Making cellular therapies available to patients

Possible regulatory pathways in Europe and Germany

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List of Abbreviations

AMG: Arzneimittelgesetz (German Medicinal Products Act)
Abs.: Absatz
APC: Ambulatory Payment Classification
Art.: Article
ATMP: Advanced Therapy Medicinal Product
ATU: Autorisation Temporaire d'Utilisation (temporary authorisation for use)
BfArM: Bundesinstitut für Arzneimittel und Medizinprodukte
CABG: Coronary artery bypass graft
CAT: Committee for Advanced Therapies
CBMP: Cell-Based Medicinal Product
CD: Cluster of Differentiation
CEP: Circulating Endothelial Precursor
CFR: Code of Federal Regulations
CHMP: Committee for Medicinal Products for Human Use
CTMP: Cellular Therapy Medicinal Products
CU: Compassionate Use
DLI: Donor Lymphocyte Infusion
DGHO: Deutsche Gesellschaft für Hämatologie und Onkologie
Dir.: Directive
DRG: Diagnosis-Related Group
EC: European Community
EMA: European Medicines Agency
EU: European Union (Europäische Union)
HSC(T): Haematopoietic Stem Cell (Therapy)
ISSCR: International Society for Stem Cell Research
GBA: Gemeinsamer Bundesausschuss
GCP: Good Clinical Practices
GewG: Gewebegesetz (German Cells and Tissues Act)
GFP. Gute Fachliche Praxis (good work practices)
GMP: Good Manufacturing Practices
GvHD: Graft versus Host Disease
HCT/P: Human Cell and Tissue Product
MAA: Marketing Authorisation Application
MAH: Marketing Authorisation Holder
MDD: Medical Device Directive
MS: Member State
NCA: National Competent Authority
NK: Natural Killer
No.: Number
Nr.: Nummer (Number)
NUB: Neue Untersuchung- und Behandlungsmethoden (new examination and treatment methods)
PCWP: Patients and Consumers Working Party
PEI: Paul Ehrlich Institut (German national competent authority for cell preparations)

Reg.: Regulation
SME: Small and Medium size Enterprise
TEP: Tissue-Engineered Product
TFG: Transfusionsgesetz (German Transfusion Act)
TPG: Transplantationsgesetz (German Transplantation Act)
TRM: Translational centre for Regenerative Medicine (Leipzig)
USA: United States of America
VEGF: Vascular Endothelial Growth Factor

Foreword

The aim of the foreword is to announce the conventions used throughout this master thesis.

For more readability, reference will be made to the European Directives and Regulations as well as to national laws without mention of their amendments, which are mentioned in the footnotes as well as in chapter 6 References.

Definitions and legal quotations will be given in their original language. Translations will be proposed for purpose of explanation. The translations from the German Medicinal Products Act (Arzneimittelgesetz, AMG) have been extracted from a non-official translation into the English language of the AMG proposed on the website of the Paul Ehrlich Institut (PEI).

Exact citations from laws are within quotation marks, in italics and coloured in blue.

The terms cells, cell preparations, cellular therapies, CBMPs, CTMPs are used in this thesis. They refer to the same concept.

1 Introduction

In the last years the fields of cellular therapies and regenerative medicine have developed in a remarkable way. The intensive research and development activities carried out in this emerging interdisciplinary area (surgery/medicine, genetics, cellular biology, medical devices, biotechnology, and ethics) bring the vision of innovative and very promising treatments. Established therapies, like haematopoietic stem cell transplantation (HSCT) after chemotherapy, have already proven safety and efficacy for years. The areas of tissue regeneration and graft engineering have enabled important medicinal progress, the latter permitting a remarkable reduction of graft versus host disease (GvHD) after HSCT. Other approaches like donor lymphocyte infusions (DLIs) provided an improvement in the graft versus leukaemia effect by the use of mismatched NK cell infusions. New clinical applications of cellular therapy now make it possible to offer patients real solutions against diseases and the possibility of tissue or organ reparation after injuries in order to restore or establish normal function, due to a new set of regulations.

But as for many other innovative and promising areas expanding so fast, misuse of cellular therapies is developing as well, especially of stem cell based therapies. Some therapeutic institutions outside but also inside the European Community (EC) still offer expensive and insufficiently controlled therapies (from the scientific and regulatory points of view) to patients with highly debilitating and life-threatening diseases, giving them hope of complete remission. This is possible in Germany in the context of the freedom of therapy (Therapiefreiheit) for physicians. National competent authorities and the European Medicines Agency (EMA), especially its Committee for Advanced Therapies (CAT) are very concerned about the use of these unregulated stem-cell based therapies.[1,2] Not only regulators but also scientific societies like the international society for stem cell research (ISSCR) warn patients, their families and physicians about those dangerous practices of delivering unproven stem cell treatments and make propositions for implementing measures against those.[3] The need for regulation of those products is evident, as unauthorised cell-based therapies usually lack data and peer-reviewed publications demonstrating their safety and efficacy. Even their quality is usually not sufficiently documented in the centres applying these treatments. As a recent reaction to the use of not fully substantiated cellular therapies in Germany, the Paul Ehrlich Institut (PEI), the national competent authority (NCA) for biological medicinal products, has denied further authorisation for stem cell transplantation to the XCell-Center in Cologne. One year ago (August 2010) in Germany, a young child died from the consequences of a stem cell injection in his brain that had been performed in this private clinic.

Even the World Health Organization (WHO) sends signals in the same direction: cellular therapies need a regulatory framework so that patients may have access to demonstrated safe and efficient products with defined scientific and ethical requirements.[4] This regulatory framework is currently in place in the European Community and its Member States (MS), like for example in Germany. The laws implemented enabled to stop the almost experimental activities of the XCell-Center as mentioned above, like injecting autologous bone marrow isolated cells into the brain of a Parkinson patient to treat this disease. While setting high hurdles will surely prevent patients from being

[1] Use of unregulated stem-cell based medicinal products, CAT and CAT Scientific Secretariat, The Lancet (2010) 376
[2] EMA/763463/2009, Concerns over unregulated medicinal products containing stem cells
[3] Patients Beware: Commercialized Stem Cell Treatments on the Web, Patrick L. Taylor and al., Cell Stem Cell (2010) 7
[4] World Health Organization Aide-Mémoire for National Health Authorities, Access to Safe and Effective Cells and Tissues for Transplantation (2006)

endangered by unsafe and inefficient products, a too rigid regulatory system could probably also reduce innovative therapy options for severely ill patients. Since the implementation of the Advanced Therapy Medicinal Products (ATMP) Regulation[5] in Europe in December 2008, a marketing authorisation was granted only for one product, a tissue-engineered product (TEP) used to repair damage to the cartilage in the knee (*ChondroCelect*).[6] Although a permanent growth in marketing authorisation applications relating to the development of ATMPs was announced, together with measures from the CAT and close collaboration between the EMA and the stakeholders in the field[7], very few products have made it to the market until now.

A compromise needs to be found enabling a sufficient regulation of cellular therapies in the European Community and the Member States without prejudice to the innovation potential of the actors developing such products. In that way, cellular therapies can be made accessible to patients under controlled condition, be it as authorised therapies on the European or national markets, as participation in clinical trials or compassionate use programmes, or as treatments under the responsibility of a treating physician.

Availability of cellular therapies to patients not only depends on regulatory considerations but also on financial and economic ones. Treatments must be affordable for patients and healthcare systems for them to be applied in the long run. Additionally, for cellular therapies feasibility in clinical routine is a major issue as trivial logistic aspects might spoil the benefits of a therapy: for example the transport of a cellular product to a centralised processing unit and back to the hospital after processing is impossible for cells needing to be re-injected immediately to a patient undergoing liver surgery.

This thesis will concentrate on the different regulatory pathways for bringing cell therapies to patients and will describe the regulatory situation for Europe and Germany. It will focus only on human cells and cell-based medicinal products (without genetic engineering). Cells and cell-based medicinal products encompass all cell preparations of human origin, with or without manipulation, manufactured with an industrial process or not, such as somatic cell therapy medicinal products, tissue-engineered products or peripheral blood stem cells. References to other cellular products or other regions of the world are made for illustrative and comparative purposes.

For convenience reasons, Annex I of this thesis gathers all the legal definitions applicable to cellular therapies in the European and German laws in one list. It can be consulted in addition to the principal text of this document.

[5] 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

[6] EMEA/414188/2009, EPAR ChondroCelect

[7] Implementing the New EU Legislation on Advanced Therapy Medicinal Products, Anne Dupraz-Poiseau and Valérie Pimpaneau, RAJ Pharma (2009)

2 How to bring cell therapies to patients

Cellular therapies availability to patients depends on several factors. The main contribution is probably coming from the regulatory framework, including ethical requirements, but economy plays a substantial role as well. Indeed, the development and application of cellular therapies is most concentrated in hospitals and academic institutions due to the innovative character of these therapies and to the need of patient proximity.

Cells are complex systems and their regulation is highly dependent on their nature and function. They are very dependent on their environment (interactions between cells, with external stimuli) and nearly all modifications of this environment can influence them. Definitions and procedures need to be used for the characterisation and classification of cells in order to regulate them adequately. In the current context of the legislation, the authorisation of cellular therapies can be regulated on the European or on the national level, resulting from the inclusion in or exclusion from specific laws of specific cell populations.

Parallel access possibilities to cellular therapies for patients without marketing authorisation but via clinical trials or compassionate use programmes and their regulation will be described in chapter 2.3.

2.1 Regulatory and legal environment

This chapter gives an overview of the legal basis for the authorisation of use of cellular therapies in Europe and Germany. The application of the legislation described in this chapter for the classification and authorisation of the different cell preparations will be described in chapter 2.2.

2.1.1 Europe

In the EC the use of cells is regulated by several legislations in the form of Directives or Regulations. Directives must be transposed into national law by the MS, Regulations are directly binding. Five main legislations must be followed for the authorisation of cells and cell preparations:

1) Directive 2001/83/EC[8] (and its ATMP relevant amendment: Directive 2009/120/EC[9])
2) Regulation (EC) 726/2004[10]
3) Regulation (EC) 1394/20075[5]
4) Directive 2004/23/EC[11]
5) Directive 2002/98/EC[12]

[8] Directive 2001/83/EC of the European Parliament and of the Council of 6 November 2001 on the Community code relating to medicinal products for human use, as amended
[9] Commission Directive 2009/120/EC of 14 September 2009 amending Directive 2001/83/EC of the European Parliament and of the Council on the Community code relating to medicinal products for human use as regards advanced therapy medicinal products
[10] Regulation (EC) No 726/2004 of the European Parliament and of the Council of 31 March 2004 laying down Community procedures for the authorization and supervision of medicinal products for human and veterinary use and establishing the European Medicines Agency, as amended
[11] 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
[12] 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

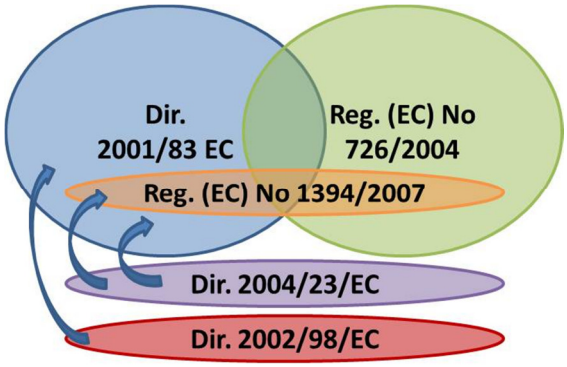

Figure 1: European legislation interaction

These five legislations set the definitions and principles for the regulation of cell-based therapies in the EC and there are interactions between them. ATMPs, as regulated in Reg. (EC) No 1394/2007, are medicinal products and both Dir. 2001/83/EC and Reg. (EC) No 726/2004 apply. Actually Reg. (EC) No 1394/2007 is a *"lex specialis"* inside Dir. 2001/83/EC.

The scopes of the legislations give guidance to find out to which extent they are applicable to the different kinds of cellular therapies. The analysis of the scopes and of the consequences on classification will be performed in chapter 2.2.

According to Art. 2 No. 1 of Dir. 2001/83/EC, it applies to "*medicinal products for human use **intended to be placed on the market** in Member States and either **prepared industrially or manufactured by a method involving an industrial process***". According to Art. 3 of the same directive, it does not apply to medicinal products intended for **clinical trials** (No. 1), "*Whole blood, plasma or **blood cells of human origin** [...]*" (No. 6), nor to ATMPs according to Art. 28 of Reg. 1394/2007 (No. 7; known as **hospital exemption**). "*Application of national legislation prohibiting or restricting the use of any specific type of human or animal cells, or the sale, supply or use of medicinal products containing, consisting of or derived from these cells*" should not be restrained by the directive (Art. 4 No. 5), meaning that national law may always be more restrictive on the use of certain kinds of cells than European law. This, in turn, could prevent cellular therapy providers to commercialise their products in some Member States although they have been granted a centralised marketing authorisation. Additionally, according to Art. 5 No. 1 of Dir. 2001/83/EC "*A Member State may, in accordance with legislation in force and to fulfil special needs, exclude from the provisions of this Directive medicinal products supplied in response to a bona fide unsolicited order, formulated in accordance with the specifications of an authorised health-care professional and for use by an individual patient under his direct personal responsibility*", which corresponds to **named-patient basis treatments**.

Art. 3 and the Annex of Reg. (EC) No 726/2004 describe its scope, mandatory for the Annex and optional for Art. 3. According to the Annex, 1a, "***Advanced therapy medicinal products** as defined in Article 2 of Regulation (EC) No 1394/2007 [...]*" are part of the mandatory scope of the regulation and have thus to be authorised according to its provisions (centralised procedure at the EMA). According to Art. 83 of Reg. (EC) No 726/2004 medicinal products falling into the scope of this regulation may be made available for **compassionate use programmes** (refer to chapter 2.3).

As a *"lex specialis"*, Reg. (EC) No 1394/2007 does not present a specific scope and applies only to **ATMPs**. Reference is made to Dir. 2004/23/EC, which has to be followed for the donation, procurement and testing of ATMPs containing human cells or tissues. Art. 28 of Reg. (EC) No 1394/2007 (which corresponds to Art. 3 No. 7 of Dir. 2001/83/EC) describes an exception for ATMPs "*which are prepared on a **non-routine basis** according to **specific quality standards**, and used within the same Member State in a hospital under the exclusive professional responsibility of a medical practitioner, in order to comply with an **individual medical prescription** for a custom-made product for an individual patient*". Those products shall be authorised nationally. Organ transplantation as well as human embryonic stem cells are not covered by the ATMP Regulation and fall in the scope of the Member States' national legislation.[13]

According to Art. 2 No. 1 of Dir. 2004/23/EC, it applies to "*the donation, procurement, testing, processing, preservation, storage and distribution of **human tissues and cells intended for human applications** and of **manufactured products derived from human tissues and cells intended for human applications***". According to Art. 2 No. 2, it does not apply to "*tissues and cells used as an **autologous graft within the same surgical procedure***" (a), to "***blood and blood components** as defined by Directive 2002/98/EC*" (b), or to organs (c). More precisely this Directive is applicable to haematopoietic peripheral blood, umbilical cord blood, bone marrow stem cells, reproductive cells, foetal tissue and cells, adult stem cells, cornea and bone but not to blood and blood products, human organs, organ tissues or tissues and cell for research purposes.[13]

According to Art. 2 No. 1 of Dir. 2002/98/EC, it applies to "*the **collection and testing of human blood and blood components**, whatever their intended purpose, and to their **processing, storage, and distribution** when **intended for transfusion***". According to Art. 2 No. 4, it does not apply to **blood stem cells**. Usually, when cell preparations are sourcing from blood they contain blood stem cells ($CD34^+$ haematopoietic stem cells). An exception would be the separation of blood Natural Killer (NK) cells or other donor lymphocyte infusions (DLIs), which would be re-transplanted. NK cell therapy is currently not widely used and the use of NK cells is allogeneic. This directive is thus of secondary interest for the purpose of this thesis.

2.1.2 Germany

The German legislation for the regulation of cells partly derives from the translation into national law of the European legislations. There are also four main laws, which need to be followed in Germany:

1) Arzneimittelgesetz (AMG)[14]
2) Transplantationsgesetz (TPG)[15]
3) Transfusionsgesetz (TFG)[16]
4) Gewebegesetz (GewG)[17]

[13] Advanced Therapy Medicinal Products in the EU: Navigating the Regulatory Maze, Ralf D. Hess, RAJ Devices (2010)
[14] Gesetz über den Verkehr mit Arzneimitteln (Arzneimittelgesetz – AMG), aktuelle gültige Fassung
[15] Gesetz über die Spende, Entnahme und Übertragung von Organen und Geweben (Transplantationsgesetz – TPG), aktuelle gültige Fassung
[16] Gesetz zur Regelung des Transfusionswesens (Transfusionsgesetz – TFG), aktuelle gültige Fassung
[17] Gesetz über die Qualität und Sicherheit von menschlichen Geweben und Zellen (Gewebegesetz), aktuelle gültige Fassung

Figure 2: German legislation and interactions

These four laws are interrelated for the regulation of cell-based therapies in Germany. The German national legislations have scopes (Anwendungsbereiche), which correspond to the scopes of the European ones as well as exceptions (Ausnahmen vom Anwendungsbereich), which correspond to scope exclusions.

The German Medicinal Products Act (AMG) is applicable for medicinal products (Arzneimittel). Section 4a Sentence 1 No. 3 AMG (§ 4a Satz 1 Nr. 3 AMG) describes exclusions to its scope for tissues which are removed from a person in order to reinsert them **without changing their material structure** into the same person **in one and the same surgical procedure** *("Gewebe, die **innerhalb eines Behandlungsvorgangs** einer Person entnommen werden, um auf diese **ohne Änderung ihrer stofflichen Beschaffenheit** rückübertragen zu werden"*). This resembles Art. 2 No. 2 of Dir. 2004/23/EC with the addition of the condition of not modifying the material structure of the procured tissue. One has to note that the definition of tissue (Gewebe) includes single cells in the German law (*"[…] sind Gewebe alle aus Zellen bestehenden Bestandteile des menschlichen Körpers, die keine Organe nach Nummer 1 sind, einschließlich einzelner menschlicher Zellen"*, refer also to annex I). Section 4b of the AMG (§ 4b AMG) describes the hospital exemption according to Art. 28 of Reg. (EC) No 1394/2007.
According to Section 1 (1) of the German Transplantation Act (§ 1 Abs. 1 TPG), it is applicable for the **donation** and **procurement** of **human organs or tissues** intended for **transfer** purposes as well as for the transfer of the organs or tissues **including the preparation of these actions** (*"die **Spende und die Entnahme** von **menschlichen Organen oder Geweben** zum Zwecke der **Übertragung** sowie für die Übertragung der Organe oder der Gewebe **einschließlich der Vorbereitung dieser Maßnahmen**. […]"*). This resembles Art. 2 No. 1 of Dir. 2004/23/EC, as described in chapter 2.1.1. The transplantation act excludes from its scope the tissues which are removed from a person in order to be reinserted back to the same person in one and the same surgical procedure (*"Gewebe, die innerhalb **ein und desselben chirurgischen Eingriffs** einer Person entnommen werden, um auf diese rückübertragen zu werden"*, § 1 Abs. 2 Nr. 1 TPG) as well as blood and blood components (*"**Blut und Blutbestandteile**"*, § 1 Abs. 2 Nr. 2 TPG). Here we find again the exclusion of autologous tissues and cells taken from and given back to the same patient within the same procedure, like in the AMG. Blood and blood components are regulated in the German Transfusion Act (Transfusionsgesetz, TFG), which is described hereafter. Blood and blood components are to be authorised on the national level and not the European one (Dir. 2002/98/EC still applies for blood cells, except stem cells). Typically, therapies derived from blood cells like HSCTs ($CD34^+$ positively selected stem cells grafts or $CD3^+/CD19^+$ cells depleted grafts) or DLIs ($CD56^+$ NK cell grafts) are in the scope of the TFG.

The German Transfusion Act does not explicitly present a scope. The TFG presents exclusions to its scope in its Section 28 (§ 28). It does not apply to autologous blood for the manufacture of tissue engineered products (*"Dieses Gesetz findet keine Anwendung auf […] **autologes Blut zur Herstellung von biotechnologisch bearbeiteten Gewebeprodukten** […]"*).

The German Tissues and Cells Act (Gewebegesetz, GewG) is implemented, among others, in the three above described national laws (AMG, TPG, TFG), which have been modified according to its provisions as can be noticed when looking at their definitions and scopes. The GewG transposes into German national law the provisions of Dir. 2004/23/EC.

2.2 Classification of cells

As can be deduced from chapter 2.1 the dependence of national laws on European laws leads to a complex inter-connexion of the national and supra-national legislations. Taken together, the definitions given in Annexes I and II and the scopes described here above help to define the right classification for cellular therapies depending on the source of the cells and their processing.

The first differentiation that should be made is the origin of the cells. Different legislations apply whether the cells are coming from blood (e.g. haematopoietic stem cell – HSC – preparations from apheresis like separated $CD34^+$ HSC) or from tissues (e.g. bone marrow cells like $CD133^+$ HSC or fat tissue cells like mesenchymal stem cells – MSC).
Cells taken from blood or cord blood are authorised nationally. More specifically, blood and cord blood isolated stem cells that are intended for haematopoietic reconstitution, e.g. $CD34^+$ HSC, are authorised according to Section 21a AMG (§ 21a AMG) as the manufacturing process of HSC is recognised as established. Additionally a manufacturing license according to Section 13 AMG (§ 13 AMG) is needed.[18] The tissue and cell procurement directive (2004/23/EC) does not apply. For blood stem cells, Dir. 2002/98/EC does not apply as described in chapter 2.1.1. But according to the definition of **somatic cell therapy medicinal products** (*"autologous (emanating from the patient himself), allogeneic (coming from another human being) or xenogeneic (coming from animals) somatic living cells, the biological characteristics of which have been substantially altered as a result of their manipulation to obtain a therapeutic, diagnostic or preventive effect through metabolic, pharmacological and immunological means"*, Dir. 2001/83/EC Annex I Part IV 2, see also Annex I) and **tissue engineered products** (*"A tissue engineered product may contain cells or tissues of human or animal origin, or both. The cells or tissues may be viable or non-viable. It may also contain additional substances, such as cellular products, bio-molecules, biomaterials, chemical substances, scaffolds or matrices"*, Reg. (EC) No 1394/2007 Art. 2 No 1 point (b), see also Annex I), cells taken from blood can also be classified as ATMPs if substantially manipulated or used in a non-homologous function (e.g. HSC with different use than haematopoietic reconstitution).[19] In that eventuality Reg. (EC) No 1394/2007 applies and foresees the application of Dir. 2004/23/EC. DLIs do not need to be authorised even on the national level and can be brought to the market in Germany based only on a manufacturing license (Herstellungserlaubnis) according to Section 13 AMG (§13 AMG).
Stem cells isolated from bone marrow (which is a tissue according to the German law) and intended for haematopoietic reconstitution, e.g. separated $CD133^+$ HSC, are authorised nationally according to Section 21a AMG (§ 21a AMG) as the manufacturing process of HSC is recognised as established. Additionally, authorisations according to Sections 20b and 20c AMG (§§ 20b und 20c AMG) are needed.[18] Manufacturing licenses (Herstellungserlaubnis) are regulated on the national level. In

[18] Der rote Ratgeber, Band 4, Rechtsrahmen für Blutstammzellen, Anforderungen und Probleme des Gewebegesetzes, DGHO
[19] Potential hämatopoetischer Stammzellen als Ausgangsmaterial für Arzneimittel für neuartige Therapien, H. Bönig, M. Heiden, J. Sch¨ttrumpf, M.M. Müller, E. Seifried, Bundesgesundheitsblatt (2011) 7

Germany the regional competent authority (Landesbehörde: Regierungspräsidium, Bezirksregierung, Gewerbeaufsichtsamt) are responsible for their granting.

For tissues and cells taken from tissues (with an intended use different from haematopoietic reconstitution) that are not prepared or altered in their composition, which are taken from a patient and given back to the same patient (autologous use) within the same surgical procedure under the professional responsibility of a physician, Dir. 2004/23/EC (Art. 2 No. 1), the AMG (§ 4a Satz 1 Nr. 3) and the TPG (§ 1 Abs. 2 Nr. 1) do not apply. Currently this exemption is mainly used for tissue grafts and organ transplantations such as coronary artery bypass grafts, where for example a vein is taken from the leg of a patient to be transplanted into the heart of the same patient during the same bypass surgical procedure.

The next dichotomy point is the processing of the cells where two cases can be identified. In the first case, the cells are processed industrially or with a not sufficiently well-known process. In the second case, they are industrially processed or the manufacturing process is not sufficiently established and well-known. One point is yet clear in both cases: the donation, procurement, and testing of the tissues and cells fall under the scope of Dir. 2004/23/EC. The issue here is that there is no legal definition of an "industrial process". During presentations held by PEI employees[20,21] the term "industrial process" (industrielles Verfahren) was described as (see also Annex II):

- sophisticated (bio-) technical or complex mechanical process
- use of high-technology or complicated process steps
- wide mechanical, mechanised and automated mass production
- production over 100 per year, processing in large level (tissue dependent)
- GMP
- production for stocking for unknown customer/patient

The interpretation of the German Medicinal Products Act also defines an industrial process as a processing performed in large-scale, in batches or series, using complex production equipment and facilities or sophisticated technical or complex mechanical processes.[22] The degree of complexity and automation of the process as well as the number of products manufactured per year seem to play an important role in these interpretations. The responsible authorities for the determination whether a process is industrial or not are the regional competent authorities (Landesbehörden) in Germany and the EMA on the European level.

If cells are manufactured using an **industrial** or **not sufficiently known process** together with **substantial manipulation** or **non-homologous use** of the cells this then implies they are classified as an ATMP and thus have to be authorised by the centralised procedure. T lymphocyte samples cultivated in large scale and primed against an antigen before being transferred to patients can fall in this category. Dir. 2004/23/EC applies for their procurement. If the ATMP fulfils the requirements of the hospital exemption (*"Any advanced therapy medicinal product, as defined in Regulation (EC) No 1394/2007, which are prepared on a **non-routine basis** according to **specific quality standards**, and used within the same Member State in a hospital under the exclusive professional responsibility of a medical practitioner, in order to comply with an **individual medical prescription** for a custom-made product for an individual patient",* as defined in Art. 28 No 2 of Reg. (EC) No 1394/2007), it qualifies for a national authorisation according to Section 4b AMG (§ 4b AMG) in Germany, thus not falling under the centralised procedure until further notice of the NCA. The hospital exemption is regarded

[20] Gewebeseminar, Regierung von Oberbayern, München, July 2008, Presentation of Prof. Dr. Tönjes
[21] TRM Seminar "Advanced Therapies", Leipzig, 17. May 2011, Presentations of Dr. Sanzenbacher
[22] Arzneimittelrecht – Kommentar, Arno Kloesel, Walter Cyran, 2010

as a transitional authorisation until sufficient data are collected to go through the centralised procedure. Within the hospital exemption, manufacturing licenses according to Section 20b or Section 13 AMG (§ 20b oder § 13 AMG) are needed as well. If the cells are **not substantially manipulated** and used in a **homologous way**, a national authorisation according to Section 21 AMG (§ 21 AMG) is possible in Germany. Section 13 AMG (§ 13 AMG) applies for the manufacturing license. T lymphocytes that are cultivated in large scale but not otherwise untouched can fall this category.
If the cells are manufactured with a **non-industrial process** or **sufficiently established process** including a **substantial manipulation** (*"cutting, grinding, shaping, centrifugation, soaking in antibiotic or antimicrobial solutions, sterilization, irradiation, cell separation, concentration or purification, filtering, lyophilization, freezing, cryopreservation, vitrification"*, Reg. (EC) No 1394/2007 Annex I, see also Annex I) within the manufacturing process or if the cells are **not used for the same essential function**, then they are classified as an ATMP as described in the preceding paragraph (e.g. bone marrow isolated stem cells that are injected in heart muscle). In case of **no substantial manipulation** and **homologous use**, the cell preparation can be authorised nationally according to Section 21a AMG (§ 21a AMG). Sections 20b and 20c AMG (§§ 20b und 20c AMG) apply as manufacturing authorisations (e.g. selected bone marrow cells intended for haematopoietic reconstitution).

Considering all the described cases, one can still speculate about the classification of cells, which would be procured from a patient and processes within one surgical procedure in order to be given back to the same patient after substantial manipulation or for a non-homologous use (e.g. $CD133^+$ cells separated from bone marrow and injected into the heart muscle within a CABG surgery procedure). This cell-based therapy should actually be classified as an ATMP as it is used in a different essential function. But the cellular product is also procured, processed and given back to the same patient within one surgical procedure, which would mean an absence of regulation (according to Section 4a AMG (§ 4a AMG)). The classification in this case depends on the way of interpretation of the interdependence between the different legislations. Does the ATMP Regulation prime over the surgical procedure? The possibility of ATMP overarching is depicted in Figure 3 and to try to propose an answer to this question, the hierarchy of the legislations will be discussed in chapter 3.2. The hospital exemption according to Section 4b AMG (§ 4b AMG) would remain a possibility in this case but Section 13 AMG (§ 13 AMG) would then apply whereas it would not in the case of a scope exclusion according to Section 4a AMG (§ 4aAMG).

The PEI proposes advice through its innovation office (Innovationsbüro), whose expertise is offered to help future applicants.[23] This innovation office offers some help for the classification of cells with two decision trees (Annex III and Annex IV). These classifications are very detailed but do not give an overall picture taking into consideration alternatives to ATMPs and how these alternatives are regulated. During the TRM Seminar "Advanced Therapies" in Leipzig on the 17th of May 2011, Dr Sanzenbacher (from the PEI) presented more general classification trees[21], from which was inspired to generate Figure 3. This flowchart proposes a summary of the possible classification ways for cells and tissues with the applicable laws on the European and German national level.

In any unclear case it is advisable for cellular therapies providers to request a classification from the CAT at the EMA, according to Art. 17 of Reg. (EC) No 1394/2007. This free procedure enables to

[23] Das Innovationsbüro am Paul-Ehrlich-Institut, B. Ziegele, L. Dahl, A.T. Muller, Bundesgesundheitsblatt 7, 2011

receive a recommendation on the classification (if ATMP or not, and if ATMP which one) within 60 days. Once the cellular product is classified it is more convenient to determine which laws apply. Since the introduction of the procedure and by November 2010, 38 classifications were already performed by the CAT.[24] However, this classification is not binding. This means that the EMA may change its opinion in time with regard to new scientific evidences. On the other hand it also means that applicants do not need to stick to the classification and may try to get their cellular product authorised in another way if they bring convincing and scientifically sound argumentation to regulatory bodies.

[24] The advanced therapy classification procedure, Overview of experience gained so far, C. Voltz-Girolt, P. Celis, M. Boucaumont, L. D'Apote, M.-H. Pinheiro, Bundesgesundheitsblatt (2010) 7

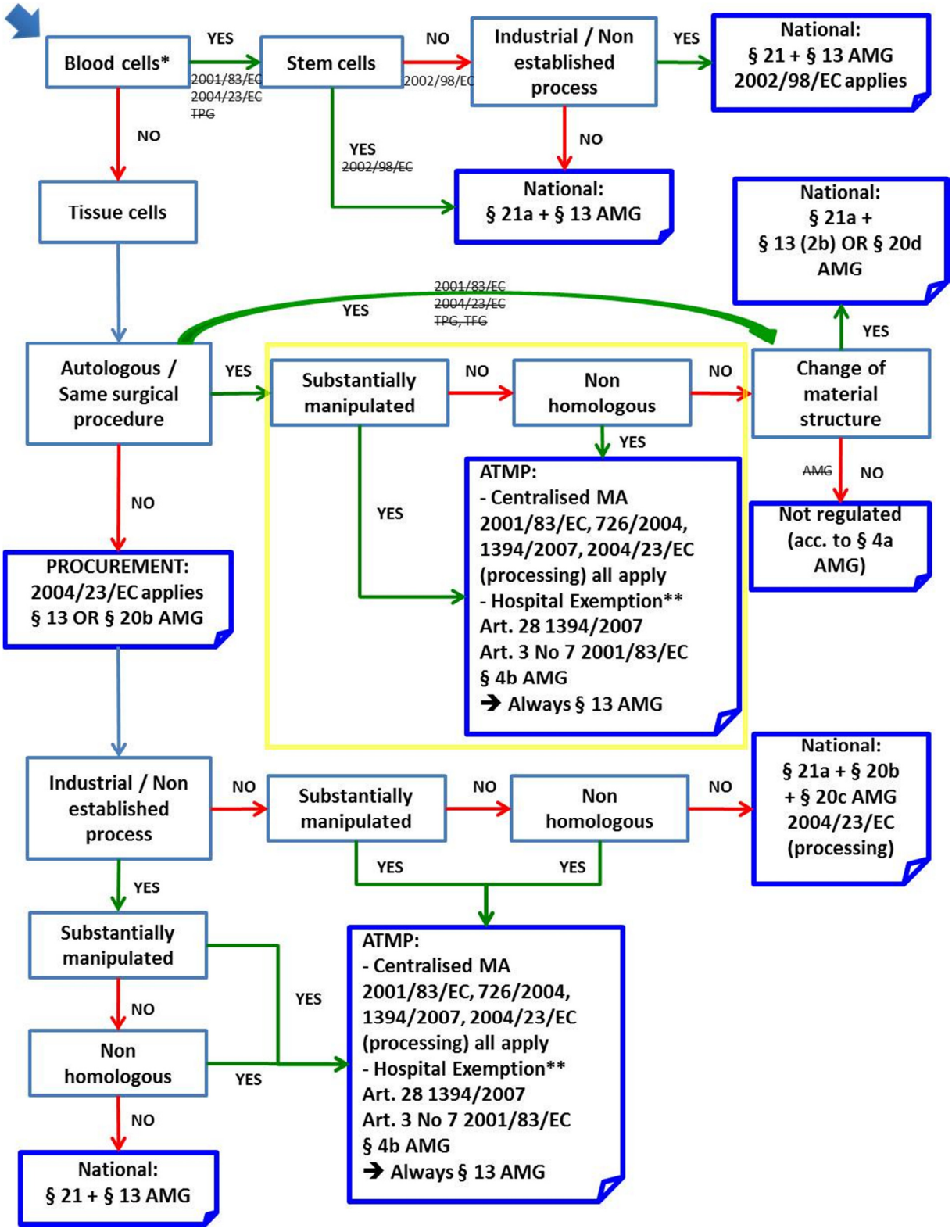

Figure 3: General cell and tissue classification flowchart

If a legislation is crossed out, it is not applicable in the considered regulatory pathway
The yellow frame represents a regulatory pathway that will be discussed in chapter 3.2
*: Blood cells, if substantially manipulated or used in a non-homologous way, are classified as ATMP, § 13 AMG applies
**: ATMP prepared on a non-routine basis according to specific quality standards, and used within the same Member State in a hospital under the exclusive professional responsibility of a medical practitioner, in order to comply with an individual medical prescription for a custom-made product for an individual patient

Besides, there is some room for interpretation as not all the terms employed in the definitions and scopes of the different European and German laws are defined themselves, as for the "**industrial process**" cited earlier.

What can be interpreted with the use of cells for "**the same essential function**" in donor and recipient? The CD133 (AC133) marker was described to be expressed on vascular endothelial growth factor receptor-2 (VEGF-2)-positive circulating endothelial progenitors (CEPs) which are recruited for neovasculogenesis.[25] It was also suggested that in adult humans CEPs may be recruited to the peripheral circulation, associated with vascular trauma.[26] A cellular therapy consisting in autologous $CD133^+$ cells separated from bone marrow and injected in the cardiac muscle after infarction during bypass surgery can thus also be interpreted as homologous use. But even non-separated bone marrow cells for the same indication have been classified as tissue-engineered product (TEP) advanced therapy by the CAT.

The "**same surgical procedure**" corresponds to the procurement and all further measures with the aim of transfer including the transfer itself that are under the responsibility of the same physician (who can also be a department head).[22] Under these premises it can be interpreted that it is possible e.g. to perform the procurement of bone marrow and the injection of separated $CD133^+$ cells into cardiac muscle during bypass surgery on separate days if under the responsibility of the same physician (e.g. department head).

Cultivation of cells and tissues seems to be considered a "**change of the material structure**" (Änderung der stofflichen Beschaffenheit) of the procured samples.[22] It is then quite evident that e.g. the positive selection of a specific cell type ($CD133^+$ cells) from bone marrow can be biologically considered as such too.

One can speak about a "**sufficiently well-known process**" if this process has been known for at least ten years in at least one Member State or if the essential processing steps are comparable to an already sufficiently well-known process.[22] In the case of immuno-magnetic cell separation, the process is considered as standard and has been established in the European Community for more than ten years. The advantage of an established process is the possibility of a simplified authorisation in Germany according to Section 21a AMG (§ 21a AMG) instead of Section 21 AMG (§ 21 AMG) as well as a cell processing authorisation according to Section 20c AMG (§ 20c AMG) instead of a manufacturing license according to Section 13 AMG (§ 13 AMG) for cells not coming from blood.

The term "**specific quality standards**" refers both to process and product quality. It especially refers to Section 14 paragraph 1 number 6a AMG (§ 14 Abs. 1 Nr. 6a AMG) where the grounds for refusing a manufacturing license are enumerated, notably if the manufacturer is not in a position to ensure that the manufacture or the testing of the medicinal products is carried out according to the **latest standards prevailing in science and technology** (*"der Hersteller nicht in der Lage ist zu gewährleisten, dass die Herstellung oder Prüfung der Arzneimittel* ***nach dem Stand von Wissenschaft und Technik*** *[…]"*) and to the eighth chapter of the medicinal products law concerning safety and quality control.[22]

Even defined terms can be subjected to different interpretations on a case-by-case basis, depending on the cellular therapy being assessed. Annex I of Reg. (EC) No 1394/2007 gives a list of "**manipulations**" (*"cutting, grinding, shaping, centrifugation, soaking in antibiotic or antimicrobial solutions, sterilization, irradiation,* ***cell separation****, concentration or purification, filtering,*

[25] Expression of VEGFR-2 and AC133 by circulating human CD34(+) cells identifies a population of functional endothelial precursors, Peichev M, Naiyer AJ, Pereira D, Zhu Z, Lane WJ, Williams M, Oz MC, Hicklin DJ, Witte L, Moore MA, Rafii S, Blood (2000)

[26] Vascular trauma induces rapid but transient mobilization of VEGFR2(+)AC133(+) endothelial precursor cells, Gill M, Dias S, Hattori K, et al. Circ Res. (2001)

lyophilization, freezing, cryopreservation, vitrification") not considered substantial, such as cell separation for example. But what effect on cells can be expected from the binding of an antibody to cellular receptors with the aim of later immuno-magnetic cell separation?

While these undefined terms can be confusing for developers of cellular therapies, they do leave a certain grade of flexibility to developers but also to the authorities. On the other hand this also creates a lack of legal certainty and may lead to local differences of interpretation throughout Europe, which cannot be the goal legislation harmonisation in the EU.

2.3 Clinical trials and compassionate use programmes

Outside the normal (marketing) authorisation pathways described in chapter 2.2 other ways exist for bringing cellular therapies to patients. These parallel ways are as controlled as an authorisation but their requirements might be easier to fulfil for a faster access of the patients to the therapies.

2.3.1 Clinical trials

It is not the aim of this thesis to describe the process of application to clinical trials. However clinical trials are one way of enabling access to cellular therapies for patients in a controlled manner. Clinical trials are regulated on the national level but efforts are made towards harmonisation with the new voluntary harmonisation procedure, which allows the equivalent of a central procedure for multi-national clinical trials in the EU. The provisions of the good clinical practices (GCP) and good manufacturing practices (GMP) have to be followed according respectively to Dir. 2001/20/EC[27] and Dir. 2003/94/EC.[28] Dir. 2004/23/EC does not exclude clinical trials from its scope.

Again, depending on the source and processing of the cells being part of the cellular therapy, different manufacturing licenses must be held by the centres involved in the clinical trials. As already mentioned, manufacturing licenses are granted by the regional competent authorities in Germany (Regierungspräsidium, Bezirksregierung). The exceptions of Section 13 (2b) AMG (§ 13 AMG (2b)) as well as the complete Section 20d AMG (§ 20d AMG) are excluded for products intended to be used in clinical trials (see Table 1). The harmonisation of different manufacturing sites can be of major importance and extremely difficult in such trials where a centralised manufacturing of the cells is not feasible.

[27] 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

[28] 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

Table 1: Manufacturing licenses

Procurement	Processing	Exception
(Cord) Blood stem cells, DLIs		§ 13 (2b) AMG, but not for clinical trials
§ 13 AMG		
Bone marrow stem cells:		§ 20d AMG, but not for clinical trials
§ 20b AMG	§ 20c AMG	
ATMPs, tissues and cells (industrial non established process)		§ 13 (2b) AMG, but **not** for manipulated or genetically engineered ATMPs and **not** for clinical trials
§ 13 AMG		
Tissues and cells (non-industrial established process)		§ 20d AMG, but not for clinical trials
§ 20b AMG	§ 20c AMG	

Clinical trials must be authorised by the NCA, which is the PEI for cellular therapies in Germany. They must also be approved by the respective ethic committee(s) and registered at the regional competent authorities. Thus clinical trials are always performed in a controlled environment (at least two regulatory bodies control them) as they are excluded when making use of exceptions to manufacturing licenses.

2.3.2 Compassionate use programmes and named-patient basis treatments

The legal basis of compassionate use in the European Union lies in Art. 83 of Reg. (EC) No 726/2004, as derogation to Art. 6 of Dir. 2001/83/EC. One can notice the missing compassionate use exemption in Dir. 2001/83/EC. According to the questions and answers document on the compassionate use of medicines in the European Union[29] "*Compassionate use is a way of making available to patients with an unmet medical need a promising medicine which has not yet been authorised (licensed) for their condition*". This kind of programmes is interesting for patients with serious and life-threatening diseases who are excluded from clinical trials for some unmet inclusion criteria (or met exclusion criteria). The use of Art. 83 (1) applies to all unauthorised medicinal products falling in the scope of Art. 3 (1) and 3 (2) of Reg. (EC) No 726/2004.[30] ATMPs fall in the mandatory scope of the regulation and thus qualify for compassionate use programmes. Another condition is that the medicinal product is either subject of a (central) marketing authorisation application in accordance with the provisions of Reg. (EC) No 726/2004 or is undergoing clinical trials.

The objectives of Art. 83 were to *"facilitate and improve the access of patients in the European Union to compassionate use programmes, favour a common approach regarding the conditions of use, the conditions of distribution and the patients targeted for the compassionate use of unauthorised new medicinal products"*, and to *"increase transparency between MSs in terms of treatment availability"*.[30] But the organisation and regulation of compassionate use are left to the Member

[29] EMEA/72144/2006 (rev), Questions and answers on the compassionate use of medicines in the European Union
[30] EMEA/27170/2006, Guideline on compassionate use of medicinal products, pursuant to Article 83 of Regulation (EC) No 726/2004

States. The Committee for Medicinal Products for Human Use (CHMP) at the EMA only gives recommendations, which are not legally binding, to complement national legislation. MSs are required to notify the EMA of any allowance of authorisation for compassionate use programmes on their territory (for standardisation purposes). National laws on compassionate use still do not exist in each MS.[31] Germany implemented a legislation on compassionate use in 2005. This was modified in 2009 to specify that medicinal products involved in CU-programmes must be free of charge. A regulation covering the administrative procedure for CU-programmes entered into force in July 2010.[32] As a comparison, France introduced CU already in 1994 with its temporary authorisations for use (autorisations temporaires d'utilisation de cohorte - ATU de cohorte). The current temporary authorisations for use document[33] also involves named-patient-ATUs. Commonly, CU-programmes must be applied for at the MS competent authority and have limited validity but can be prolonged.

As introduced by the mention of its existence in France, named-patient basis treatments (as describes in Art. 5 of Dir. 2001/83/EC) must not be confused with CU-programmes. The latter are applicable only to groups of patients. In the case of a named-patient basis treatment, the physician must directly get into contact with the manufacturer of the product. Single patients can beneficiate from new products (including cellular therapies) but the regulatory control of this option cannot be guaranteed like for CU.

CU must also be differentiated from off-label use, which is the use of an already authorised product in a not yet authorised indication. For cellular therapies, this would surely be as dangerous as using unauthorised cell preparations in an uncontrolled manner.

2.4 Consequences on the availability of cellular therapies

The availability of cellular therapies surely depends on the way they get market access. The way of getting market access depends mostly on the nature and the function of the cell preparation itself. A blood haematopoietic stem cell infusion for haematopoietic reconstitution (according to the current regulation: blood stem cells, not substantially manipulated, homologous use: Sections 13 and 21a AMG (§§ 13 und 21a AMG)) will be more easily authorised than a bone marrow haematopoietic stem cell infusion for the improvement of heart function (tissue cells, not substantially manipulated, non-homologous use: ATMP, Section 13 AMG (§ 13 AMG) and central marketing authorisation, or hospital exemption). Depending on the planned cellular therapy lower or higher hurdles will have to be overcome for obtaining first a manufacturing license (national law: Sections 13, 20b, 20c AMG (§§ 13, 20b, 20c AMG) or exemption with Sections 13 (2b) and 20d AMG (§§ 13 (2b) und 20d AMG)) and then if applicable a marketing authorisation (national law: Sections 21 and 21a AMG (§§ 21, 21a AMG) or central marketing authorisation: Art. 6 of Reg. (EC) No 726/2004, or hospital exemption). As a facilitating procedure within the ATMP Regulation, the hospital exemption could mean an easier and faster market access for ATMPs fulfilling the provisions of Art. 28 of Reg. (EC) No 726/2004 and Section 4b AMG (§ 4b AMG). As already mentioned, the exemption for autologous settings within the same surgical procedure are mainly used for organ and tissue transplantations. So if the classification of the cells being part of the cellular therapy plays such an important role, several terms used in the

[31] Jones Day Commentary, Compassionate use in Europe: a patchy framework for early market entry, August 2010
[32] Verordnung über das Inverkehrbringen von Arzneimitteln ohne Genehmigung oder ohne Zulassung in Härtefällen (Arzneimittel-Härtefall-Vorordnung – AMHV), aktuelle gültige Fassung
[33] Temporary Authorisations for Use (ATU), C. Bélorgey, Agence Française de Sécurité Sanitaire des Produits de Santé, June 2001 (English version)

legislation should be better defined or defined at all. The interpretation of these terms and thus the classification of therapeutic cells might differ between a cellular therapy provider, wanting his innovative product to get rapid market access, and the regulatory bodies, who would rather prefer the product being too highly controlled than not enough. Maybe clearer definitions could reduce argumentation time between applicants and regulators. On the other hand, different interpretation of terms could open regulatory ways of bringing cellular therapies faster to market, making them more rapidly available to patients. But different interpretation of terms or clauses (e.g. hospital exemption) by NCAs does for sure not go in the sense of European harmonisation.

The availability of cellular therapies also depends on the actors developing and bringing the cellular therapies to the market. Small and medium size biotechnology companies are the most involved in the development of cellular therapies, together with hospitals and academic institutions. Where companies can be interested in the position of marketing authorisation holder (MAH), hospitals or academic centres developing innovative therapies do certainly not aim at holding a marketing authorisation, but rather only at treating patients with their therapies. A competition is created. One has also to consider that after getting a hypothetical marketing authorisation, risk management, pharmacovigilance, and clinical follow-up activities have to be carried out. Do hospitals have the resources to manage all these post marketing surveillance activities? Additionally, they might not dispose on enough funds to be able to afford a central marketing authorisation application (MAA) at the EMA, or to maintain expensive GMP-compliant facilities and a quality system. This is certainly one of the reasons for the incentives proposed to them during the transitional period, before full application of the ATMP Regulation. By the end of this period (31 December 2011, or 31 December 2012 for TEPs), providers having cellular therapies (which now need to comply with the ATMP Regulation) legally on the market on the 30 December 2008 must own a marketing authorisation. The latter is free of charge for hospitals if the MAA is made within the transitional period. Hospitals (and SMEs) have also access to higher fee reductions than those already planned for “normal” applicants for products of particular public health interest in the community. In addition, as some of the diseases to be treated by cellular therapies are quite rare, the application for an orphan designation can bring further incentives. Nonetheless, if hospitals fail to get marketing authorisations for their concerned therapies in time, not only new cellular therapies will encounter difficulties to find their way to the patients, but also existing therapies from which patients are already beneficiating could be made unavailable. In parallel, most of the therapies hospitals have in development, also in collaboration with tissue banks, have not yet reached the step of clinical trials, which means complicated approval under the new Regulation. Or will the legislation have advanced when these products are ready for authorisation?

It should now be evaluated if collaboration between hospitals or academic institutions, developing new therapies, and the industry, contributing with funds and experience on the pharmaceutical and biological levels, could lead to the successful and rapid availability of cellular therapies.

The possibility of performing clinical trials with innovative and promising cellular therapies may then seem to be more attractive. While staying in the control of the regulators and being subjected to ethical considerations, the hurdles to overcome look more achievable. Hospitals are already involved in clinical trials and the linked activities stay in their field of competence. The setting up and maintenance (cost) of GMP facilities for obtaining the manufacturing licenses may remain a problem

for the clinics but less than a centralised authorisation procedure as hospitals have often been involved in manufacturing for several years.

Compassionate use programmes and named-patient basis treatments can certainly be seen on the same level like clinical trials regarding the requirements to fulfil to enable them. CU needs a notification of the national competent authorities (not from the ethical committee), which have the right not to allow them. A minimal control is thus guaranteed. Moreover, the manufacturing of cellular products is still subjected to the provisions of manufacturing licenses, like for clinical trials, thus also guaranteeing the quality of the product. Unlike clinical trials, for which legal basis exists in each Member State of the Community, CU-programmes still need a legal basis in some MSs. Whereas they are evidently an option for making cellular therapies available in Germany, CU-programmes do not offer the same opportunities everywhere throughout the European Community.

3 Discussion

3.1 A possible over-regulation?

Although the ATMP Regulation provided a necessary regulatory framework for advanced therapies in Europe, some reservation was expressed regarding certain requirements set and its ability to flexibly adapt to rapid changes of technologies in the field.[34] This new regulatory framework was set up as a two-stage strategy, building firstly on existing and new European legislation and secondly on more technical requirements (i.e. guidelines) that were not all completed by its implementation date.[35] Cellular therapy medicinal products (CTMPs) present some particularities that cannot be addressed by the current standards. New Requirements (including GMP requirements) need to be drawn for these particular medicines, some of which are already available or under development. Also, a right characterisation and classification of the cellular products is the key for their regulation. The CAT recognises that new strategies for development and scientific assessment of advanced therapies are needed and already made a proposition that part of the compliance requirements could be provided as post-marketing obligations.[36]

The CAT is assessing how the current regulatory framework could be made more accessible for the providers of cellular therapies.[37,38] The EMA admits the complexity of the legislation, which prevents providers bringing their therapies to the market due to a lack of resources to comply with the regulatory standards set, and wants to foster the development of advanced therapy by strengthening the dialogue with the stakeholders and the help given to them.[36,37,38] This collaboration between developers and regulators was predicted before the implementation of Reg. (EC) No 1394/2007, to ensure a "practicable" legislation.[39] In the USA, the Food and Drug Administration (FDA) has already established a dialogue with the industry ("Critical Path Initiative") to act in a pro-active fashion regarding the development of new medical products.[35]

In total only five applications for marketing authorisation of ATMPs have been sent to the EMA by July 2011 (three in 2009, one in 2010 and one in 2011), from which two received a negative draft opinion from the CHMP and two were withdrawn (including one of those having received a negative draft opinion).[40] To date, only one ATMP has found its way to a marketing authorisation, it was in June 2009 (*ChondroCelect*). This is why the CAT has adopted a work programme for 2010-2015.[41] The key issues of this programme are described like for example the very close end of the transitional period, the need for training of stakeholders and of new assessment tools or the reimbursement processes in the EU. Six objectives are drawn:

[34] Exploratory assessment of the current EU regulatory framework for development of advanced therapies, Singh P., Brévignon-Dodin L., Dash, S. P., Journal of Commercial Biotechnology (2010) 16
[35] Regulatory enablers and regulatory challenges for the development of tissue-engineered products in the EU, Laure Brévignon-Dodin, Bio-Medical Materials and Engineering (2010)
[36] Challenges with advanced therapy medicinal products and how to meet them, CAT and CAT Scientific Secretariat, Nature Reviews, Drug Discovery (2010) 9
[37] EMA gets to work on bringing more advanced therapies to market, Francesca Bruce, RAJ Pharma (2010)
[38] EMA/CAT/718256/2010, Committee for Advanced Therapies adopts five-year work programme to foster development of advanced therapies
[39] ATMP in practice: Towards a new industry landscape in tissue engineering, Brevignon-Dodin L., Singh P., Journal of Commercial Biotechnology (2008) 0
[40] EMA/CAT/576474/2011, Monthly Report, Committee for Advanced Therapies (CAT), July 2011 meeting
[41] EMA/CAT/235374/2010, Committee for Advanced Therapies (CAT) Work Programme 2010 – 2015

1) To successfully respond to implementation of the provisions of Article 29 of Regulation (EC) 1394/2007: assessment of products legally on the EU market.
2) To facilitate development of ATMPs and access to marketing authorisation procedure.
3) To promote the use of available regulatory procedures and introduce potential improvements.
4) To explore possibilities offered by the current regulatory framework when applied to ATMPs with a view to improving existing procedures and reflecting on alternative procedures.
5) To contribute to foster innovation.
6) To promote access and availability to ATMP for EU patients.

The regulation of advanced therapies should be more practicable once the intentions of this work programme have been achieved. However, by this time important damage may already be done as cellular therapies developers may already have abandoned their efforts due to insurmontable hurdles. The clinical routine in the hospitals performing the cellular therapies must be taken into account by the revision of the legislation. The aim of future discussions will be to adapt the regulatory framework and make it evaluate to enable the right regulation of cell-based therapies by the regulatory bodies while not hindering development and the innovation potential of the industry and academic institutions. [42]

The EMA and the CAT are not working alone; a report on the situation of ATMP Regulation is expected from the EU Commission for December 2012.[34]

3.2 The hierarchy in the European legislation

Is there a hierarchy, a chronological or rational order in which the legislations have to be read? Reg. (EC) No 1394/2007 is a "lex specialis" in the context of Dir. 2001/83/EC. Logically, if this Directive is not applicable, nor is the Regulation. Even the definitions used in the ATMP Regulation base on those of Dir. 2001/83/EC and Dir. 2004/23/EC (Art. 2 No. 1). Coming back to Art. 2 No. 1 of Dir. 2001/83/EC, as already mentioned in chapter 3.1.1, it applies to *"medicinal products for human use intended to be **placed on the market** in Member States […]"*. There is no definition of "placed on the market" in the field of medicinal products in the European law. The field of medical devices brings a definition in Dir. 93/42/EEC[43] (*"´placing on the market´ means the first making available in return for payment or free of charge of a device other than a device intended for clinical investigation, with a view to distribution and/or use on the Community market, regardless of whether it is new or fully refurbished"*, Dir. 93/42/EEC Art. 1 (h), see also Annex I) and its transposition into the German national law, the Medical Device Act (Medizinproduktegesetz[44], see also Annex I). This term has been interpreted by the European Commission[45] in the way that *a product must be **made available** with a view to distribution or use*.

Many of the advanced therapy products developed in Europe are intended for autologous use. Autologous cell therapies in the same surgical procedure cannot be considered placed on the market. The donated cells are not made available as they stay the propriety of the donor/recipient even

[42] Erfahrungsbericht aus dem Ausschuss für neuartige Therapien (CAT), M. Reiss, I.C. Büttel, C.K. Schneider, Bundesgesundheitsblatt (2011) 7
[43] Council Directive 93/42/EEC of 14 June 1993 concerning medical devices, as amended
[44] Gesetz über Medizinprodukte (Medizinproduktegesetz - MPG), aktuelle gültige Fassung
[45] European Commission, Interpretative Document of the Commission's Services: Placing on the Market of Medical Devices, 16 November 2010

during their processing and may not be used for any other purpose than the autologous application. One can represent this schematically with a decision tree and illustrate it with examples.

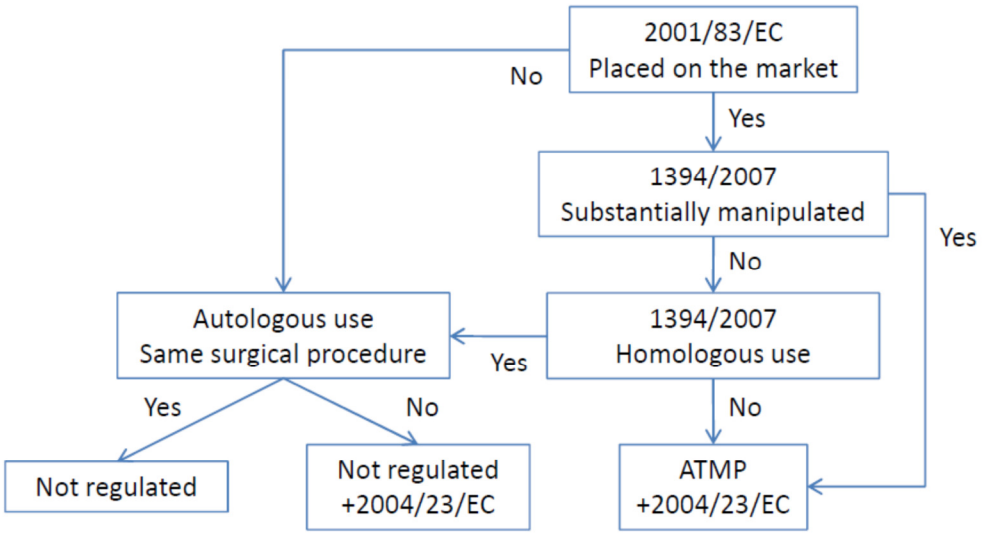

Figure 4: ATMP classification decision tree (source: modified from Kenneth Kleinhenz[46])

In Figure 4, "Not regulated" refers to the European legislation. Let us consider the example of the autologous transplantation of $CD133^{+}$ haematopoietic stem cells separated from bone marrow into cardiac muscle during a bypass surgical procedure (hypothesis: cell separation is not considered a substantial manipulation). If not considering the placement on the market, the decision tree would be read as follows (Figure 5).

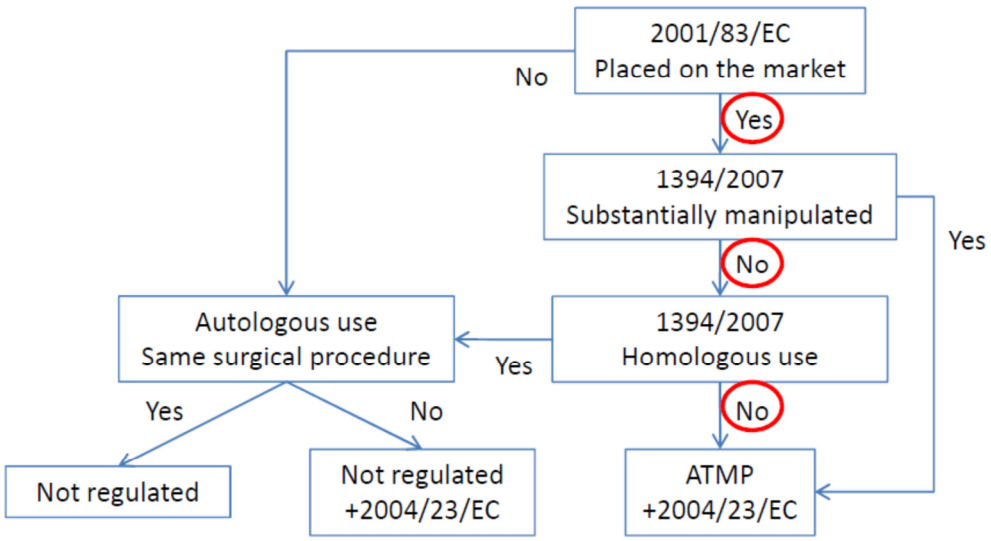

Figure 5: Example without consideration of the placement on the market

The cellular therapy presented in the example is classified as an ATMP. It has to be authorised through the centralised procedure. Dir. 2004/23/EC applies. The hospital exemption could then be a solution. For the same example but considering that the cellular therapy is not actually placed on the market, the decision tree would be read as follows – Figure 6).

[46] Navigating the Cell Therapy Regulatory Pathway: An Alternative Solution, Kenneth K. Kleinhenz, Personal communication

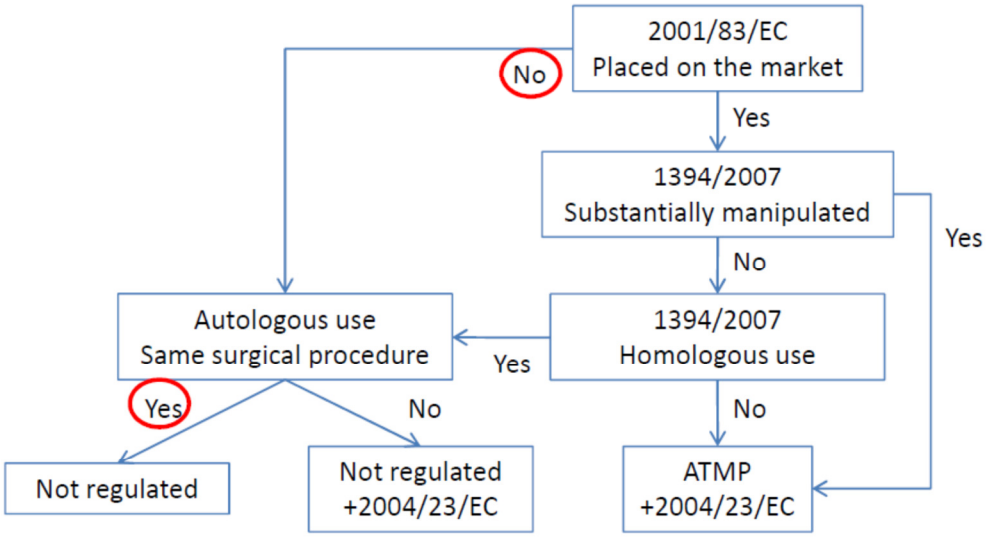

Figure 6: Example with consideration of non-placement on the market

The cellular therapy is not regulated on the European level and Dir. 2004/23/EC is not applicable in this autologous setting. This would be the less burdensome scheme for hospitals carrying out the cellular therapy (and thus the best available for patients) with an authorisation pathway on the national level probably not even involving manufacturing licenses.

In the USA, human cell and tissue products (HCT/Ps) are regulated under 21 CFR 1271. The regulators there have already foreseen the case of autologous use in the same surgical procedure. According to 21 CFR 1271.15 (b) *"You are not required to comply with the requirements of this part if you are an establishment that removes HCT/P's from an individual and implants such HCT/P's into the same individual during the same surgical procedure"*. The "practice of medicine" principle also facilitates the authorisation of HCT/Ps in the USA.

3.3 An open door for medical device clinical trials?

Going further with the example laid down in chapter 3.2, the fact that there are not regulated cells opens the possibility of performing clinical trials in the medical device setting according to the provisions of Dir. 93/42/EEC. In the previous example, the separation of the cells is performed with a CE-certified medical device. The Medical Device Directive (MDD) gives the opportunity to carry out clinical trials with already certified devices in order to extend their clinical application (intended use). The object of the clinical trials would then not be the cells separated with the medical device, as they are not regulated (outside medicinal product clinical trials), but the medical device itself. The provisions of clinical trials with medical devices are as demanding as those for medicinal products thus still guaranteeing the safety of the patients. But the subsequent marketing authorisation as a medical device application (with a clinical indication for patients in its intended use) would certainly be less burdensome than an application for an ATMP.

Clinical trials with medical devices must be applied for at the national competent authority (the BfArM gives the authorisations in Germany) and the responsible ethic committee(s). The manufacturer himself applies the CE-mark on the device and declares its conformity to the Essential Requirements of Dir. 93/42/EEC, which corresponds to the marketing authorisation for the European market. Depending on the classification of the medical device a Notified Body must be involved in

the CE-marking of the medical device or not. High-risk products (class III) need the involvement of the Notified Body. Besides, Notified Bodies also monitor and inspect the maintenance of the quality management system (according to ISO 13485) of the manufacturer, if applicable.

But can the fact of having non-regulated cells in a medical device clinical trial make omit the fact of having cells at all? The scope of Dir. 93/42/EEC clearly excludes *"human blood, blood products, plasma or **blood cells of human origin** or to devices which incorporate at the time of placing on the market such blood products, plasma or cells, with the exception of devices referred to in paragraph 4a"* (Art. 1 No. 5 (e)) as well as *"**transplants or tissues or cells of human origin** nor to products incorporating or derived from tissues or cells of human origin, with the exception of devices referred to in paragraph 4a"* (Art. 1 No. 5 (f)). If considering a cell separation step being part of a surgical procedure with an autologous use of the separated cells, the only "manipulation" taking place is the action of the medical device, which could as such be assessed in a clinical trial. So there is no cellular product manufacturing in this case, but a continuous surgical procedure (involving the use of a medical device) carried out under the responsibility of the treating physician. The cellular product is then not being placed on the market. A convincing argumentation still needs being developed but such an approach should be feasible.

3.4 Who is going to pay?

Making cellular therapies available to patients in the regulatory way is only the first step. The therapies must also be affordable for the patients and for the national healthcare systems. Reimbursement is a national issue, which each Member State manages on its own according to the healthcare system in place. The requirements of the assessing bodies must be considered.

The development of cellular therapies is very expensive and the developers need to compensate their investments. But to be reimbursed, cellular therapies have to show their efficacy and the benefits for the patients. The assessment of the benefits is performed nationally. In Germany, it seems like the *Gemeinsamer Bundesausschuss* (GBA), the responsible organism for reimbursement issues in Germany, has decided to consider ATMPs as method more than as medicinal product.
Outpatient and inpatient regulations have to be distinguished. While new examination and treatment methods (Neue Untersuchung- und Behandlungsmethoden – NUB) are considered uneconomical in principle (exceptions do exist) in the outpatient case, they can be reimbursed prior GBA investigation in the inpatient case, as hospitals can agree on treatment remuneration with local health insurances. Thus the German healthcare system guarantees early access to innovative products during the registration process of NUB into the diagnosis-related group (DRG) system in the inpatient setting. Indeed, reimbursement has to by applied for in the DRG system and there usually exists no DRG for a new method. Up to three years can pass until a new method gets registered in the DRG catalogue.[47] For example, reimbursement basis exist in Germany for bone marrow transplantation or stem cell transfusion (A04A: *Knochenmarktransplantation / Stammzelltransfusion, allogen, außer bei Plasmozytom odermit Graft-versus-host-Krankheit Grad III und IV, mit In-vitro-Aufbereitung*; Bewertungsrelation 31.641 = 93 778.23 Euros).

[47] Erstattungsfähigkeit neuartiger Arzneimitteltherapien, A.P.F. Ehlers, A. Wenke, Bundesgesundheitsblatt (2011) 7

Decisions need to be taken in other Member States and the reimbursement situation (not only for cellular therapies) will remain a patchwork until harmonisation of this process is decided on the community level.

Patients participating in clinical trials receive the cellular therapies free of charge as for all clinical trials throughout Europe. In Germany, patients participating in compassionate use programmes will also receive the cellular therapy free of charge. In other countries, even a CU legislation is missing so no statement can actually be made for Europe as CU is regulated nationally. On the other hand, manufacturers of cellular products having to make their products available free of charge for clinical trials and CU may encounter difficulties as the work they involved in the development of their products gets no retribution by that time and this may compromise their existence.

As a comparison, in the USA, HSCT is recognised as acceptable therapy for patients and reimbursed by governmental and private payers since about 1980. In-between cells and cell therapies are regulated as pharmacological drugs, which provided clarification regarding the applicable regulations.[48] The payments follow the DRG strategy for inpatient services and the ambulatory payment classification (APC) for outpatient services. Reimbursement codes need to be applied for and reimbursement rates fixed for new therapies, which is currently occurring for *Provenge* (Dendreon), an autologous dendritic cell therapy for use in advanced prostate cancer. Developers of therapies need to determine very early if an appropriate code exists and which rates it has, else new codes must be created with new rates, which is quite a high hurdle.

3.5 Patient awareness

In the European Union, medicinal products that have not yet been granted a marketing authorisation cannot be advertised. The same applies to clinical trials and compassionate use programmes. A key element to make cellular therapies available to the patients who need them is that these patients are aware of the existence of such a therapy. As there is no advertising possible, it is important that physicians implicated in clinical trials or CU processes, as well as hospital surgery personnel who are aware of cellular therapies being carried out have a good communication with their patients. They are the only link between innovative and promising new therapies and the patients who need them.

The participation of the patients in the development of innovative cellular therapies (as well as for all treatments) is essential for the improvement of their treatments. The creation of the Patients and Consumers Working Party (PCWP) at the EMA[49] will surely be beneficial for the communication between patient organisation and regulatory bodies as well as patient awareness about available therapies.

[48] Hematopoietic Stem Cell Transplantation and Implications for Cell Therapy Reimbursement, Richard T. Maziarz and Dawn Driscoll, Cell Stem Cell (2011) 8

[49] Participation of patients in the development of advanced therapy medicinal products, F. Bignami, A.J. Kent, M. Lipucci di Paola, N. Meade, Bundesgesundheitsblatt (2011) 7

4 Conclusion and outlook

To respond to a lack of regulation of innovative therapies in Europe and the linked abuses with stem cell therapies performed without any substantiated safety or efficacy data, a new regulation for advanced therapy medicinal products was implemented in December 2008. Together with the national legislation this Regulation brought a harmonised framework for the control of cellular therapies among other advanced therapies.

Depending on the classification of a cellular therapy, the regulatory pathway for its authorisation differs. A national authorisation (also the case for clinical trials and compassionate use) seems more achievable than a centralised marketing authorisation. Some escape ways can be found with specific interpretations of unclear terms or by making use of the hospital exemption. A new approach, namely the authorisation of cellular therapies within a surgical procedure in an autologous setting as a medical device application could also reveal promising and facilitate the market access to some cellular products.

The new European framework is maybe still too rigid and not yet adapted to this new class of advanced therapy products that need more tailored requirements. The Committee for Advanced Therapies at the EMA is now reviewing the legislation and working towards more collaboration with the stakeholders and a report from the European Community is awaited in 2012. The situation has moved from the availability to patients of not always safe and efficient cellular therapies to the high hurdles to overcome to get a safe and efficient therapy onto the market and might end up with a limited availability of meaningful and promising therapies. A compromise needs to be found between adequate control of innovative therapies and acceptable times to market entry (that is to say patient availability). The current and future publication of tailored guidelines for the development of advanced therapies will surely contribute to a more adapted regulatory frame.

But after overcoming the regulatory hurdles, cellular therapies will have to find their way through reimbursement so that they are not staying just nice theoretical therapeutic possibilities that nobody can afford using. In this domain, which is the responsibility of each Member State, answer still need to be given and a European harmonisation process of the general reimbursement issue might be helpful in the future. Finally, patients may never have access even to an existing cellular therapy if they are not aware of its existence. Information channels must go through the treating physicians and surgeons who are the key elements for circulating information to their patients. The fact that patient organisations have now their own working party at the EMA with the PCWP will probably be beneficial for information dissemination.

Developers must find the right combination between several parameters to optimise the availability of their cellular therapies for patients:

- collaboration with the regulators
- choice of the right regulatory pathways
- orientation towards the more easy ways through interpretation of not clarified terms
- exploration of new ways of authorisations
- early enquiry for reimbursement strategies
- collaboration with physicians to influence them towards the information of patients

Taking a glance overseas might inspire European legislation, as e.g. the FDA accepts to authorise cell separating medical devices with clinical indications without regulating directly the cells separated with the device. The European way of regulation would need to be revisited but medical device application could be one option in the future of cellular therapy regulation, at least in the field of autologous and directed (known recipient) allogeneic therapies.

5 Summary

Cellular therapies have been rapidly evolving in the last years and the opposition between regulation and scientific innovation is seemingly increasing since the introduction of the new Advanced Therapy Medicinal Products (ATMP) Regulation in Europe. On the one hand it is clear that such revolutionary therapies need to be controlled having in mind the experimental and scientifically unsubstantiated clinical applications that used to be performed with stem cell therapies in Europe, and especially in Germany such as the injection of bone marrow stem cells in the brain supposedly to treat Parkinson's disease. On the other hand the plan enunciated by the Committee for Advanced Therapies (CAT) to foster scientific innovation in the field of advanced therapies does not seem achieved taking account of the one and only ATMP that was granted a centralised marketing authorisation since 2009 and the stagnation or even decrease in the yearly ATMP applications.

Depending on the nature and the function of the cells involved in a cellular therapy a classification of the latter is made determining the way of authorisation it has to follow: centralised marketing authorisation for ATMPs or national accreditation for blood stem cells for example ($CD34^+$ haematopoietic stem cell grafts after chemotherapy). Some provisions of the legislation regarding cellular therapies leave some room for interpretation, which can in turn mean that developers and regulators may come to another classification of a cellular therapy and thus another way of authorisation. This can be an opportunity for developers if they can achieve acceptance of their argumentation by the regulators. The complexity of the European legislation can also lead to misinterpretation if the law texts are not read in the right order. Starting a classification directly reading the ATMP Regulation will certainly lead to an ATMP classification whereas starting with the medicinal product mother Directive could lead to scope exclusion (e.g. for autologous bone marrow isolated stem cells used in the same surgical procedure that are not actually placed on the market). The impact of the classification of the cells on the availability delay of the cellular product is determinant. A maybe faster and simpler way of bringing cellular therapies to the market would be the use of the medical device route. Cells that are gained or processed through a medical device could be the object of an authorisation together with this device, which would have a clinical end point in its intended use. Thus medical device clinical investigations could be performed and therapies linked to the use of the medical device could be authorised on the European market under the CE mark. The medical device authorisation pathway is simpler but still guarantees quality, safety and efficacy.

But there are other ways than a marketing authorisation to make cellular therapies available to patients such as the participation in clinical trials or in compassionate use programmes. Whereas the requirements and provisions for clinical trials are harmonised on the European level, compassionate use programmes remain in the responsibility of the Member State and not everyone have implemented a legislation to regulate them.

When the cellular therapy is on the market, it does not mean that patients directly have access to it. For products with marketing authorisations, adequate reimbursement strategies must be set-up so that patients and national healthcare systems can afford use them. Clinical trials do not present this drawback for patients, as the access to the cellular product being assessed is free of charge for the patients. So it is as well within compassionate use programmes in Germany. On the other hand, what

is an advantage for patients leads to the absence of retribution for the developers of the therapies, which may threaten their existence.

Thus, improving the availability of cellular therapies to patients in Europe and Germany is mainly but not only a regulatory task.

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Declaration

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

Düsseldorf den Christophe Klumb

Annex I: Legal definitions

1. ***Active substance*** *[Section 4 (19) German Medicinal Products Act], see also No. 50*

Active substances are substances which are intended for use as medically active constituents in the manufacture of medicinal products or which, through their use in the manufacture of medicinal products, are intended to become medically active substances.

2. ***Advanced therapy medicinal product*** *[Dir. 2001/83/EC, Art. 1 No. 4a]*

A product as defined in Article 2 of Regulation (EC) No 1394/2007 of the European Parliament and of the Council of 13 November 2007 on advanced therapy medicinal products

3. ***Advanced therapy medicinal product*** *[Reg. (EC) No 1394/2007, Art. 2 No. 1 point (a)]*

´Advanced therapy medicinal product´ means any of the following medicinal products for human use:
— a gene therapy medicinal product as defined in Part IV of Annex I to Directive 2001/83/EC,
— a somatic cell therapy medicinal product as defined in Part IV of Annex I to Directive 2001/83/EC,
— a tissue engineered product as defined in point (b)

4. ***Advanced therapy medicinal product*** *[Section 4 (9) German Medicinal Products Act], see also No. 6*

Advanced therapy medicinal products are gene therapy medicinal products, somatic cell therapy medicinal products or tissue engineered products pursuant to Article 2, paragraph 1, letter a of Regulation (EC) No. 1394/2007 of the European Parliament and the Council of 13th November 2007 on advanced therapy medicinal products and amending Directive 2001/83/EC and Regulation (EC) No. 726/2004 (OJ EC No. L 324 of 10th December 2007, p. 121).

5. ***Arzneimittel*** *[§ 2 Abs. 1 AMG], see also No. 30*

Arzneimittel sind Stoffe und Zubereitungen aus Stoffen,
1. die zur Anwendung im oder am menschlichen oder tierischen Körper bestimmt sind und als Mittel mit Eigenschaften zur Heilung oder Linderung oder zur Verhütung menschlicher oder tierischer Krankheiten oder krankhafter Beschwerden bestimmt sind oder,
2. die im oder am menschlichen oder tierischen Körper angewendet oder einem Menschen oder einem Tier verabreicht werden können, um entweder
a) die physiologischen Funktionen durch eine pharmakologische , immunologische oder metabolische Wirkung wiederherzustellen, zu korrigieren oder zu beeinflussen oder
b) eine medizinische Diagnose zu erstellen.

6. ***Arzneimittel für neuartige Therapien*** *[§ 4 Abs. 9 AMG], see also No. 4*

Arzneimittel für neuartige Therapien sind Gentherapeutika, somatische Zelltherapeutika oder biotechnologisch bearbeitete Gewebeprodukte nach Artikel 2 Absatz 1 Buchstabe a der Verordnung (EG) Nr. 1394/2007 des Europäischen Parlaments und des Rates vom 13. November 2007 über Arzneimittel für neuartige Therapien und zur Änderung der Richtlinie 2001/83/EG und der Verordnung (EG) Nr. 726/2004 (ABI. L 324 vom 10.12.2007, S. 121).

7. ***Allogeneic use*** *[Dir. 2004/23/EC Art 3 (p)]*

´allogeneic use´ means cells or tissues removed from one person and applied to another;

8. ***Autologous transfusion*** *[Dir. 2002/98/EC Art. 3 (d)]*

´autologous transfusion´ shall mean transfusion in which the donor and the recipient are the same person and in which pre-deposited blood and blood components are used;

9. ***Autologous use*** *[Dir. 2004/23/EC Art. 3 (q)]*

´autologous use´ means cells or tissues removed from and applied in the same person.

10. ***Blood component*** *[Dir. 2002/98/EC Art. 3 (b)]*

´blood component´ shall mean a therapeutic constituent of blood (red cells, white cells, platelets, plasma) that can be prepared by various methods;

11. ***Blood product*** *[Dir. 2002/98/EC Art. 3 (c)]*

´blood product´ shall mean any therapeutic product derived from human blood or plasma;

12. ***Blood preparations*** *[Section 4 (2) German Medicinal Products Act], see also No. 14*

Blood preparations are medicinal products which are or which contain, as medically active substances, blood, plasma or serum conserves obtained from blood, blood components or preparations made from blood components.

13. ***Blutprodukte*** *[§ 2 Satz 1 Nr. 3 TFG]*

[..] sind Blutprodukte Blutzubereitungen im Sinne von § 4 Abs. 2 des Arzneimittelgesetzes, Sera aus menschlichem Blut im Sinne des § 4 Abs. 3 des Arzneimittelgesetzes und Blutbestandteile, die zur Herstellung von Wirkstoffen oder Arzneimitteln bestimmt sind.

14. ***Blutzubereitungen*** *[§ 4 Abs. 2 AMG], see also No. 12*

Blutzubereitungen sind Arzneimittel, die aus Blut gewonnene Blut-, Plasma- oder Serumkonserven, Blutbestandteile oder Zubereitungen aus Blutbestandteilen sind oder als Wirkstoffe enthalten.

15. ***Cells*** *[Dir. 2004/23/EC Art. 3 (a)]*

´cells´ means individual human cells or a collection of human cells when not bound by any form of connective tissue;

16. ***Direct use*** *[Dir. 2006/17/EC Art. 1 (c)]*[50]

´direct use´ means any procedure where cells are donated and used without any banking;

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

17. ***Engineered*** *[Reg. (EC) No 1394/2007 Art. 2 No. 1 point (c)]*

Cells or tissues shall be considered ´engineered´ if they fulfil at least one of the following conditions:
— the 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.

18. ***Entnahme*** *[§ 1a Satz 1 Nr. 6 TPG]*

[…] ist Entnahme die Gewinnung von Organen oder Geweben;

19. ***Fertigarzneimittel*** *[§ 4 Abs. 1 AMG], see also No. 20*

Fertigarzneimittel sind Arzneimittel, die im Voraus hergestellt und in einer zur Abgabe an den Verbraucher bestimmten Packung in denVerkehr gebracht werden oder andere zur Abgabe an Verbraucher bestimmte Arzneimittel, bei deren Zubereitung in sonstiger Weise ein industrielles Verfahren zur Anwendung kommt oder die, ausgenommen in Apotheken, gewerblich hergestellt werden. Fertigarzneimittel sind nicht Zwischenprodukte, die für eine weitere Verarbeitung durch einen Hersteller bestimmt sind.

20. ***Finished medicinal products*** *[Section 4 (1) German Medicinal Products Act], see also No. 19*

Finished medicinal products are medicinal products which are manufactured beforehand and placed on the market in packaging intended for distribution to the consumer or other medicinal products intended for distribution to the consumer, in the preparation of which any form of industrial process is used or medicinal products which are produced commercially, except in pharmacies. Finished medicinal products are not intermediate products intended for further processing by a manufacturer.

21. ***Gewebe*** *[§ 1a Satz 1 Nr. 4 TPG]*

[…] sind Gewebe alle aus Zellen bestehenden Bestandteile des menschlichen Körpers, die keine Organe nach Nummer 1 sind, einschließlich einzelner menschlicher Zellen;

22. ***Gewebezubereitungen*** *[§ 4 Abs. 30 AMG], see also No. 47*

Gewebezubereitungen sind Arzneimittel, die Gewebe im Sinne von § 1a Nr. 4 des Transplantationsgesetzes sind oder aus solchen Geweben hergestellt worden sind. Menschliche Samen- und Eizellen, einschließlich imprägnierter Eizellen (Keimzellen), und Embryonen sind weder Arzneimittel noch Gewebezubereitungen.

23. ***Herstellen*** *[§ 4 Abs. 14 AMG], see also No. 27*

Herstellen ist das Gewinnen, das Anfertigen, das Zubereiten, das Be- oder Verarbeiten, das Umfüllen einschließlich Abfüllen, das Abpacken, das Kennzeichnen und die Freigabe.

24. ***Human application*** *[Dir. 2004/23/EC Art. 3 (l)]*

´human application´ means the use of tissues or cells on or in a human recipient and extracorporal applications;

25. ***Inverkehrbringen*** *[§ 4 Nr. 17 AMG], see also No. 28*

Inverkehrbringen ist das Vorrätighalten zum Verkauf oder zu sonstiger Abgabe, das Feilhalten, das Feilbieten und die Abgabe an andere.

26. ***Inverkehrbringen*** *[§ 3 Nr. 11 MPG]*

Inverkehrbringen ist jede entgeltliche oder unentgeltliche Abgabe von Medizinprodukten an andere. Erstmaliges Inverkehrbringen ist die erste Abgabe von neuen oder als neu aufbereiteten Medizinprodukten an andere im Europäischen Wirtschaftsraum. Als Inverkehrbringen nach diesem Gesetz gilt nicht
a) die Abgabe von Medizinprodukten zum Zwecke der klinischen Prüfung,
b) die Abgabe von In-vitro-Diagnostika für Leistungsbewertungsprüfungen,
c) die erneute Abgabe eines Medizinproduktes nach seiner Inbetriebnahme an andere, es sei denn, dass es als neu aufbereitet oder wesentlich verändert worden ist.
Eine Abgabe an andere liegt nicht vor, wenn Medizinprodukte für einen anderen aufbereitet und an diesen zurückgegeben werden.

27. ***Manufacturing*** *[Section 4 (14) German Medicinal Products Act], see also No. 23*

Manufacturing is the producing, preparing, formulating, treating or processing, filling as well as decanting, packaging, labelling and release of medicinal products.

28. ***Marketing*** *[Section 4 (17) German Medicinal Products Act], see also No. 25*

Marketing is the keeping in stock for sale or for other forms of supply, the exhibiting and offering for sale and the distribution to others.

29. ***Medicinal product*** *[Dir. 2001/83/EC Art. 1 No. 2]*

(a) Any substance or combination of substances presented as having properties for treating or preventing disease in human beings; or
(b) Any substance or combination of substances which may be used in or administered to human beings either with a view to restoring, correcting or modifying physiological functions by exerting a pharmacological, immunological or metabolic action, or to making a medical diagnosis.

30. ***Medicinal product*** *[Section 2 (1) German Medicinal Products Act], see also No. 5*

Medicinal products are substances or preparations made from substances which:
1. are intended for use on or in the human or animal body and are intended for use as remedies with properties for the curing, alleviating or preventing of human or animal diseases or disease symptoms or
2. can be used in or on the human or animal body or can be administered to a human being or an animal, either:
a) to restore, correct or to influence the physiological functions through a pharmacological,

immunological or metabolic effect, or
b) to make a medical diagnosis.

31. ***Nicht routinemäßig hegestellt*** *[§ 4b Abs. 2 AMG], see also No. 35*

Nicht routinemäßig hergestellt im Sinne von Absatz 1 Satz 1 Nummer 2 werden insbesondere Arzneimittel,
1. die in geringem Umfang hergestellt werden, und bei denen auf der Grundlage einer routinemäßigen Herstellung Abweichungen im Verfahren vorgenommen werden, die für einen einzelnen Patienten medizinisch begründet sind, oder
2. die noch nicht in ausreichender Anzahl hergestellt worden sind, so dass die notwendigen Erkenntnisse für ihre umfassende Beurteilung noch nicht vorliegen.

32. ***Organ*** *[Dir. 2004/23/EC Art. 3 (e)]*

´organ´ means a differentiated and vital part of the human body, formed by different tissues, that maintains its structure, vascularisation and capacity to develop physiological functions with an important level of autonomy;

33. ***Organe*** *[§ 1a Satz 1 Nr. 1 TPG]*

[…] sind Organe, mit Ausnahme der Haut, alle aus verschiedenen Geweben bestehenden Teile des menschlichen Körpers, die in Bezug auf Struktur, Blutgefäßversorgung und Fähigkeit zum Vollzug physiologischer Funktionen eine funktionale Einheit bilden, einschließlich der Organteile und einzelnen Gewebe eines Organs, die zum gleichen Zweck wie das ganze Organ im menschlichen Körper verwendet werden können, mit Ausnahme solcher Gewebe, die zur Herstellung von Arzneimitteln für neuartige Therapien im Sinne des § 4 Absatz 9 des Arzneimittelgesetzes bestimmt sind;

34. ***Placing on the market*** *[Dir. 93/42/EEC Art. 1 (h)]*

´placing on the market´ means the first making available in return for payment or free of charge of a device other than a device intended for clinical investigation, with a view to distribution and/or use on the Community market, regardless of whether it is new or fully refurbished;

35. ***Prepared on a non-routine basis*** *[Section 4b (2) German Medicinal Products Act], see also No. 31*

Prepared on a non-routine basis pursuant to sub-section 1 sentence 1 number 2 are, in particular, medicines:
1. which are manufactured in small quantities, and in the case of which, based on a routine manufacturing procedure, variations in the procedure which are medically justified for an individual patient, are carried out, or
2. which have not yet been manufactured in sufficient quantities so that the necessary data to enable a comprehensive assessment are not yet available.

36. ***Procurement*** *[Dir. 2004/23/EC Art. 3 (f)]*

´procurement´ means a process by which tissue or cells are made available;

37. ***Processing*** *[Dir. 2004/23/EC Art. 3 (g)]*

´processing´ means all operations involved in the preparation, manipulation, preservation and packaging of tissues or cells intended for human applications;

38. ***Preservation*** *[Dir. 2004/23/EC Art. 3 (h)]*

´preservation´ means the use of chemical agents, alterations in environmental conditions or other means during processing to prevent or retard biological or physical deterioration of cells or tissues;

39. ***Produkte menschlicher Herkunft*** *[§ 2 Satz 1 Nr. 1 AMWHV]*[51]

[…] sind Produkte menschlicher Herkunft für die Arzneimittelherstellung bestimmte Wirkstoffe im Sinne von § 4 Abs. 19 des Arzneimittelgesetzes, die menschlicher Herkunft sind, oder Stoffe im Sinne von § 3 Nr. 3 des Arzneimittelgesetzes, die menschlicher Herkunft sind, in bearbeitetem oder unbearbeitetem Zustand, ausgenommen Blutprodukte im Sinne von § 2 Nr. 3 des Transfusionsgesetzes in der Fassung der Bekanntmachung vom 28. August 2007 (BGBl. I S. 2169) und andere Blutbestandteile,

40. ***Somatic cell therapy medicinal product*** *[Dir. 2001/83/EC Annex I Part IV 2.]*

For the purposes of this Annex, somatic cell therapy medicinal products shall mean the use in humans of autologous (emanating from the patient himself), allogeneic (coming from another human being) or xenogeneic (coming from animals) somatic living cells, the biological characteristics of which have been substantially altered as a result of their manipulation to obtain a therapeutic, diagnostic or preventive effect through metabolic, pharmacological and immunological means. This manipulation includes the expansion or activation of autologous cell populations ex vivo (e.g., adoptive immuno-therapy), the use of allogeneic and xenogeneic cells associated with medical devices used ex vivo or in vivo (e.g., micro-capsules, intrinsic matrix scaffolds, bio-degradable or not).

41. **Stoffe** [§ 3 Satz 1 Nr. 3 AMG], see also No. 44

[…] Tierkörper, auch lebender Tiere, sowie Körperteile, -bestandteile und Stoffwechselprodukte von Mensch oder Tier in bearbeitetem oder unbearbeitetem Zustand,

42. ***Storage*** *[Dir. 2004/23/EC Art. 3 (j)]*

´storage´ means maintaining the product under appropriate controlled conditions until distribution;

43. ***Substance*** *[Dir. 2001/83/EC Art. 1 No. 3]*

Any matter irrespective of origin which may be:
— human, e.g.
human blood and human blood products;
— animal, e.g.
micro-organisms, whole animals, parts of organs, animal secretions, toxins, extracts, blood products;
— vegetable, e.g.

[51] Verordnung über die Anwendung der Guten Herstellungspraxis bei der Herstellung von Arzneimitteln und Wirkstoffen und über die Anwendung der Guten fachlichen Praxis bei der Herstellung von Produkten menschlicher Herkunft (Arzneimittel- und Wirkstoffherstellungsverordnung - AMWHV), aktuelle gültige Fassung

micro-organisms, plants, parts of plants, vegetable secretions, extracts;
— chemical, e.g.
elements, naturally occurring chemical materials and chemical products obtained by chemical change or synthesis.

44. ***Substance*** *[Section 3 No. 3 German Medicinal Products Act], see also No. 41*

[…] the bodies of animals, including those of living animals, as well as parts of the body, body constituents and metabolic products of human beings or animals, whether in the processed or crude state,

45. ***Substantial manipulation*** *[Reg. (EC) No 1394/2007 Annex I]*

"Following are not considered substantial manupiulations:"
cutting, grinding, shaping, centrifugation, soaking in antibiotic or antimicrobial solutions, sterilization, irradiation, cell separation, concentration or purification, filtering, lyophilization, freezing, cryopreservation, vitrification.

46. ***Tissue*** *[Dir. 2004/23/EC Art. 3 (b)]*

´tissue´ means all constituent parts of the human body formed by cells;

47. ***Tissue preparations*** *[Section 4 (30) German Medicinal Products Act], see also No. 22*

Tissue preparations are medicinal products which are tissues within the meaning of Section 1a number 4 of the Transplantation Act or are manufactured from such tissues. Human sperm or egg cells including impregnated egg cells (germ cells) and embryos are neither medicinal products nor tissue preparations.

48. ***Tissue engineered product*** *[Reg. (EC) No 1394/2007 Art. 2 No 1 point (b)]*

´Tissue engineered product´ means a product that:
— contains or consists of engineered cells or tissues, and
— is presented as having properties for, or is used in or administered to human beings with a view to regenerating, repairing or replacing a human tissue.
A tissue engineered product may contain cells or tissues of human or animal origin, or both. The cells or tissues may be viable or non-viable. It may also contain additional substances, such as cellular products, bio-molecules, biomaterials, chemical substances, scaffolds or matrices.
Products containing or consisting exclusively of non-viable human or animal cells and/or tissues, which do not contain any viable cells or tissues and which do not act principally by pharmacological, immunological or metabolic action, shall be excluded from this definition.

49. ***Übertragung*** *[§ 1a Satz 1 Nr. 7 TPG]*

[…] ist Übertragung die Verwendung von Organen oder Geweben in oder an einem menschlichen Empfänger sowie die Anwendung beim Menschen außerhalb des Körpers;

50. ***Wirkstoffe*** *[§ 4 Abs. 19 AMG], see also No. 1*

Wirkstoffe sind Stoffe, die dazu bestimmt sind, bei der Herstellung von Arzneimitteln als arzneilich wirksame Bestandteile verwendet zu werden oder bei ihrer Verwendung in der Arzneimittelherstellung zu arzneilich wirksamen Bestandteilen der Arzneimittel zu werden.

Annex II: Non-legal definitions

Industrielles Verfahren *(bzw. nicht industrielles Verfahren)*[20,21]

Kriterien für ein "industrielles Verfahren":

1. Anspruchsvolles (bio-)technisches oder aufwändiges maschinelles Verfahren
2. Einsatz technologisch hochwertiger oder komplizierter Verfahrensschritte
3. "Breite", maschinelle, mechanisierte und automatisierte Massenherstellung
4. Produktion über 100 Stück pro Jahr / Be-Verarbeitung in größerem Umfang (Gewebe-abhängig)
5. GMP
6. Produktion auf Vorrat für einen nicht bekannten Abnehmerkreis

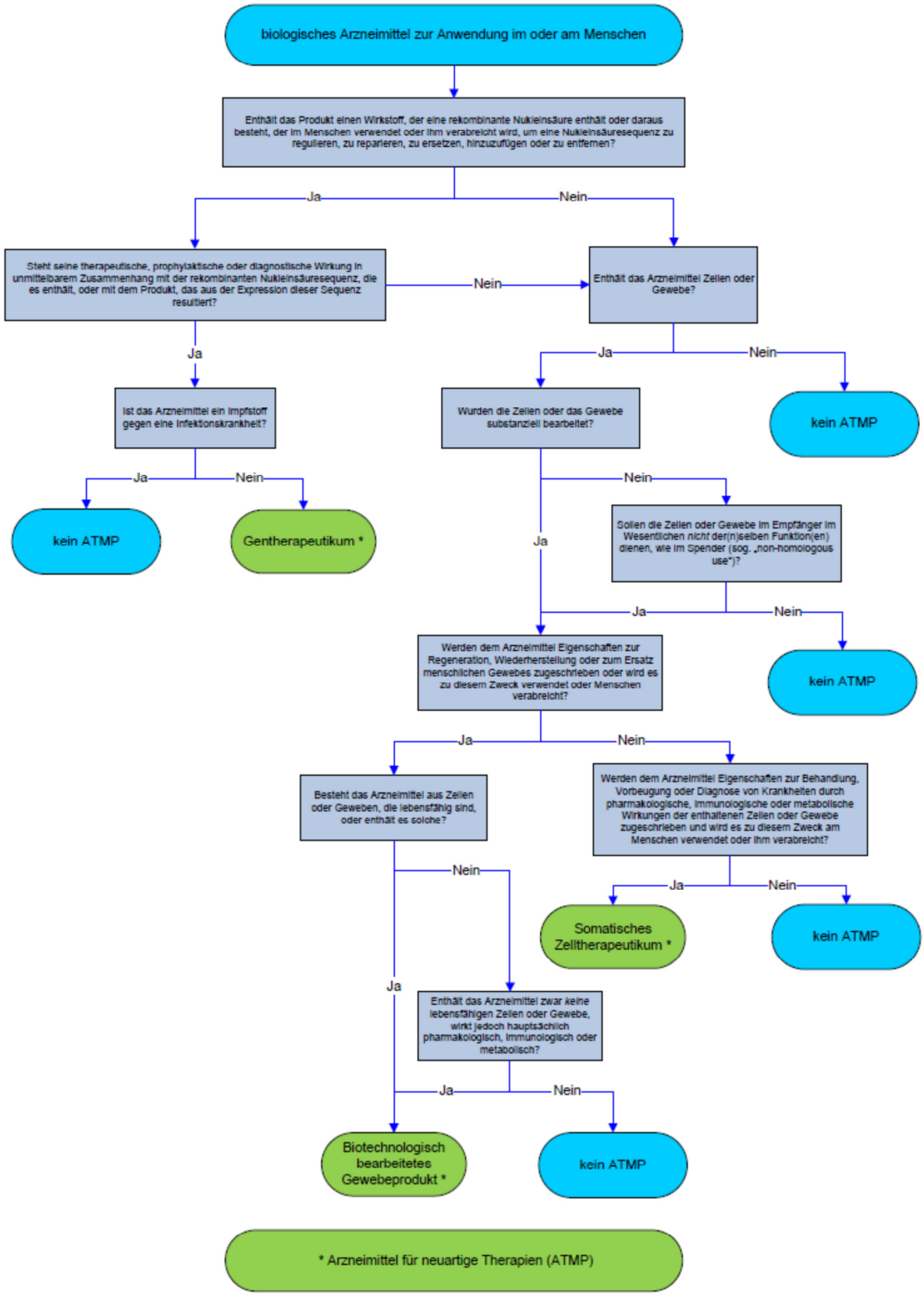
Kriterien für ein "nicht industrielles Verfahren":

1. Verarbeitung erfolgt mit einfachen, handwerklichen Verfahren
2. Wesentliche Be- und Verarbeitungsverfahren sind in der EU hinreichend bekannt
3. Wirkungen und Nebenwirkungen sind aus dem wissenschaftlichen Erkenntnismaterial ersichtlich
4. Be- und Verarbeitungsverfahren neu, aber mit bekanntem Verfahren vergleichbar
5. GFP
6. Abschätzbares Gefärdungspotential
7. Verarbeitung erfolgt im Einzellfall oder für überschaubaren Abnehmerkreis

Industrielles Verfahren[22]

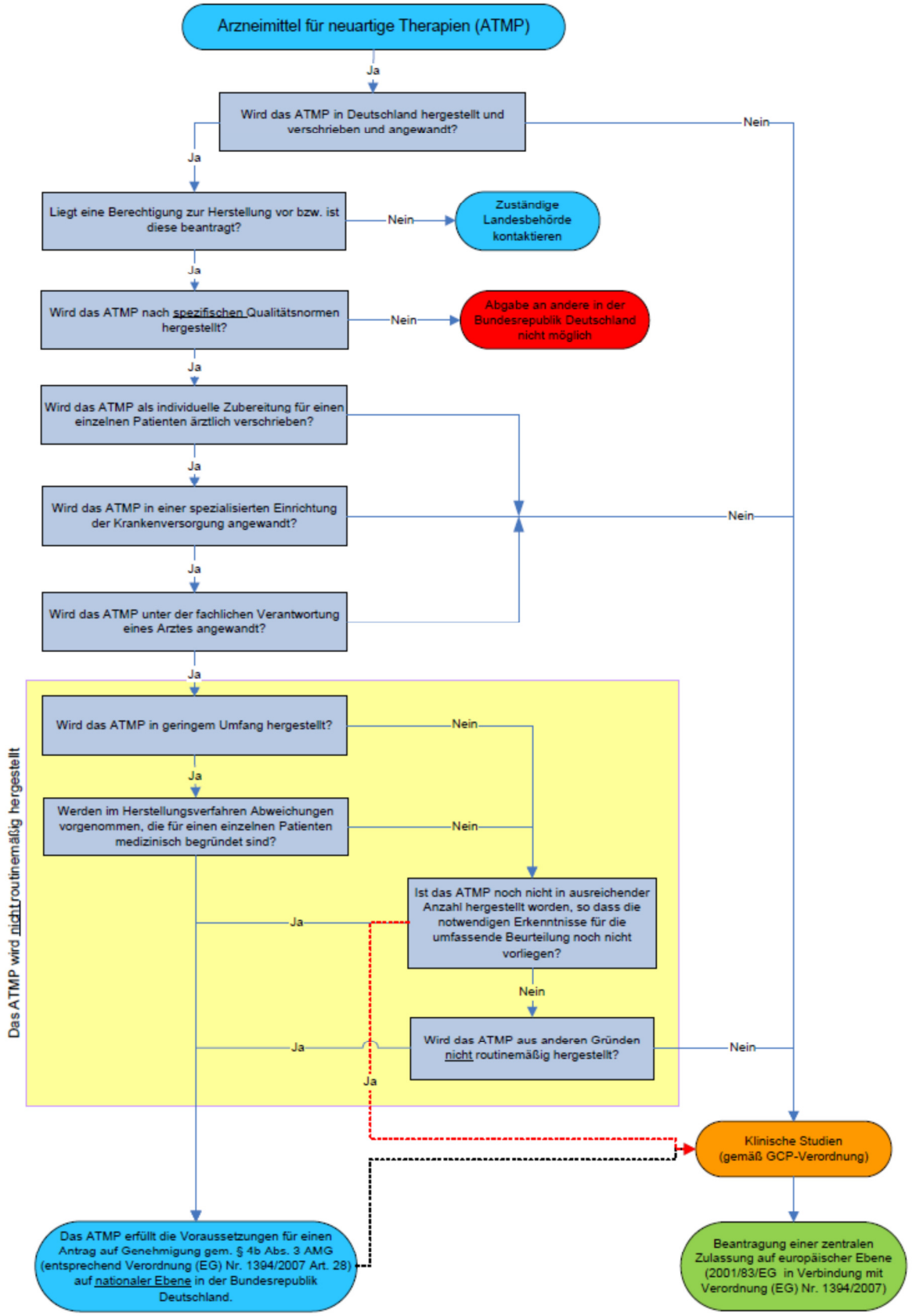
"Die Be- oder Verarbeitung geschieht
- in großem Maßstab, in Chargen (vgl. 4 Abs. 16) oder Serien,
- unterEInsatz aufwendiger Produktionseinrichtungen und –anlagen oder
- anspruchvoller technischer oder aufwändiger maschineller Verfahren (AuB zu § 20c)"

Annex III: PEI decision tree for ATMP classification



Source: http://www.pei.de/SharedDocs/Downloads/pu/innovationsbuero/entscheidungsbaum-atmp,templateId=raw,property=publicationFile.pdf/entscheidungsbaum-atmp.pdf

Annex IV: PEI decision tree for hospital exemption



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