk-based approach.

5.6.5 Fees / Incentives

The following incentives in form of a reduced fee for the authorisation procedure of advanced therapy medicinal products are offered: a 90% reduction of the fee for scientific advice if the company belongs to the group of small and medium-sized enterprises (SME), 65% fee reduction for other types of companies. For the application of the marketing authorisation a 50% reduced fee is offered to SMEs and hospitals as well as for the first year of marketing authorisation. Further incentives are a scientific recommendation on the classification of ATMPs for all applicants and an advice on the certification of quality and non-clinical data for SMEs.

5.7 Requirements on GCP / GMP and GLP

5.7.1 GCP

The requirements on Good Clinical Practice (GCP) for all medicinal products are determined in the Commission Directive 2005/28/EC amending Directive 2001/20/EC laying down principles and guidelines for good clinical practice [42]. More details are offered by the consolidated ICH guideline to Good Clinical Practice E6 which is based on Directive 75/318/EEC [68]. These legislations form the basis for Good Clinical Practice. In

the Regulation (EC) No. 1394/2007 an adoption of the requirements of the GCP for ATMPs is requested. The European Commission has published a detailed guideline on GCP specific for advanced therapy medicinal products in December 2009. A final adoption will be enforced once more experience regarding the specificities of ATMPs are obtained. This guideline is based on the Commission Directive 2005/28/EC and includes all legal requirements relating to ATMPs such as Regulation (EC) No. 1394/2007 as the general regulation, Directive 2001/20/EC regarding testing, Commission Directive 2006/86/EC concerning traceability, Directive 2004/23/EC dealing with human tissue and cells for donation, procurement and testing of the tissues and cells, Directive 2002/98/EC regarding quality and safety standards for collection, testing, processing, storage and distribution of human blood and blood components, as well as the corresponding implemented guidances such as the guideline to xenogeneic cell therapy medicinal products.

5.7.2 GMP

GMP requirements are laid down in Directive 2003/94/EC, in Volume 4 of the *Rules governing medicinal products*, in the EU guidelines for Good Manufacturing Practice including the Council Directive 86/609/EEC and in a directive to the general requirements for animal quarters, care and quarantine [35]. Special needs for the manufacturing of biological medicinal products are contained in Annex 2 of the EU GMP guideline covering products such as vaccines, immune sera, antigens, hormones, cytokines, enzymes, products of fermentation including monoclonal antibodies and products derived from recombinant DNA. The latter one has been revised in April 2010 expanding the applicability of the guideline to further biological products such as transgenic derived products and ATMPs. This guideline is still in the draft version. The guidance includes the requirements of the Regulation 1394/2007/EC and Directive 2009/120/EC amending Directive 2001/83/EC. In April 2010 a draft version on GMP for ATMPs was adopted.

5.7.3 GLP

GLP requirements are implemented in Directive 2004/10/EC replacing the Directive 87/18/EC [69]. This Directive regulates all medicinal products.

5.8 Pharmacovigilance

Directive 2010/84/EC has recently been revised amending Directive 2001/83/EC regarding pharmacovigilance [62]. It includes obligations for all member states to give more transparency on information regarding pharmacovigilance issues, regarding measures for evaluation and monitoring risks on the environment, regarding the obligation for the marketing authorisation holder to establish a pharmacovigilance system including monitoring of the authorised medicinal product, regarding risk management systems and a continuous update on data regarding safety and efficacy. For biological products additional monitoring is required for authorisation of the product. All products with the need of additional monitoring will be listed and published by the EMA. The Directive

2010/84/EC is established for all biological products authorised nationally or by a decentralised (MRP/DCP) procedure. Pharmacovigilance for advanced therapy medicinal products and centrally authorised biological products is regulated by the Regulation (EU) No. 1235/2010 [65]. Similar to biological medicinal products regulated through the Directive, centrally authorised biological products and ATMPs need to be monitored additionally. Furthermore, a risk management system for ATMPs and for biological products with a substantial change to the authorised product such as biosimilars, products with a new active substance or a new manufacturing process, is required. Medicinal products obliged to an additional monitoring will be labelled accordingly, e.g. with a black symbol. A continuous monitoring of safety and providing all available information regarding medicinal products are required as well. Both, Regulation and Directive will come into force from July 2012 on.

5.9 Clinical trials

The clinical trial Directive 2001/20/EC is valid for all medicinal products and conventional biological products [19]. Clinical trials on ATMPs must be conducted in accordance with the principles regulated in this Directive as well. Because of the complexity of all biological medicinal products the approaches to phase I and II trials may be adapted.

5.10 Ethic concerns

ATMPs as well as conventional biological medicinal products conform to the same ethical principles. Recommendations of the “European Group on Ethics in Science and New Technologies” are considered.

6. Discussion

The demarcation of ATMPs to conventional biological products is mainly established in the Regulation (EC) No. 1394/2007 and the consolidated Directive 2001/83/EC. Directive 2001/83/EC contains the definition of gene therapy products and somatic cell therapy products as well as the requirements on the marketing authorisation application of ATMPs. The Regulation (EC) No. 1394/2007 contains the definition of the tissue engineering products and the combined products as well as all other regulations on ATMPs. These facts demonstrate that the classification of ATMPs and thus, the demarcation of specialised therapeutic biological products to other biological products have a significant impact on regulatory requirements. Conventional biological medicinal products are either regulated through Regulation (EC) No. 726/2004 or Directive 2001/83/EC. In some cases they are authorised nationally. However, a harmonised regulation covering all biological products does not exist.

Regarding significance and limitations of this classification the following questions will be discussed:

•Are the classification criteria clear and suitable to distinguish ATMPs from other

medicinal products?
•Does it make sense to limit the ATMP to these three classification groups?
•Justify the differences in ATMPs and conventional biological medicinal products, especially biotechnological products, the differences in the regulation?
•Which impact has the demarcation in view of health protection and health market?

6.1 Are the classification criteria clear and suitable to distinguish ATMPs from other medicinal products?

The classification of ATMPs focuses on two main aspects, the therapeutic aspect of an ATMP and the definition of an active substance in the ATMP. The therapeutic aspect is also included in many definitions for biological medicinal products as described in chapter 3.1 of this master thesis and resembles that for chemical medicinal products. The definition uses broad terms such as the intended purpose for treating, preventing or diagnosis of diseases and thus, is not suitable as a unique classification criterion specific for ATMPs.

The definition of the active substance contained in the ATMP represents the main criterion for the gene therapy medicinal product including several different active substances. According to the definition in annex I, part IV of Directive 2001/83/EC the ATMP may contain viral vectors or viruses, genetically modified cells, non-viral vectors such as plasmids or naked nucleic acid such as DNA or RNA. Those substances vary strongly in their complexity leading even in the same class of a gene therapy medicinal product to different engineered approaches. Cell and tissue products can be prepared using almost all human, including allogeneic and autologous, cells or tissues as well as animal cells or tissues. The inclusion of cells independent of their source is a necessary step to ensure the same regulation for similar products. At first view, this classification criterion seems to be more useful than the above described criteria of the therapeutic aspect. But at a closer look some aspects in the definition of the active substances are missing or are not clearly defined. For example, derivatives of cells or tissue as a part of the active substances are missing in the definition. Those substances are even included in Directive 2004/23/EC and have to comply for all quality and safety issues including traceability as all other tissues and cells. If such derivatives do not contain cells or tissues which are substantially manipulated they are not covered by the ATMP Regulation and consequently, safety requirements as required for ATMPs would not be stipulated for them. Not covered in Regulation (EC) No. 1394/2007 is also the use of specific types of cells, such as embryonic stem cells for ethical reasons. Such cells are only regulated by the Member States. On one hand, this decision contradicts harmonisation regarding all manipulated cells. On the other hand, it hardly would be possible to achieve a common position within the European Union regarding the use of embryonic stem cells.

It is noticeable that the definitions for somatic cell therapy products and tissue engineered products are not clearly distinct. The difference seems to be only in the intended purpose of the product. Somatic cell therapy products are used for treating, preventing and diagnosis whereas tissue engineered products are used for regenerating, repairing and

replacing. A clear separation of both products would have been desirable. The weak differentiation of both classes might even lead to a problem when cells are used as an active substance which comply with the requirements for somatic cell therapy product regarding active substance and substantially manipulation but are intended for a classical purpose of tissue engineered products (regenerating, repairing). Those cells do not strictly meet the requirements of somatic cell therapy products and thus, cannot classify as an ATMP. Otherwise, a clear line will be difficult to draw as both product classes share many properties.

For the classification of biological medicinal products as potential ATMPs a classification procedure is offered and performed by the CAT. At least now it is obvious that the criteria for the classification are not considered as simple and clear indicating that such a procedure is obviously needed.

Additionally, for somatic cell therapeutic products and tissue engineered products a further classification aspect, the function of the therapeutic product, is included in the classification criteria. This seems to be more a side aspect further defining the criteria of the active substance. Cells or tissues must either be substantially manipulated or show a different essential function within the recipient as compared to the function in the donor. The term “essential” is not further defined and may lead to different interpretations.

A further example which is not clearly defined according to the classification criteria is the use of cells, tissue or genes from transgenic animals. The definitions in the Directive or the Regulation do not describe the source of genes, cells or tissue precisely. Therefore, normal animals and transgenic animals are not distinguished and thus, neither are their cells or tissues from their normal counterparts. If cells or tissues are not substantially modified or their “essential” function differs in donor and recipient, the definition for ATMPs is not fulfilled. Consequently, such products would be regulated differently even if the risks for such products might be as high as for ATMPs.

Another issue concerns vaccines for infectious diseases. This class of biological medicinal products has been excluded from the ATMP definition. The reason for the re-definition was a discussion about the terms “vaccine” and “vaccination”. Vaccination is usually defined as the protection of healthy people, mainly children, against infectious diseases. Furthermore, the classification of a vaccine as a gene therapy medicinal product might lead to concerns and rejections of those vaccines due to the overall negative public opinion on gene technology in the EU. This vaccine clause was originally not included in Directive 2003/63/EC and has been added in Directive 2009/120/EC, amending Directive 2001/83/EC. From a scientific point of view, if a vaccine complies to the definition of a gene therapy medicinal product meaning that it contains the same active substances as outlined in the Directive and if it is produced in a similar manner as other gene therapy medicinal products, the requirements applied for these medicinal products should also be applied for such vaccines. Even if vaccines have many specialised guidelines not all of them cover all new regulations which are now valid for ATMPs, especially safety issues or pharmacovigilance. Also the monitoring for risks is missing leading to an overall more liberal regulation of vaccines as compared to gene therapy medicinal products.

An interesting special case where a “vaccine” against infectious diseases can be classified as an ATMP is shown in example 8 in chapter 3.3.4. In this case the therapeutic gene does not act directly against a surface molecule of the target cell but results in expression of an enzyme which recognises a nucleic acid sequence specific for the virus, cuts the sequence and thereby kills the virus. Interestingly, this biological medicinal product is not used within the human body but is used *in vitro* on tissue (cornea) prior its transplantation into the patient. Even if this “vaccine” is used for prevention of an infectious disease which is the definition of a “classical” vaccine, it differs from them by the indirect treatment scheme outside of the human body.

Borderline products between ATMPs and medical devices are included in the classification of ATMPs. This makes sense as especially tissue engineered products or cell therapy medicinal products may include medical devices. For example autologous cultured chondrocytes (Example 5 in chapter 4) are integrated in a scaffold to influence the growth direction [53]. Interestingly, combined ATMPs do not follow the rule of other combined medicinal products. The classification of the combined medicinal products applies to that component which is responsible for the primary act upon the human body [5]. If an ATMP is a component in a combined product the ATMP will be defined as primary actor in any case. The only exception is the use of non-viable cells or tissues with accessory action. This definition might be in most cases acceptable as ATMPs are quite complex and need a stronger regulation, especially if those biological medicinal products are administered to the human body. Furthermore, there will probably exist more cases of combined products using ATMPs in which the ATMP component will take over the main role. Example 7 in chapter 3.4 shows a borderline case of combined ATMPs in which the cell component is a liver carcinoma cell line and the medical device component a hollow fibre cartridge. The carcinoma cell line is not in direct contact with the human body but works indirectly in a manner that the cells produce metabolites which are released into the patient’s plasma, pumped through the fibre cartridge and then back into the vein of the patient. According to the definition for somatic cell therapy medicinal products in Directive 2001/83/EC, annex I, part IV, the cells do not have to be administered directly to the patient. On the other hand, in the definition for gene therapy medicinal products, products which are expressed by gene products are explicitly mentioned. However, products derived by (manipulated) cells are not included in this definition. Thus, the definition for ATMP is not quite clear. In this case, the classification as a combined somatic cell therapy product falling under the regulation of (EC) No. 1394/2007 and 2001/83/EC might be acceptable if the metabolites released by the carcinoma cell line are not completely examined and a further monitoring required.

Unfortunately, a further aspect is missing in the definition of the Regulation which might be more useful to distinguish different biological products: the biological mechanism of action. Different products which work in identical manner in the human body should not be regulated differently only because they fall under different categories. This will be outlined in the example below.

Naked nucleotides can be chemically synthesized as oligonucleotides or biologically produced using micro-organisms. The main difference between the synthesised DNA/RNA and the purified nucleotides from a biological source is the backbone of the

plasmid, which has been used for the transformation of micro-organisms. This part can be enzymatically removed, if necessary, to make both products structurally and functionally identical. Regarding the definition of Directive 2001/83/EC ATMPs are stated as biological products meaning that the active substance is necessarily of biological origin (Annex I, part I Directive 2001/83/EC). Thus, synthetically manufactured oligonucleotides used as naked DNA are excluded. They also do not comply to the biotechnological processes listed in Annex I of the Regulation (EC) No. 726/2004 and therefore, are classified as a chemical medicinal product. However, the biological mechanism of action of both products is identical. Only because of their classification, their regulatory requirements differ considerably. For ATMPs certain non-clinical and clinical data are required as outlined in several guidances which do not cover chemical medicinal products. This different, less strict procedure does not fit to the safety requirements of medicinal products based on nucleotides and hence, their exclusion from the definition of ATMPs might be a problem.

Cells or genes derived from plants are not included in the classification criteria of ATMPs, too. Even if plants share less properties with human cells or genes and therefore might be regarded as non-dangerous it would have been useful to include them in the definition of the classification groups. Especially for genes can be considered: the principal risks of nucleotide sequences are the same regardless if they are obtained from plants, micro-organisms or by chemical synthesis.

6.2 Does it make sense to limit the ATMP to these three classification groups?

The Commission has brought those three types of products together, as it was expected that these products have a major impact on public health by improving patient's quality life and changing medical practice significantly [3]. The selection of the three therapeutic classes, gene therapy, somatic cell therapy and tissue engineering and their combination with medical devices as a specialised group of biological medicinal products, represents the present status of the state of the art. To establish an additional regulation for biological medicinal products of these three classes was at least a reaction to the progress made in technology in the pharmaceutical area. The decision to include these three classes of therapeutic products makes sense as these products share similar characteristics and bear a similar risk potential.

Other emerging fields such as nano technology might soon gain a similar medical importance as these three therapeutic products, therefore needing to be included into the ATMP regulation, too. However, this technology has not been sufficiently developed yet to allow a regulation which includes useful parameters for directing this technology, as mentioned on the EMA homepage under "Medicines and emerging science".

6.3 Justify the differences in ATMPs and conventional biological medicinal products also a stronger regulation for ATMPs?

ATMPs are expected to bear a higher risk potential than other biological medicinal products [4]. Therefore, the regulation for ATMPs has especially a focus on safety requirements. To obtain the marketing authorisation additional data regarding safety,

efficiency and quality are needed. Further requests for ATMPs are post-authorisation requirements such as traceability and additional monitoring for adverse effects [28]. For more details, please see chapter 4 of this thesis. Those requirements are obliged for all biological therapeutic medicinal products which are classified as ATMPs. However, ATMPs differ in their complexity as broadly as conventional biological medicinal products do and also differ strongly in their risk regarding safety, quality and efficacy. Unfortunately, the regulation does not even distinguish between low risk products like autologous tissues such as cartilage transplants and high risk products for ATMPs such as gene therapy products expressed by a viral vector. Thus, a risk-based classification between similar biological medicinal products could be useful.

6.4 Which impact has the demarcation in the view of health protection and health market

One of the main objectives of the new Regulation for ATMPs is providing a high level of health protection. This goal is achieved by a focus on higher risk protection of the therapeutic products and the establishment of a centralised procedure in order to make this technology more transparent throughout all European countries. The latter point does not differ between conventional biological medicinal products which are regulated by Regulation (EC) No. 726/2004 and ATMPs. However, the marketing of products does not depend on the regulatory instruments alone but also on the market situation in the individual countries, the profit margins and the national reimbursement. In case of ATMPs it is likely that these products will be more expensive as the costs for additional data for clinical and non-clinical data will be added to the price, especially, when these products are only for a small number of patients. Even the incentives offered by the EMA will not compensate the considerably higher expenses. The question if the public health systems are able and willing to cover these extra costs has to be discussed.

7. Conclusion and Outlook

A new regulation covering ATMPs was necessary as a good regulation was missing in this field. Even Regulation (EC) No. 726/2004 which regulates biotechnological products as well as products of new not further specified technologies has not added special regulation for ATMPs. The new Regulation on ATMPs provides adoptions to all important regulatory issues. Of significant interest are the harmonised procedure and the focus on safety aspects.

ATMPs comprise therapeutic products based on nucleic acids, cells and tissues believed to have a major impact on human health. In principal, the classification in these groups is necessary and including products with similar risk potential. However, the classification shows weaknesses because it is limited to products with certain therapeutic aspects and a specific set of active substances. Unfortunately, other biological medicinal products having similar function or effect mechanisms in the human body are not included. Additionally, including products of further new technologies with similar risk potential such as transgenic animals would have been useful. A classification of ATMPs in low and high risk

groups may be considered. A major advantage of this new Regulation of ATMPs is that the classification procedure will be performed by a central committee leading to harmonised decisions regarding the classification.

8. Summary

Biotechnology has evolved a broad variety of divergent medicinal products including hormones and blood factors as well as vaccines and monoclonal antibodies for chronic, acute and rare diseases, such as cancer, hepatitis C, diabetes, multiple sclerosis and rheumatoid arthritis. Many of those biological medicinal products are either regulated through Regulation (EC) No. 726/2004 or Directive 2001/83/EC depending on the manufacturing process used or their application. In some cases they are authorised nationally. However, a harmonised regulation covering all biological products does not exist. Such medicinal products are indicated as conventional biologics in this master thesis.

New emerging fields of biotechnology are therapies based on gene therapy, somatic cell therapy or tissue engineering. Such innovative therapeutics are summarised under the term advanced therapy medicinal products (ATMP). ATMPs offer new opportunities for treatment of rare or previously untreated diseases, early detection of dysfunctions of the human body or others, e.g. skin replacement products.

In 2007 a regulation for ATMPs, Regulation (EC) No. 1394/2007, has been adopted to overcome the lack of a clear and coherent legal framework and to boost research in this field. The intention was to harmonise the regulation of these therapies and to adapt technical specifications to ATMP products. The regulation involves a classification procedure for these products. This is important for companies in case the classification of the case is ambiguous as the application of ATMP requires more data regarding quality and safety compared to other biological products.

The aim of the master thesis is to give an overview of the classification and demarcation of ATMPs as compared to other biological medicinal products. The criteria defined for the classification of ATMPs are mainly established in the Regulation (EC) No. 1394/2007 and the consolidated Directive 2001/83/EC demonstrating that the classification of ATMPs and thus, the demarcation of specialised therapeutic biological products to other biological products have a significant impact on regulatory requirements. Key aspects of the regulatory requirements are highlighted. Significance and limitations of this classification are discussed, especially regarding clarity and suitability of the classification criteria, the limitation of the ATMPs to the three classification groups gene therapy medicinal products, somatic cell medicinal products and tissue engineered products and the impact of the demarcation in view of health protection and health market. Furthermore, the differences of ATMPs and biotechnological medicinal products justifying the question of a demarcation are discussed.

List of Abbreviations

AADC	Aromatic L-amino-acid decarboxylase
AAV	Adeno-Associated Virus
ABCA4 gene	gene coding for the protein „ATP-binding cassette, sub-family A, member 4“, belongs to a family of proteins that transport molecules across cell membranes
abciximab	antibody against CD41 7E3 (also known as c7E3 Fab), manufactured by Centocor, marketed by Eli Lilly, trade name ReoPro, http://www.drugbank.ca/drugs/BTD00041
ADA	Adenosin desaminase
AIDS	Acquired immune deficiency syndrome
AMG	German pharmacopoeia (AMG)
ATMP	Advanced therapy medicinal product
CAT	Committee for Advanced Therapy (belongs to EMA)
CBER	Center for Biologics Evaluation and Research (belongs to FDA)
CD3	Cluster of Differentiation 3 (CD = cell surface antigen suitable to "differentiate“ certain cells from other cells having other CDs at their surface), CD3 is a co-receptor of the T-cell receptor
CD52	Cluster of Differentiation 52 (specific cell surface antigen for mature lymphocytes, not present on stem-cells
CD8+	"Cluster of Differentiation 8 positive (= containing CD8); CD8 is mainly present on cytotoxic T-cells and functions as a co-receptor of the T-cell receptor binding to MHC (major histocompatibility complex)
CFR	Code of Federal Regulations
CH1	Cyclohydrolase 1
CHMP	Committee for Human Medical Products (belongs to EMA)
CLI	Critical limb ischemia
CMD(h)	Coordination Group for Mutual Recognition and Decentralised Procedures (human)
CPMP	Committee for Proprietary Medicinal Products (= now CHMP)
CTMP	Somatic Cell Therapy Medicinal Products
daclizuman	trade name Zenapax, antibody against CD25=alpha subunit of IL-2 receptor, Hoffmann La Roche Inc., http://www.drugbank.ca/drugs/BTD00007
DNA	Deoxyribonucleic Acid
EC	European Community
EEC	European Economic Community, renamed the European Community (EC) in 1993
EMA	European Medicines Agency
EMEA	European Medicines Agency
EU	European Union
FDA	Food and Drug Administration
FGF 1	Fibroblast growth factor type 1
GCP	Good Clinical Practice
GLP	Good Laboratory Practice
GM-CSF	Granulocyte macrophage colony-stimulating factor

GMO	Genetically modified organisms
GMP	Good Manufacturing Practice
GTMP	Gene Therapy Medicinal Products
GTP	Guanosine triphosphate
HSV-1	Herpes simplex virus-1
HSV-Tk gene	gene coding for the protein „Herpes simplex virus-tymidine kinase“, enzyme involved in DNA-synthesis
ICH	International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use
ITF	Innovation Task Force
LPL	Lipoprotein lipase
MAH	Marketing authorisation holder
microRNA	short RNA (= miRNA) with size of on avarage around 22 nucleotides
mRNA	messenger ribonucleic acid (= nucleic acid coding for a protein)
MRP/DCP	Mutual Recognition Procedure / Decentralized Procedure
muromonab	muro = murine = originated from mouse, mon = monoclonal, ab = antibody; trade name Orthoclone, OKT3, marketed by Janssen-Cilag
MYO7A gene	gene coding for the protein „Myosin VIIA“, needed for intracellular movement of membranes and organelles
NtA	Notice for Applicants
PAP-GM-CSF	prostatic acid phosphatase-granulocyte-macrophage colony-stimulating factor
PASS	Post-authorisation safety studies
PCR	Polymerase Chain Reaction (enzymatic method for amplification of nucleic acids)
PMF	Plasma Master file
PSA	Prostate specific antigen, protein used as biomarker to diagnose prostate cancer
PSUR	Periodic safety update reports
rituximab	trade names Rituxan and MabThera, antibodiy against CD20, developed by IDEC Pharmaceuticals
RMS	Risk management system
RNA	Ribonucleic acid
SMEs	Small- and medium-sized enterprises
SmPC	Summary of Product Characteristics
SPC	Summary of Product Characteristics
TEP	Tissue engineered products
TK gene	Thymidine kinase gene, enzyme involved in DNA-synthesis
TSE/BSE	Transmissible spongiform encephalopathies (TSE) / Bovine spongiform encephalopathy (BSE)
VAMF	Vaccine Master File
VEGF-C	Vascular endothelial growth factor C, important for endothelial cell growth and survival, and for growth of blood and lymphatic vessels
VLDL	Very low density lipoprotein

Literature

1 Walsh G. Biopharmaceuticals, Biochemistry and Biotechnology. John Wiley and Sons Ltd. **Second Edition**, 551 pages (2003).

2 Walsh G. Pharmceutical benchmarks 2010. Nat Biotechnol. **28**, 917-924 (2010).

3 The Commission of the European Communities. Communication from the Commission to the Council, the European Parliament, the European Economic and Social Committee and the Committee of the Regions on the mid term review of the Strategy on Life Sciences and Biotechnology. http://ec.europa.eu. Doc.-Ref.: COM(2007) 175 final, **10.04.2007**, p. 1-12 (2007).

4 Schneider, C.K. and Celis, P. Opinion: Challenges with advanced therapy medicinal products and how to meet them. Nat Rev Drug Discov. **9**, 195-201 (2010).

5 Jekerle V. et al. Legal basis of the Advanced Therapies Regulation. Bundesgesundheitsbl. **53**, 4-8 (2009).

6 Celis P. and Pedone E. The Committee for Advanced Therapies at the European Medicines Agency and the Advanced Therapies Certification Procedure. Drug Development. **4**, 64-67 (2009).

7 Garidel P. et al. Characterization of Proteins and Related Analytical Techniques. 44-70

8 O'Connor, A.M.. Introduction to biotech drugs. Regulatory Rapporteur. **6**, 4-7 (2009).

9 Kozlowski S. Protein Therapeuctics and the Regulation of Quality: A Brief History. Biopharm Internat. **20**, 37-55 (2007).

10 Kaufmann, S.H.E. et al. Neue Impfstoffkonzepte auf Basis moderner Erkenntnisse der Immunologie. Bundesgesundheitsbl. **11,** 1069-1082 (2009).

11 Oda N. et al. Clinical course and outcome of heart transplant recipients, Single center experience at the National Cardiovascular Center in Japan. Int Heart J. **51**, 264-271 (2010).

12 The Council of the European Communities. Council Directive 87/22/EEC of 22 December 1986 on the approximation of national measures relating to the placing on the market of high-technology medicinal products, particularly those derived from biotechnology. Official J Europ Union. **L 015, 17.01.1987**, p. 38-41 (1987).

13 The Council of the European Communities. Council Directive 89/342/EEC of 3 May 1989 extending the scope of Directives 65/65/EEC and 75/319/EEC and laying down additional provisions for immunological medicinal products consisting of vaccines, toxins or serums and allergens. Official J Europ Union. **L 142, 25.05.1989**, p. 14-15 (1989).

14 The Council of the European Communities. Council Directive 89/381/EEC of 14 June 1989 extending the scope of Directives 65/65/EEC and 75/319/EEC on the approximation of provisions laid down by Law, Regulation or Administrative Action relating to proprietary medicinal products and laying down special provisions for medicinal products derived from human blood or human plasma. Official J Europ Union. **L 181, 28.06.1989**, p. 44-46 (1989).

15 The Council of the European Communities. Council Directive 90/220/EEC of 23 April 1990 on the deliberate release into the environment of genetically modified organisms. Official J Europ Union. **L 117, 08.05.1990**, p. 15-27 (1990).

16 The Council of the European Communities. Council Directive 90/219/EEC of 23 April 1990 on the contained use of genetically modified micro-organisms. Official J Europ Union. **L 117, 08.05.1990**, p. 1-21 (1990).

17 The Council of the European Communities. Council Regulation (EEC) No 2309/93 of 22 July 1993 laying down Community procedures for the authorization and supervision of medicinal products for human and veterinary use and establishing a European Agency for the Evaluation of Medicinal Products. Official J Europ Union. **L 214, 24.08.1993**, p. 1-35 (1993).

18 European Parliament and the Council of the European Union. Directive 2001/83/EC of the European Parliament and of the Council of 6 November 2001 on the Community code relating to medicinal products for human use. Official J Europ Union. **L 311, 28.11.2001**, p. 67-128 (2001).

19 European Parliament and the Council of the European Union. Directive 2001/20/EC of the European Parliament and of the Council of 4 April 2001 on the approximation of the laws, regulations and administrative provisions of the Member States relating to the implementation of good clinical practice in the conduct of clinical trials on medicinal products for human use. Official J Europ Union. **L 121, 01.05.2001**, p. 34-44 (2001).

20 European Parliament and the Council of the European Union. Directive 2002/98/EC of the European Parliament and of the Council of 27 January 2003 setting standards of quality and safety for the collection, testing, processing, storage and distribution of human blood and blood components and amending Directive 2001/83/EC. Official J Europ Union. **L 33, 08.02.2003**, p. 30-40 (2003).

21 European Parliament and the Council of the European Union. Directive 2004/23/EC of the European Parliament and of the Council of 31 March 2004 on setting standards of quality and safety for the donation, procurement, testing, processing, preservation, storage and distribution of human tissues and cells. Official J Europ Union. **L 102, 07.04.2004**, p. 48-58 (2004).

22 The Commission of the European Communities. Commission Directive 2003/63/EC of 25 June 2003 amending Directive 2001/83/EC of the European Parliament and of the Council on the Community code relating to medicinal products for human use. Official J Europ Union. **L 159, 27.06.2003**, p. 46-94 (2003).

23 European Medicines Agency, Committee for Proprietary Medicinal Products (CPMP). Points to consider on the manufacture and quality control of human somatic cell therapy medicinal products. www.ema.europa.eu. Doc.-Ref.: CPMP/BWP/41450/98, **31.05.2001**, p. 1-11 (2001).

24 European Medicines Agency, Committee for Medicinal Products for Human Use (CHMP). Guideline on xenogenic cell-based medicinal products. www.ema.europa.eu. Doc.-Ref.: EMEA/CHMP/CPWP/83508/2009, **22.10.2009**, p. 1-14 (2009).

25 European Medicines Agency, Committee for Medicinal Products for Human Use (CHMP). Guideline on human cell-based medicinal products. www.ema.europa.eu. Doc.-Ref.: EMEA/CHMP/410869/2006, **11.01.2007**, p. 1-24 (2007).

26 European Medicines Agency, Committee for Medicinal Products for Human Use (CHMP). Concept paper on the revision of the note for guidance on the quality, pre-clinical and clinical aspects of gene transfer medicinal products. www.ema.europa.eu. Doc.-Ref.: EMA/CHMP/GTWP/BWP/234523/2009, **17.12.2009**, p. 1-4 (2009).

27 European Commission. Press release: Advanced therapies: breakthrough in treating cancer or burned skin. http://ec.europa.eu. Doc.-Ref.: MEMO/05/429, **16.11.2005**, p. 1-4 (2005).

28 The European Parliament and the Council of the European Union. Regulation (EC) No 1394/2007 of the European Parliament and of the Council of 13 November 2007 on advanced therapy medicinal products and amending Directive 2001/83/EC and Regulation (EC) No 726/2004. Official J Europ Union. L 324, 10.12.2007, p. 121-137 (2007).

29 Kantoff M.D. et al. Sipuleucel-T Immunotherapy for Castration-Resistant Prostate Cancer. N Engl J Med. **363**, 411-422 (2010).

30 Salmikangas P. et al. Regulatory requirements for clinical trial and marketing authorisation application for cell-based medicinal poducts. Bundesgesundheitsbl. **53,** 24-29 (2009).

31 TiGenix N.V, Leuven, Belgium. Pressrelease: Positive 5-year ChondroCelect follow-up, Results to be presented at ESSKA. www.tigenix.com. **08.06.2010**, p. 1-3 (2011).

32 Burnett JR. and Hooper AJ. Alipogene tiparvovec, an adeno-associated virus encoding the Ser(447)X variant of the human lipoprotein lipase gene for the treatment of patients with lipoprotein lipase deficiency. Curr Opin Mol Ther. **11**, 681-691 (2009).

33 Whiteside, P. A. Biotechnology medicinal products: Back to basics. Regulatory Rapporteur. **8**, 4-5 (2011).

34 European Medicines Agency, Committee for Proprietary Medicinal Products (CPMP). ICH Topic Q 5 C, Quality of Biotechnological Products: Stability Testing of Biotechnological/Biological Products. www.ema.europa.eu. Doc.-Ref.: CPMP/ICH/138/95, ICH Topic **Q5C, July 1996** , p. 1-9 (1996).

35 European Commission, Enterprise and Industry Directorate-General. Volume 4: EU Guidelines for Good Manufacturing Practice for Medicinal Products for Human and Veterinary Use. http://ec.europa.eu. Doc.-Ref.: ENTR/C/8/SF D(2010) 380334, **09.04.2010**, p. 1-26 (2010).

36 Co-ordination Group for Mutual Recognition and Decentralised Procedures - Human (CMDh). Guidance for applicants on biologicals, Question 1 (June 2007) What is the definition of a biological medicinal product?. **[online]**. http://www.hma.eu/215.html, (2007).

37 European Commission. Commission communication on the Community marketing authorisation procedures for medicinal products. Official J Europ Union. **C 229, 22.07.1998**, p. 4-17 (1998).

38 European Biopharmaceutical Enterprises (EBE). What are biopharmaceuticals?. **[online]**. http://www.ebe-biopharma.org/index.php?option=com_content&task=view&id=26&Itemid=102, (2011).

39 Radar R.A. (Re)defining biopharmaceutical. Nat Biotechnol. **26**, 743-751 (2008).

40 European Parliament and the Council of the European Union. Regulation (EC) No 726/2004 of the European Parliament and of the Council of 31 March 2004 laying down Community procedures for the authorisation and supervision of medicinal products for human and veterinary use and establishing a European Medicines Agency. Official J Europ Union. **L 136, 30.04.2004**, p. 1-33 (2004).

41 European Medicines Agency. list of documents on Centralized Procedure. **[online]**. http://www.ema.europa.eu/ema/index.jsp?curl=pages/about_us/document_listing/document_listing_000278.jsp&murl=menus/about_us/about_us.jsp&mid=WC0b01ac05800b5ca1, (2011).

42 The Commission of the European Communities. Commission Directive 2005/28/EC of 8 April 2005 laying down principles and detailed guidelines for good clinical practice as regards investigational medicinal products for human use, as well as the requirements for authorisation of the manufacturing or importation of such products. Official J Europ Union. **L 91, 09.04.2005**, p. 13-19 (2005).

43 The Commission of the European Communities. Commission Directive 2003/94/EC of 8 October 2003 laying down the principles and guidelines of good manufacturing practice in respect of medicinal products for human use and investigational medicinal products for human use. Official J Europ Union. **L 262, 14.10.2003**, 14.10.2003 (2003).

44 Further missing requirements are fulfilled by special guidelines to specific types of biological products, mainly to vaccines [44 überblick EMA]. Information sheet: Biological medicinal products. www.ema.europa.eu. http://www.ema.europa.eu/docs/en_GB/document_library/Brochure/2011/03/WC500104227.pdf, p. 1-2 (2011).

45 European Medicines Agency, Committee for Advanced Therapies (CAT). Procedural advice on the provision of scientific recommendation on classification of Advanced Therapy Medicinal Products in accordance with Article 17 of Regulation (EC) No 1394/2007. www.ema.europa.eu. Doc.-Ref.: EMA/CAT/99623/2009, **15.01.2010**, p. 1-10 (2010).

46 The Council of the European Communities. Councel Directive 93/42/EEC of 14 June 1993 concerning medical devices. Official J Europ Union. **L 169, 12.07.1993**, p. 1-60 (1993).

47 The Council of the European Communities. Council Directive of 20 June 1990 on the approximation of the laws of the Member States relating to active implantable medicinal devices (90/385/EEC). Official J Europ Union. **L 189, 20.07.1990**, p. 17-41 (1990).

48 European Parliament and the Council of the European Union. Directive 98/79/EC of the European Parliament and of the Council of 27 October 1998 on in vitro diagnostic medical devices. Official J Europ Union. **L 331, 07.12.1998**, p. 1-37 (1998).

49 European Parliament and the Council of the European Union. Directive 2000/70/EC of the European Parliament and of the Council of 16 November 2000 amending Council Directive 93/42/EEC as regards medical devices incorporating stable derivates of human blood or human plasma. Official J Europ Union. **L 313, 13.12.2000**, p. 22-24 (2000).

51 Chan DW et al. Prostate-specific antigen as a marker for prostatic cancer: a monoclonal and a polyclonal immunoassay compared. Clin Chem. **33**, 16-20 (1987).

52 CHEMIE.DE Information Service GmbH. Streptamer isolated donor lymphocytes classified by the EMEA as non ATMP's. www.bionity.com. News: **05.05.2010**, (2010).

53 Saris G.B et al. Treatment of symptomatic cartilage defects of the knee: characterized chondrocyte implantation results in better clinical outcome at 36 months in a randomized trial compared to microfracture.. Am J Sports Med. **37,** Suppl 1, 10S-19S (2009).

54 Vital Therapies, Inc,. San Diego, USA. Fact Sheet: Vital therapies, Targeting liver disease. www.vitaltherapies.com. **April 2011**, p. 1-2 (2011).

55 Grosse S. et al. Meganuclease-mediated inhibition of HSV-1 invection in cultured cells. Molecular Therapy. **19**, 694-702 (2011).

56 European Medicines Agency, Committee for Proprietary Medicinal Products (CHMP). Note for Guidance on the Quality, Preclinical and Clinical Aspects of Gene Transfer Medicinal Products. www.ema.europa.eu. Doc.-Ref.: CPMP/BWP/3088/99, **24.04.2001**, p. 1-33 (2001).

57 European Medicines Agency, Committee for Proprietary Medicinal Products (CPMP). Note for Guidance on Preclinical Pharmaceutical and Toxicological Testing of Vaccines. www.ema.europa.eu. Doc.-Ref.: CPMP/SWP/465/95, **17.12.1997**, (1997).

58 European Medicines Agency, Committee for Proprietary Medicinal Products (CPMP). ICH Topic S6 Preclinical Safety Evaluation of Biotechnology-Derived Pharmaceuticals. www.ema.europa.eu. Doc.-Ref.: CPMP/ICH/302/95, **March 1998**, p. 1-10 (1998).

59 The Commission of the European Communities. Commission Directive 2003/32/EC of 23 April 2003 introducing detailed specifications as regards the requirements laid down in Council Directive 93/ 42/EEC with respect to medical devices manufactured utilising tissues of animal origin. Official J Europ Union. **L 105, 26.04.2003**, p. 1-6 (2003).

60 European Medicines Agency, Committee for Proprietary Medicinal Products (CPMP). Pharmaceutical Aspects of the Product Information for Human Vaccines. www.ema.europa.eu. Doc.-Ref.: EMEA/CPMP/BWP/2758/02, **26.11.2003**, p. 1-16 (2003).

61 European Medicines Agency, Committee for Proprietary Medicinal Products (CPMP). Warning on transmissible agents in summary of product characteristics (SPCs) and package leaflets for plasma-derived medicinal products. www.ema.europa.eu. Doc.-Ref.: CPMP/BPWG/BWP/561/03, **22.10.2003**, p. 1-9 (2003).

62 European Parliament and the Council of the European Union. Directive 2010/84/EU of the European Parliament and of the Council of 15 December 2010 amending, as regards pharmacovigilance, Directive 2001/83/EC on the Community code relating to medicinal products for human use. Official J Europ Union. **L 348, 31.12.2010**, p. 74-99 (2010).

63 European Medicines Agency, Committee for Medicinal Products for Human Use (CHMP). Guideline on risk management systems for medicinal products for human use. www.ema.europa.eu. Doc.-Ref.: EMEA/CHMP/96268/2005, **14.11.2005**, p. 1-32 (2005).

64 European Medicines Agency, Committee for Medicinal Products for Human Use (CHMP). Guideline on safety and efficacy follow-up – Risk management of Advanced Therapy Medicinal Products. www.ema.europa.eu. Doc.-Ref.: EMEA/149995/2008, **20.11.2008**, p. 1-22 (2008).

65 European Parliament and the Council of the European Union. Regulation (EU) No 1235/2010 of the European Parliament and of the Council of 15 December 2010 amending, as regards pharmacovigilance of medicinal products for human use, Regulation (EC) No 726/2004 laying down Community procedures for the authorisation and supervision of medicinal products for human and veterinary use and establishing a European Medicines Agency, and Regulation (EC) No 1394/2007 on advanced therapy medicinal products. Official J Europ Union. **L 348, 31.12.2010**, p. 1-16 (2010).

66 The Commission of the European Communities. Commission Regulation (EC) No 1234/2008 of 24 November 2008 concerning the examination of variations to the terms of marketing authorisations for medicinal products for human use and veterinary medicinal products. Official J Europ Union. L 334, 12.12.2008, p. 7-24 (2008).

67 The Commission of the European Communities. Commission Regulation (EC) No 1084/2003 of 3 June 2003 concerning the examination of variations to the terms of a marketing authorisation for medicinal products for human use and veterinary medicinal products granted by a competent authority of a Member State. Official J Europ Union. **L 159, 27.06.2003**, p. 1-23 (2003).

68 European Medicines Agency, Committee for Proprietary Medicinal Products (CPMP). ICH Topic E 6 (R1) Guideline for Good Clinical Practice. www.ema.europa.eu. Doc.-Ref.: CPMP/ICH/135/95, **July 2002**, p. 1-48 (2002).

69 The European Parliament and the Council of the European Union. Directive 2004/10/EC of the European Parliament and of the Council of 11 February 2004 on the harmonisation of laws, regulations and administrative provisions relating to the application of the principles of good laboratory practice and the verification of their applications for tests on chemical substances (codified version. Official J Europ Union. **L 50, 20.02.2004**, p. 44-59 (2004).

Hiermit erkläre ich an Eides statt, die Arbeit selbstständig verfasst und keine anderen als die angegebenen Hilfsmittel verwendet zu haben.

Dr. Gabriele Noffz