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SaxoCell Clinics

Advanced Therapy Medicinal Products (ATMPs) - an introduction to the scientific, clinical and regulatory framework

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Advanced Therapy Medicinal Products

An introduction to the scientific, clinical and regulatory framework of ATMPs

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1 Introduction

Undoubtedly, developments in medical science and the therapeutic armamentarium across various indications have shown unforeseen advances over the past decades. Hence, the aim and challenge of health research today is to achieve the highest possible level of therapeutic effectiveness for every patient, while, ideally, at the same time minimizing potential side effects. The main prerequisite for such personalized approaches is the understanding of basic disease mechanisms and the identification of specific biological control points for the development of a specific condition. Disease and therapy-relevant genes, proteins and other molecules are in the focus of current research into targeted treatment options with the aim to generate tailored therapies for specific patients or patient groups[1]. Advances in biomedical research and the broad use of high-throughput technologies provide precious insights into biological mechanisms building the base for personalized medicine. This path away from "one-fits-all" approaches holds the potential for hitherto unseen outcomes in terms of the patients' responses to treatment, survival and quality of life[1].

Whereas conventional, often unspecific drugs usually contain chemicals or proteins as active substances, recent advances in science and technology have led to the emergence of medicinal products consisting of genetically modified cells and tissues[2]. While they can also be subsumed under the umbrella term of „biologic drugs" or "biologics", these newly developed products have differentiated and unique characteristics that warrant classification as a distinct type of drugs. These specialized medicinal products are therefore referred to as "advanced therapy medicinal products - ATMPs"[2]. ATMPs are defined according to a specific classification, which will be described in this document. What is common to them as a group is the fact that they represent a new category of substances dedicated to deal especially with diseases in which traditional medicine has proven to be ineffective up to now, i. e. (so far) incurable or orphan diseases and chronic conditions that conventional drugs are unable to treat adequately[2]. In particular the fields of genetic, metabolic and degenerative neurological diseases, hemato-oncological malignancies as well as serious cardiologic and orthopedic conditions are considered as areas of interest for the use of ATMPs[3].

"Cell- and gene-based therapies form one of the pillars of regenerative medicine. They have the potential to transform quality of life and improve the health status of patients with genetic and cellular defects, including genetic diseases, neurodegenerative diseases and tissue malignancies, amongst others"

(Yu et al., 2018)[4]

The highly innovative, biologically complex but personalized nature of these products harbors multiple challenges in terms of clinical development and the pathway to market

authorization. In the framework of a strictly regulated environment, promising findings from basic lab research efforts must in a first instance be transferred to certified GMP facilities in order to work on and generate processes that are thoroughly designed and documented and which are reproducible at high quality and safety standards. This, in the best case, paves the way for the establishment of a regulatory dossier enabling the corresponding research group or company to submit their product for clinical research within a given clinical trial protocol. This translation into research involving actual patients entails all formal requirements that come with clinical trials regulations enacted by for instance the European Union (EU). These regulations are fundamentally important and represent the basis of the trustable nature of modern societies' medicines portfolios. But this comes at a cost. Even in the context of conventional chemicals, the preparation and conduct of clinical trials is an enormous effort in terms of personnel and financial resource deployment. Clinical trials involving ATMPs push these limits even further as the aforementioned comprehensive regulatory requirements for ATMP-based investigational products as well as the complex handling of these medicines significantly increase the organizational aspects and budget requirements of corresponding trials compared to conventional clinical research projects.

Whereas "big pharma" has the man- and financial power to manage such ambitious projects within their portfolio, academic institutions with an interest and focus on investigator-initiated trials (IITs) reach their limits when diving into clinical research involving ATMPs. Fundraising for IITs from public funding bodies, such as DFG[a], DKH[b] or BMBF[c] is limited even for conventional clinical trial initiatives. For trials with ATMPs the bar is set even higher and funding acquisition is a real challenge.

As a consequence, current academic efforts in ATMP clinical research often rely on funding from the pharmaceutical industry. Hence, strategic partnerships between academia and industry are essential and offer significant benefits for all involved parties. The SaxoCell cluster is an excellent example for such collaborative activities. Within the framework of the cluster, partners from universities, university-affiliated organizations and biotech companies bundle competencies and efforts in order to drive new developments in the field of academically driven ATMP research.

In this working paper we will provide an overview on definitions and characterization of ATMPs as well as the framework and pitfalls of the regulatory environment and the conduct of clinical trials with these products.

[a] DFG: Deutsche Forschungsgemeinschaft
[b] DKH: Deutsche Krebshilfe
[c] BMBF: Bundesministerium für Bildung und Forschung

2 Definitions and overview

According to the European Medicines Agency (EMA), advanced therapy medicinal products (ATMPs) are “medicines for human use that are based on genes, tissues or cells”[5]. Within the European regulatory framework they are classified under the umbrella of “biological products”, i. e. as “medicines whose active substance is made by a living organism”[6]. Biologics outside the ATMP definition, which have been approved and used for many years, include for instance vaccines, recombinant proteins, monoclonal antibodies or blood-derived products. In general, biologics are a heterogeneous group of substances differing from conventional chemical drugs in terms of structure, size, mechanism of action and sensitivity to various degradation pathways[7]. Biologics are not manufactured by “machines” with highly standardized and equally reproducible chemical and physical procedures. They are built in living organisms (e. g. animals, humans, bacteria, plants, viruses), which implies a certain variability of the associated biological pathways and production processes. As a result, the individual parameters of biological products in a certain category are not absolutely identical and there is a risk for malfunction and immunogenicity if this complex manufacturing process is impaired[8]. Hence, the manufacturing of biological medicinal products is associated with extensive risk-based regulatory procedures in order to assure the production of safe and functional substances.

Within the group of biological products, ATMPs represent a new level of complexity in manufacturing and associated regulatory procedures. In the EU, the term “ATMPs” is used to describe therapies based on genes, cells or tissues according to Regulation (EC) 1394/2007[9]. The ATMP definition implies that they are cells or tissues having undergone substantial manipulation or that the used products are not applied with the same intention in the recipient than what the function of the (non-manipulated) cells or tissues was in the donor. ATMPs are therefore more difficult to manufacture than non-ATMPs as they involve one or more of several components (e. g. vectors, cells, genes), all of which are significantly more complex than chemical medicines or conventional biologics[10].

2.1 Definitions of differentiation

ATMPs represent a novel type of personalized treatments for human use offering patient-specific therapy. The spectrum of what these products can offer in terms of therapeutic portfolio includes the following[11]:

- Correction of defective patient DNA
- Treatment of diseases by adding mRNA
- Adding gene-corrected cells
- Instruct the body to kill defective cells
- Replace or prevent diseases by adding cells

As outlined above, the ATMP definition according to Regulation (EC) 1394/2007[9] states that they are biological products having undergone substantial manipulation before being used and applied in their therapeutic target setting. Hence, in order to classify as such, the respective active therapeutic substance must be based on at least one of the following[12,13]:

- A technology to modify the patient's genome
- Recombinant nucleic acids or genes
- Substantially manipulated cells
- Cells intended for a different essential function in the patient vs. the donor or engineered tissue

In order to fully comprehend this definition, it is important to understand what the term "substantial manipulation" implies. The Regulation (EC) 1394/2007[9] indirectly delivers this information in its Annex I by providing a list of possible manipulations applied to cells or tissues that should not be considered as substantial. These are:

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

Hence, all manipulations beyond this list that are applied to cells or tissues subsequently serving as medicinal products should be considered as substantial and form the basis for their classification as an ATMP.

Figure 1 below summarizes the very basic ATMP principles and provides a first idea on what the basis of these new medicinal products is.

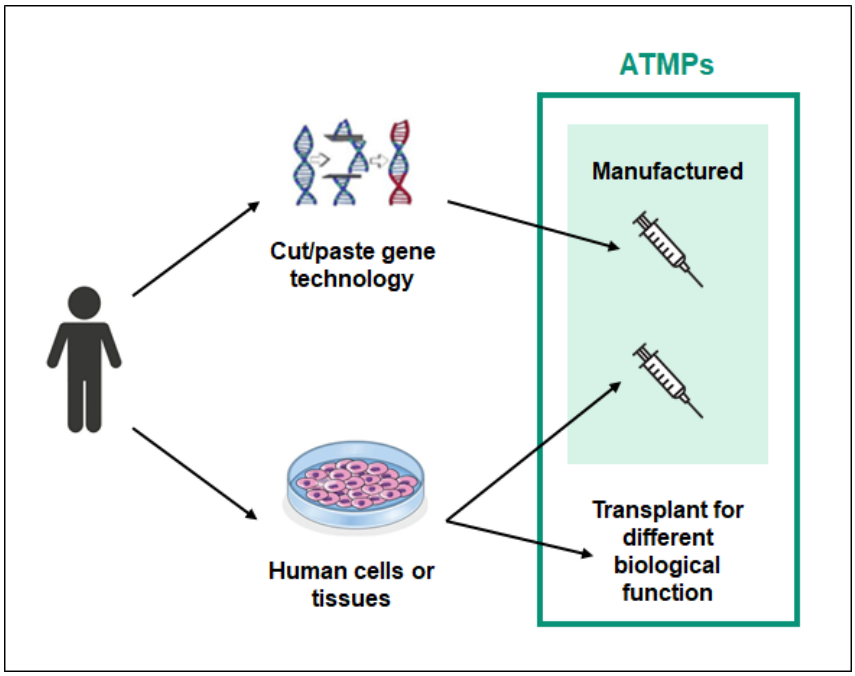


Figure 1: ATMP introduction
(adapted from Heather Main, The Niche, ipscell.com)[11]

The complex processes through which ATMPs are manufactured must strictly follow the Good Manufacturing Practices (GMP) defined by the EU[14].

2.2 Classification of ATMPs

Whereas ATMPs are, from a regulatory and legal point of view, overarchingly referred to as "cell therapy and gene therapy products" in the US[d] and as "gene-, cell-, and tissue-based therapies" in Japan[e], they are broadly broken down into three major classes in the EU[f] - based on their origin and the way they are produced and used[15]: (1) gene therapy medicines (GTMPs), (2) somatic cell therapy medicines (sCTMPs) and (3) tissue engineered medicines (TEPs)[5,16] (see Table 1 below).

Legal definitions of ATMPs are important because they facilitate the classification of a product and by this determine its development plan according to the regulatory framework. Correct classification at an early stage is an essential step as this determines the itinerary to follow in research as well as preclinical and clinical studies[15].

[d] Responsible US agency: Food and Drug Administration (FDA)
[e] Responsible Japanese agencies: Pharmaceuticals and Medical Devices Agency (PMDA); Ministry of Health, Labour and Welfare (MHLW)
[f] Responsible EU agency: European Medicines Agency (EMA)

Table 1: Types of ATMPs according to EU regulation

Gene therapy medicinal products (GTMPs)	Gene therapy medicines **introduce, remove or change parts of a patient's genetic code** and are designed to result in therapeutic, prophylactic or diagnostic effects, usually in the context of treating genetic, metabolic, cellular or inflammatory disorders as well as certain cancer diseases. Gene therapy medicines are applied by **introducing** directly to the patient either a **vector carrying genetic material** (*in vivo*) or by **transplanting cells to the patient** that have previously been engineered to **produce therapeutic proteins and/or factors** (*ex vivo*)[4,5,12].
Somatic cell therapy medicinal products (sCTMPs)	Somatic cell therapy medicines contain **cells or tissues**, which have been **manipulated** in order to change their biological characteristics or cells or tissues that will be used **in other functions than their original** biological intention in the body. Again, these products are used with the intention to cure, diagnose or prevent diseases[4].
Tissue engineered products (TEPs)	Tissue engineered medicines comprise **cells or tissues** that have been **modified** so that they can be applied to **repair, regenerate or replace human tissue**[4].

If an ATMP qualifies to fall within the definition of either a GTMP, sCTMP, or TEP, it is considered to be a GTMP[9].

ATMPs do not include vaccines for prevention or treatment of infectious diseases, oligonucleotides and related synthetic molecules and cells or tissues for transplantation unless ATMP definitions are met[16] (also see overview in Appendix).

2.3 Combined ATMPs

The term **„combined ATMP" (cATMP)** does not, as the wording might suggest, refer to a combination of several of the above described ATMP classes. cATMPs can be gene, cell, or tissue based (i. e. based on one of the three ATMP classes), but they also contain one or more medical devices as an integral part of the medicinal product they belong to.

An example of a combined ATMP would be cells embedded in a matrix or scaffold. This is often used in tissue engineering as scaffolds provide the structural support for cell attachment and subsequent tissue development[17].

Therefore, whereas GTMPs, cCTMPs and TEPs are regulated by the Medicinal Products directives 2001/83/EC[18] and 2009/120/EC[19] as well as the Regulation (EC)

726/2004[20], which all refer specifically to ATMPs, combined ATMPs are in addition regulated by the Medical Devices Regulation (EU) 2017/745.

2.4 Autologous vs. allogeneic products

Tissue- and cell-based products can be derived from either **autologous** or **allogeneic** origin. In the case of autologous products, the patient's own tissue or cells are collected and then, for instance after genetic manipulation, re-administered to the patient. Allogeneic products encompass that the patient's own tissue or cells are replaced with new, healthy ones coming from a compatible donor.

In this context it is to be noted that an ATMP, which is derived from both autologous and allogeneic cells or tissues, is considered a medicinal product for allogeneic use.

2.5 Overview: ATMP origins and classes

Figure 2 below provides a comprehensive view on the type of ATMPs, their classification and use.

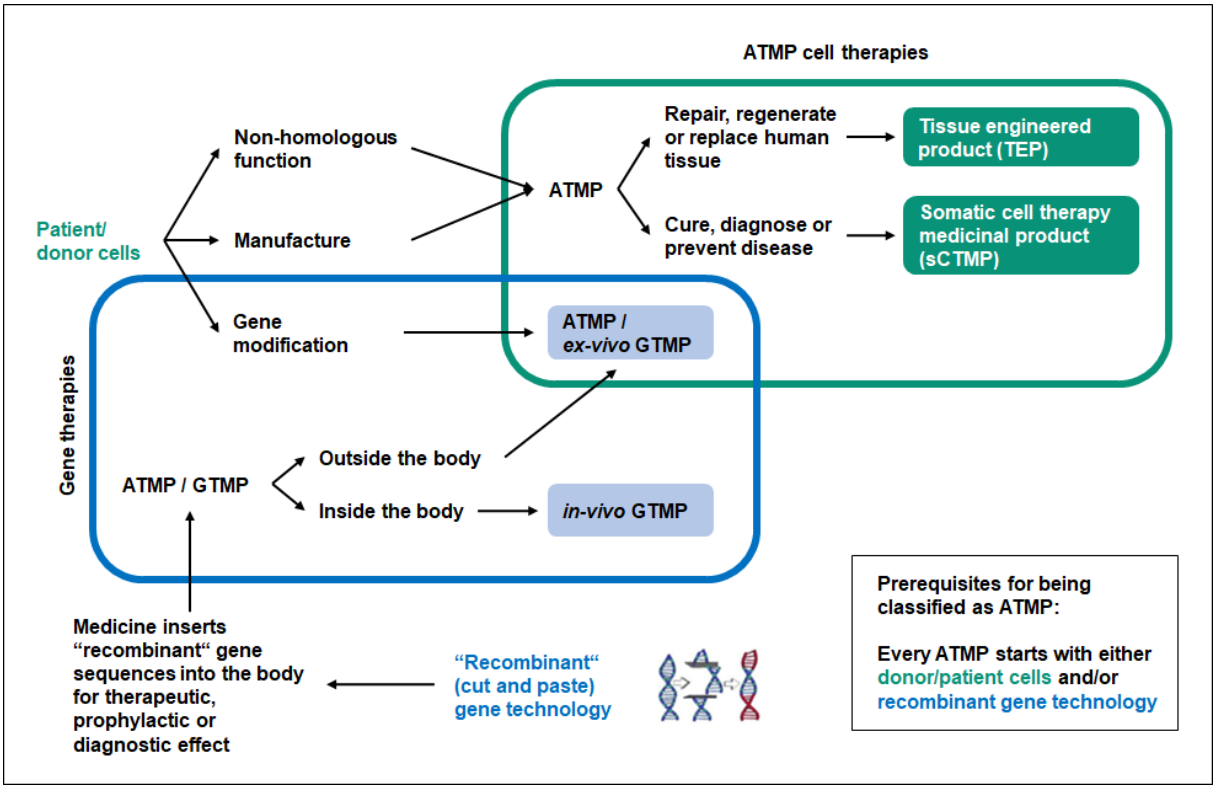


Figure 2: ATMP therapy overview
(adapted from Heather Main, The Niche, ipscell.com)[11]

3 ATMP classes: deeper dive

3.1 Gene therapy medicinal products (GTMPs)

As already briefly covered in the previous section, GTMPs are biological medicinal products that modify a person's genetic information to treat or cure a disease. Their active ingredients contain or exist of a nucleic acid (i. e. carrier of the genetic information) and they are used to regulate, repair, replace, add to, or remove a nucleic acid sequence. The associated medicinal effect is per definition in direct connection to the recombinant nucleic acid sequence contained in the product or in direct connection with the product, which is formed on the basis of this genetic information[21].

There are five main therapeutic strategies that can be targeted with the help of gene therapy approaches[22] (see Table 2 below):

Table 2: Gene therapy strategies

Gene addition	Gene addition inserts a new copy of a gene into the target cells in order to produce (more) of a certain protein. For this, the aforementioned virus vector strategy (mostly AAV) is used to carry the gene into the cells[22].
Gene correction	Gene correction therapies aim at modifying a portion of a gene using innovative gene editing technologies (e. g. CRISPR/cas9, TALEN or ZFN) to remove faulty elements of a gene or DNA region. The goal of this procedure is to produce a protein that functions in a normal manner instead of in a way that contributes to disease[22].
Gene silencing	Gene silencing prevents the production of a distinct protein by targeting the respective messenger RNA (mRNA). In this process, degradation of the mRNA takes place so that the associated protein is not produced. Gene silencing is an interesting option for the treatment of diseases where too much of a protein is expressed[22].
Reprogramming	Reprogramming aims at changing the characteristics of certain cells by adding one or more genes to them. For instance cells in a certain tissue can be reprogrammed by this technique in order to produce enzymes normally produced by another type of cells in the same tissue so that the lack of this enzyme, which is caused by dysfunctional cells, can be balanced. An example would be the reprogramming of specific pancreatic cells in order to account for the lack of insulin caused by defective islet

	cells of the pancreas. Also, CAR (chimeric antigen receptor) T cell therapy falls into this category[22].
Cell elimination	This technique usually aims at eliminating malignant tumor cells. Introduction of so called “suicide genes” causing cell death can be used to achieve such elimination. Besides targeting malignant cells, this strategy can also be used to contain overgrowth of benign (tumor) cells[22].

Besides the above classification, gene therapies can broadly be broken down into whether the treatment is administered to cells in (*in vivo*) or outside (*ex vivo*) of the patient’s body[22].

3.1.1 *In vivo* gene therapy approaches

In vivo gene products are administered directly to the patient, which means that the cells, which are targeted by the used GTMP, remain in the body of the patient[22]. This transfer of genetic material can be done locally to a specific organ or in a systemic way through IV (intravenous) delivery.

In vivo gene therapy requires a vector to „transport“ the genetic material, which is typically a virus. Such a vector is able to pass genetic material into the patient’s cells and viruses are used as gene delivery systems because they can efficiently force cells into taking up the new gene. The most commonly used delivery system among viral vectors are adeno-associated viral vectors (AAV vectors)[23]. AAVs are especially well studied in pre-clinical settings. In humans there is still relatively limited experience but AAVs are nevertheless the safest, most effective and most widely used gene delivery vehicles to date[24].

In vivo gene transfer has an advantage over *ex vivo* strategies as it avoids the (both practically and financially) burdensome process of extracting cells from the patient, to manipulate them in the lab and to then re-transfer the genetically altered cells back into the patient[25].

Some challenges, however, seem to remain with this type of therapy and call for further efforts. These include improvement of effective transport of the vector to the targeted cells or organ, binding of the vector to the cell, transfer of the genetic material to the nucleus as well as toxicity and immunity induced by expression of virus and/or transgene peptides[25].

3.1.2 *Ex vivo* gene therapy approaches

In the context of *ex vivo* gene or cell therapy, the targeted cells are removed from the patient (or donor) and gene therapy product is administered to the cells outside of the

body before they are re-applied to the patient[22]. This technique involves the following sequential steps and procedures:

- Isolation of the relevant cells (from a patient or donor)
- Growing the cells in culture
- Genetic modification of the cultured cells
- Selection of the genetically modified cells and growing them
- Transplantation of the modified cells (back) to the patient

For *ex vivo* approaches, autologous cells are isolated directly from the patient and are genetically modified to obtain a therapeutic effect. CAR-T cell therapy is one example for this approach. “CAR” stands for “chimeric antigen receptor” and CAR-T cells are produced by extracting T cells from a patient via apheresis and by subsequently re-engineering them in the laboratory to produce specific (chimeric) receptors on their surface (=CARs). CARs are synthetic molecules, they do not exist naturally and the receptors are chimeric in that they combine both antigen-binding and T cell activating functions into a single receptor. The CARs recognize certain proteins or antigens on the type of cancer cells they are designed for targeting and bind to them. The modified T cells (CAR-T cells) are then expanded in a lab facility and infused back into the patient. In the body, the cells continue to multiply and, with the help of their chimeric receptor, recognize and eliminate cancer cells harboring the target antigen[26].

Autologous *ex vivo* cell therapies are successful approaches and several products for this approach have been approved within the past years in Europe (list of approved products in the EU at the date of publication of this document see section 3.5). The big advantage of autologous cell therapies is the fact that the products come without immunologic mismatch between donor and recipient[27].

However, autologous approaches have some disadvantages:

- **They are not available on demand**. The cells must be extracted and processed for every individual patient. The process until the CAR-T cells can be transferred to the patient can take several weeks - a significant delay for patients with aggressive disease in urgent need of therapy[27]
- **They come at variable quality**. The cells are extracted from patients with a disease. This hold potential for two risks: (1) the therapeutic product can be contaminated with cancer cells or (2) there might be a low number of functional cells available for processing[28].
- **They are expensive**. Autologous cell therapies can only be produced via individualized manufacturing processes for one patient. This makes them very expensive (around 300.000 €)[28].

On the other hand, allogeneic cell therapies use cells derived from healthy donors. The advantage of allogeneic therapies is the potential to offer “off the shelf” availability through cell production at higher volumes in standardized processes[27]. They could

hence be ready to use as soon as a patient in need is identified. However, a significant challenge in developing allogeneic cell therapies is the genetic dissimilarity between the donor and the recipient, leading to immunological incompatibility[29]. To date, no allogeneic cell therapy has been approved but research in order to develop strategies to reduce the risk for Graft Versus Host Disease (GVHD) and immune rejection is ongoing[29]. Once these challenges have been overcome, the future of cellular therapies will most probably lie in allogeneic approaches. As opposed to autologous therapies, allogeneic approaches offer the potential to make cell therapies widely accessible and affordable on the long run[27].

Figure 3 below schematically represents *in vivo* vs. *ex vivo* gene therapy.

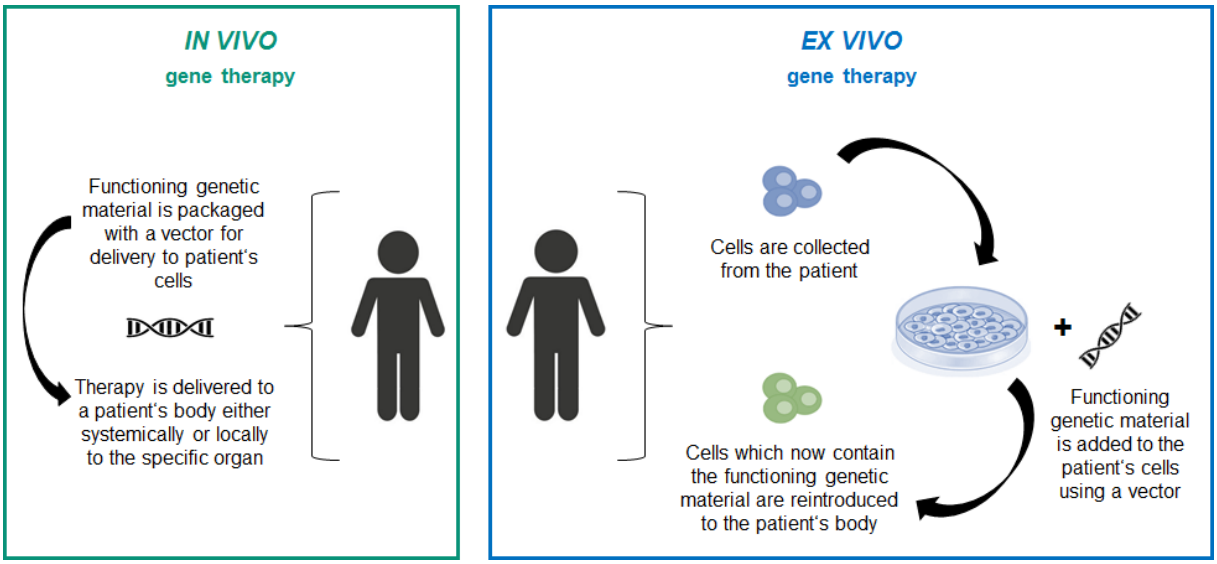


Figure 3: *in vivo* vs. *ex vivo* gene therapy
(adapted from www.thegenehome.com: Ex Vivo & In Vivo Gene Therapy Techniques[30])

GTMP examples are:

- **Zolgensma** (*in vivo* gene therapy approach): The gene therapy product Zolgensma has been shown to slow down the progress of muscular dystrophy in patients affected by spinal muscular atrophy (SMA). Clinical studies have demonstrated improved motor development and extended survival of the treated patients. SMA is an inherited disease that can cause death in infancy. One of the few treatment options is Zolgensma, manufactured by Novartis. With a price of over 2.2 million €, Zolgensma is one of the most expensive drugs in the world.
  SMA is caused by an inherited defect in the SMN1 gene. If a child inherits defective gene copies from both parents, specialized nerve cells in the spinal cord can only survive for a short time[31]. These motor neurons carry impulses from the brain to numerous muscles throughout the body. If these impulses are missing, the muscles cannot develop properly.

Zolgensma is an *in vivo* gene therapy, which introduces a functional variant of the SMN1 gene into body cells. It received FDA approval as the first-ever systemically delivered Adeno-associated virus (AAV)-mediated gene therapy in May 2019. EU approval by EMA was accorded one year later and is still ongoing.

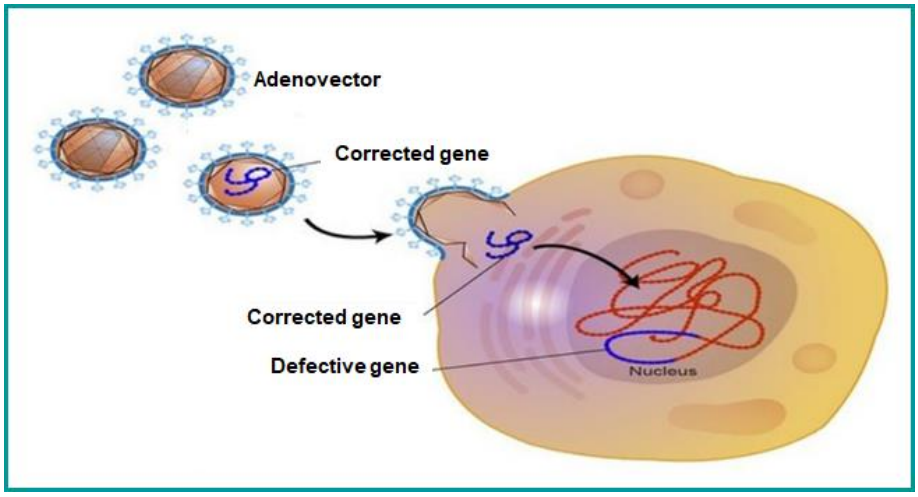


Figure 4: Principle of Zolgensma gene therapy
(adapted from Aruta, D, www.labroots.com[32])

- **Yescarta** (*ex vivo* gene therapy approach): Yescarta is a CD19-directed genetically modified autologous T cell immunotherapy indicated for the treatment of relapsed or refractory diffuse large B-cell lymphoma (DLBCL) and primary mediastinal large B-cell lymphoma (PMBCL) as well as relapsed or refractory follicular lymphoma (FL). It is a CAR-T cell treatment approach designed to bind to and eliminate CD19-expressing B cells and is engineered with a CD28 costimulatory domain[33]. Yescarta has been approved in Europe since August 2018.

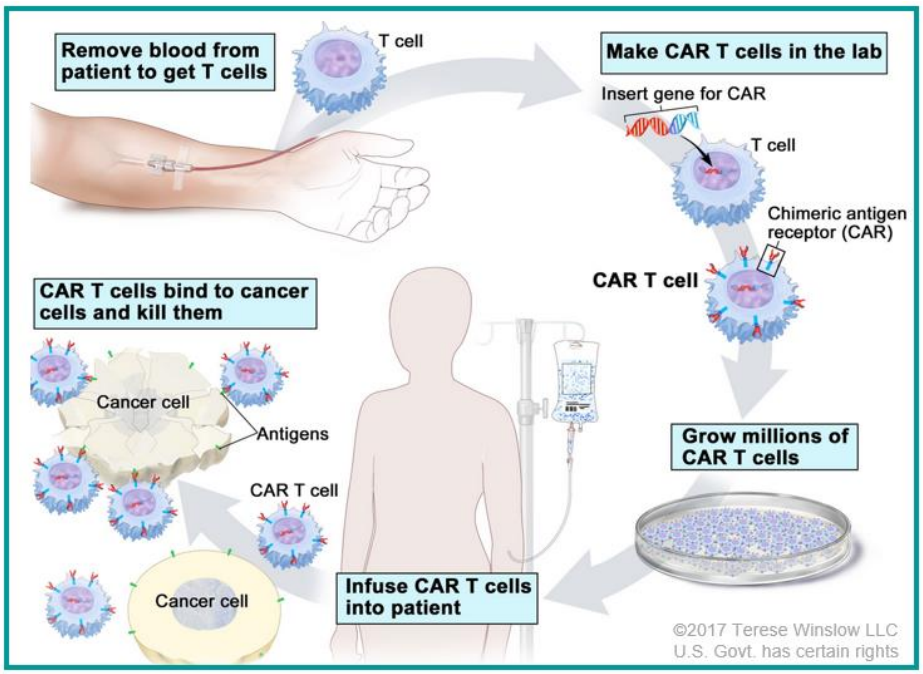


Figure 5: Principle of Yescarta treatment
(also applicable to other CAR T cell approaches, figure taken from National Cancer Institute, NIH Website[34])

3.2 Somatic cell therapy medicinal products (sCTMPs)

sCTMPs are defined as a group of ATMPs consisting of or containing cells and tissues that were substantially manipulated so that their biological, structural or physiological characteristics are changed. Also, they are, in the patient, not intended to be used for the same essential body function(s) as originally / biologically intended[35]. The cells or tissues can be of autologous (derived from the patient him/herself), allogeneic (obtained from a donor) or xenogeneic (derived from a donor of an animal species) origin[36]. These cells must have undergone substantial manipulation before being applied to the patient in order to qualify as sCTMP.

The classification of an ATMP can be challenging in some cases. This is especially the case regarding the classification as sCTMP or TEP because both products include cells[15]. The main difference between sCTMPs and TEPs lies in the therapeutic action of these medicinal products. The sCTMPs are intended for treating, preventing, or diagnosing a disease through its pharmacological, immunological, or metabolic action. In contrast, TEPs are administered for regenerating, repairing, or replacing a human tissue. Therefore, when developers have doubts about the classification in one of these two categories, the decision-making should be performed based on the mode of action of the ATMP[15].

3.2.1 Fields of sCTMP use and types of cells

sCTMPs can be broadly grouped by their mechanism of action, such as immunological or regenerative activities[14].

Based on new developments in the field of adoptive immunotherapy, immune cells have gained importance especially for the treatment of malignant hematological diseases, solid tumor as well as autoimmune diseases. Hence, they are in many cases the basis for sCTMP production[14]. sCTMP are used in different fields of medicine, including mainly regenerative medicine, anti-tumor therapy, immune regulation and drug delivery[14].

Cells for use in regenerative medicine:

Regenerative medicine is a multifaceted area of medicine dedicated to the repair and regeneration of cells, tissues and organs in the context of events that have led to compromising their function (e. g. congenital defects, disease, trauma or aging). Pluri- or multipotent stem cells (iPSCs, MSCs) as well as precursor cells (CPCs, LSCs, fibroblasts) are principal candidates for products used in regenerative medicine as they are thought to be effective for the correction of damaged organs[14]. Mesenchymal stromal cells (MSCs) are the most widely studied and used cells in this context. MSCs are characterized by their ability in self-renewal and differentiation into tissue-specific specialized cells and they are exploited for instance for the use in Parkinson's, Alzheimer's, heart disease, osteoarthritis, AIDS, diabetes as well as amyotrophic lateral sclerosis (ALS)[14].

Cells for use in anti-tumor therapy:

Anti-tumor activity can be expected from numerous immunological cell types. For this, they can be educated in vitro by specific cytokines (e. g. IL-2, IL-7, IL-15, IL-21, IFNγ, TNFα, LPS)[14]. Immune-cells can also be altered to be become antigen-specific and by this bind to certain receptors in order to induce or interrupt specific cascades that play a role in tumor biology.

Cells for immuno-regulation:

Immune-regulation can be achieved by educating certain types of immunological cells by immunoregulatory cytokines (IL-4, IL-10, IL-13, TGF-β) so that they are changed from pro-inflammatory/antitumor mediators to anti-inflammatory/immune-regulating cells (e. g. conversion of effector T cells to T regulator cells)[14].

Cells for drug delivery:

There is evidence that MSCs and mononuclear cells are able to uptake and release certain molecules without affecting their chemical activities and with the benefit of homing (i. e. active attachment of stem cells to a specific site) to damaged tissue. MSCs are the most appropriate cells for drug delivery purposes as they are easily available and expandable in large quantities in vitro, they have adequate dimensions for drug uptake and an innate homing capability when injected *in vivo*[14].

Figure 6 below summarizes the mentioned sCTMP categories and cells used in their context.

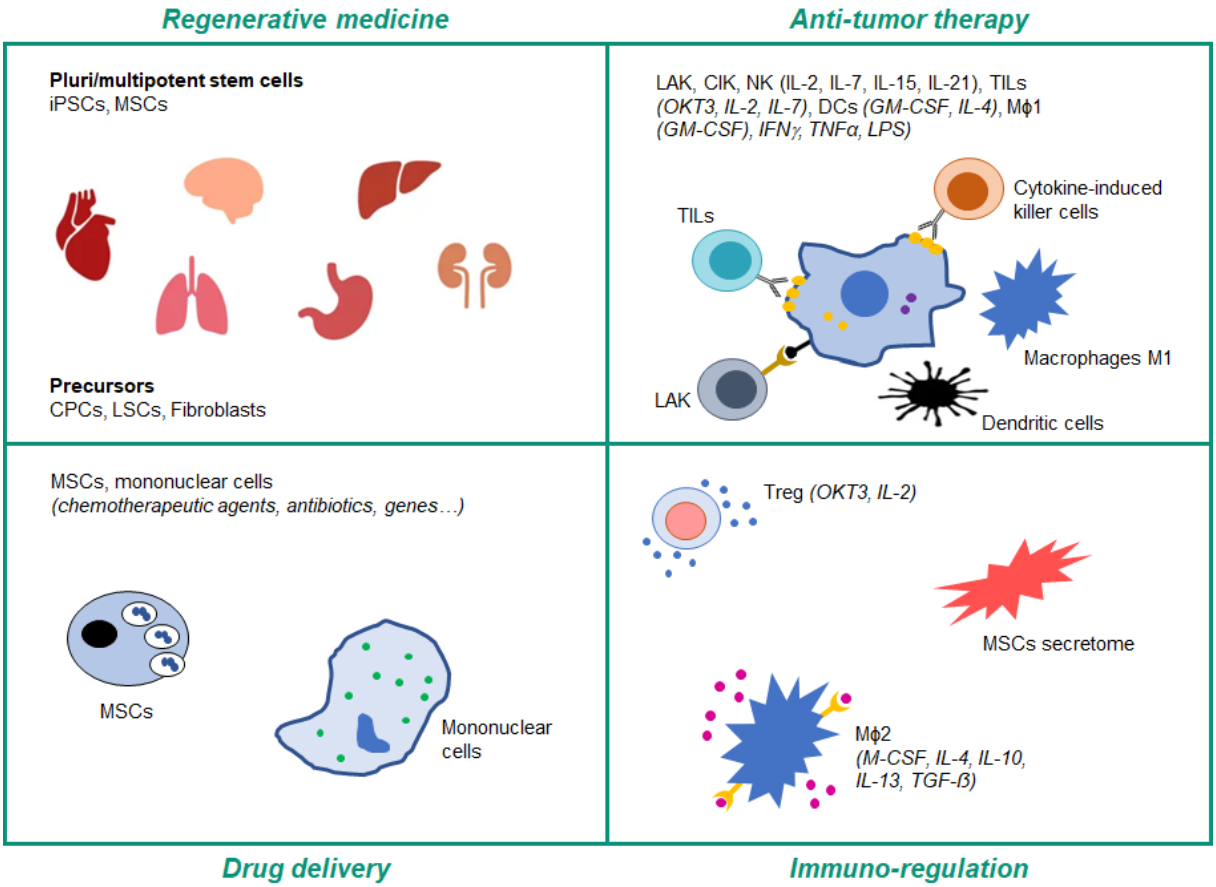


Figure 6: Cell types used as CTMPs
(adapted from Lisini, D. et al. in Stem Cell Production: Processes, Practices, and Regulation[14])

sCTMPs examples are:

- **Alofisel**: Alofisel is a living stem cell therapy. It is a suspension of expanded allogeneic, adipose-derived mesenchymal stem cells for the treatment of complex perianal fistulas.

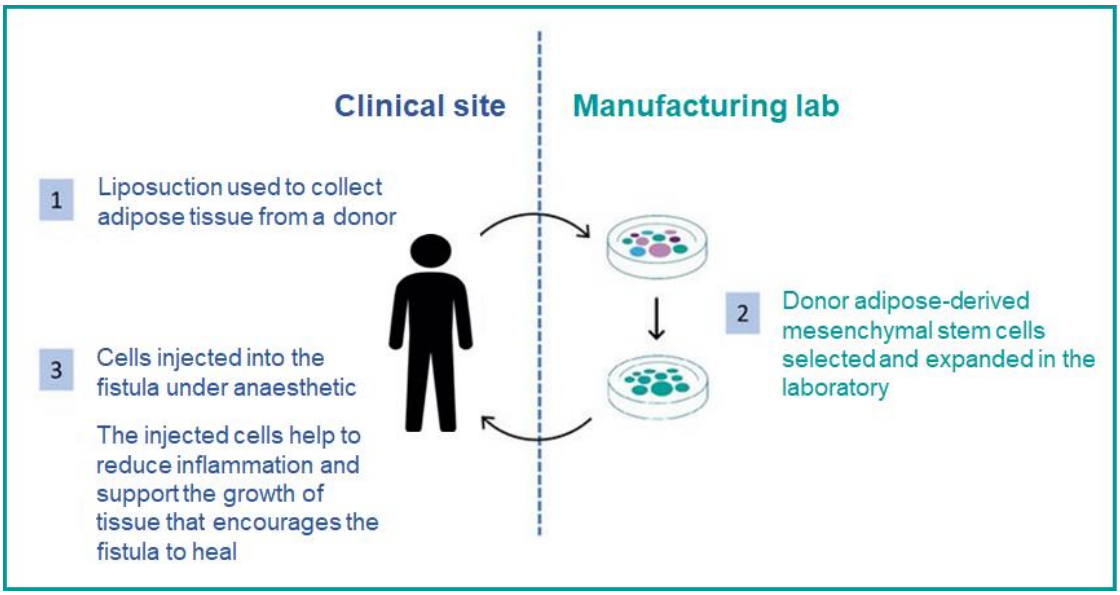


Figure 7: Representation of the Alofisel manufacturing and treatment process
(figure adapted from Introduction to advanced therapies – presentation by the Midlands-Wales Advanced Therapy Treatment Centre[37])

- **Amesanar**: Amesanar is a stem cell therapy for chronic wounds composed of allogeneic ABCB5-positive mesenchymal stromal cells isolated from human skin. ABCB5-positive stem cells have an anti-inflammatory effect because they interact with immune cells (macrophages, T-cells, B-cells) and change the previously pro-inflammatory environment in a positive way[38]. The ABCB5+ MSCs, which constitute about two to three percent of the total dermal cell population, are obtained from donor skin. The cells are isolated and multiplied with the help of a patented process and the resulting product consists of more than 90 percent ABCB5+ cells. The product comes in a pre-filled syringe and is applied directly on the wound[39].

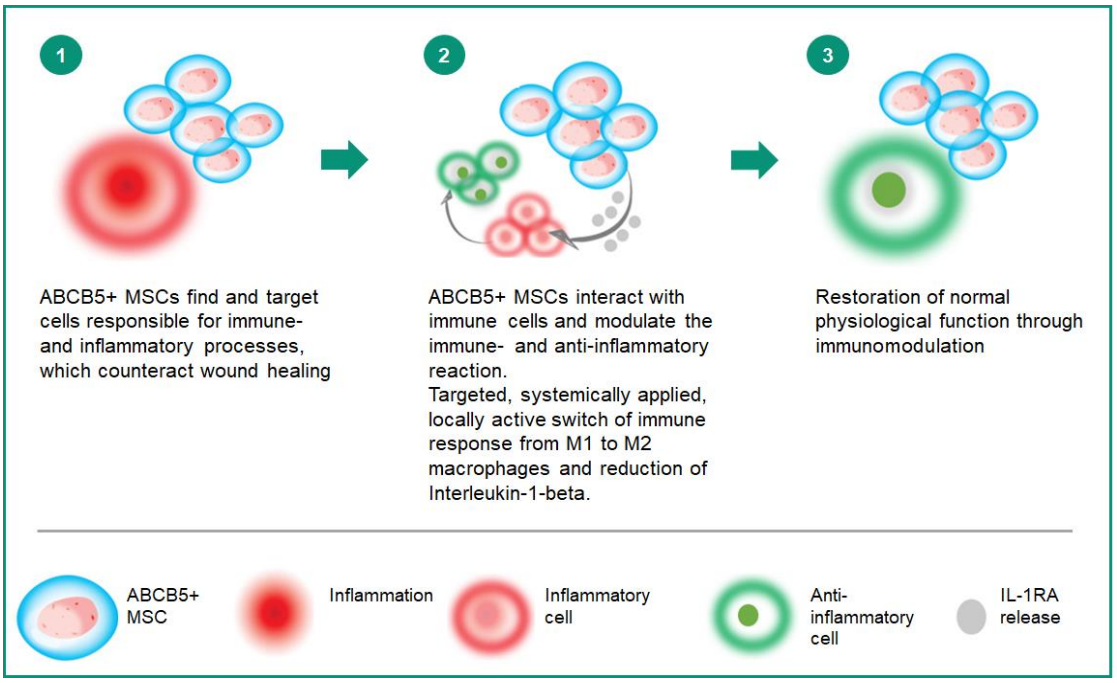


Figure 8: Representation of the mechanism of action of Amensanar (figure adapted from RHEACELL press release[40])

3.3 Tissue engineered products (TEPs)

In recent years, a wide range of tissue-based products has emerged with the aim to provide new therapeutic alternatives to conventional approaches in the context of hitherto uncured conditions. TEPs are made of bioengineered cells or tissues, which that can be combined with materials supporting their structure (i. e. scaffolds), molecules that favor the cellular environment (i. e. signaling molecules) or medical devices. TEPs are intended for the repair, replacement, restoration, or regeneration of a damaged tissue in patients[41,42]. Examples of TEPs are artificial skin or cartilage products[43].

Within a given TEP, the involved cellular components can be integrated in the form of free cells (e. g. cell suspension) or they can be embedded in a scaffold. The latter can provide an appropriate physiological environment[44], support cell viability, stimulate cell integration into the surrounding tissue and it can promote the generation of functional tissue[45]. Scaffolds should present biomodulation or bioactivity[46] and must be bioresorbable, biocompatible, and biodegradable. Also, they must show low immunogenicity[47], a suitable chemical surface, chemical resistance, and a significantly porous structure to permit the diffusion of nutrients, oxygen, catabolites, or therapeutic proteins and they must offer cell adhesion, migration, proliferation, and differentiation, influencing the cell behavior[46].

Currently, TEPs have limited use in humans, but examples would be artificial skin or cartilage products[43].

Figure 9 below depicts general steps of tissue engineering processes.

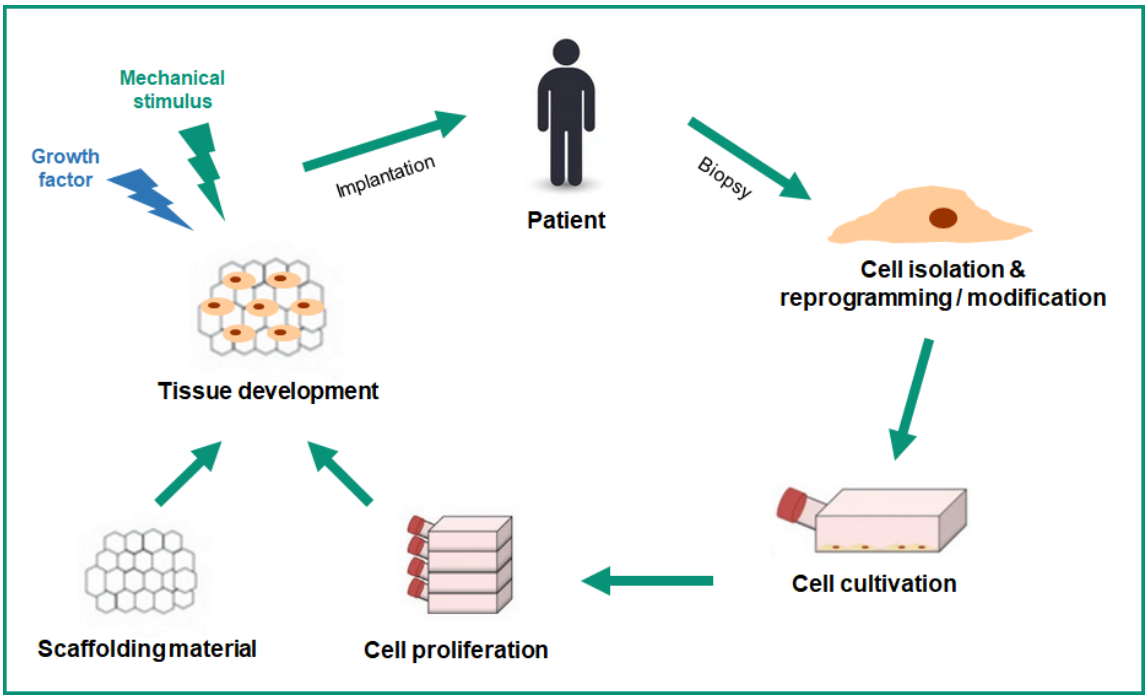


Figure 9: Steps of the tissue engineering process
(adapted from Grabska-Zielińska et al. in Materials, 2021[48])

TEP examples are:

- **Holoclar**: Holoclar's active substance are *ex vivo* expanded autologous human corneal epithelial cells containing stem cells. It is designed for the treatment of corneal lesions, with associated corneal stem cell deficiency, due to ocular burns. The product has been approved by EMA in 2015 and still has market authorization[49].

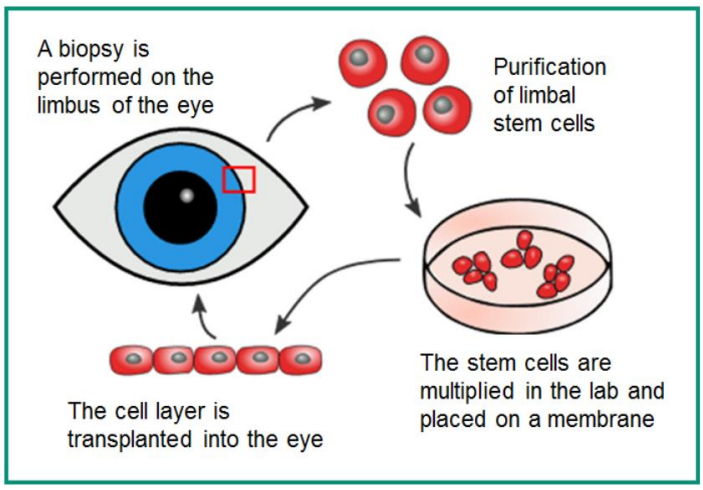


Figure 10: Steps of the Holoclar therapy process
(adapted from Henn, V. wissensschau.de, 2020[50])

- **Spherox**: Spherox is a medicine used to repair defects to the cartilage in the knee in patients who are experiencing symptoms such as pain and problems moving the knee. It contains spheroids (spherical aggregates) of chondrocytes (cells found in healthy cartilage), that have been prepared from the patient's own tissues. Spherox holds EU market authorization since 2017[51].

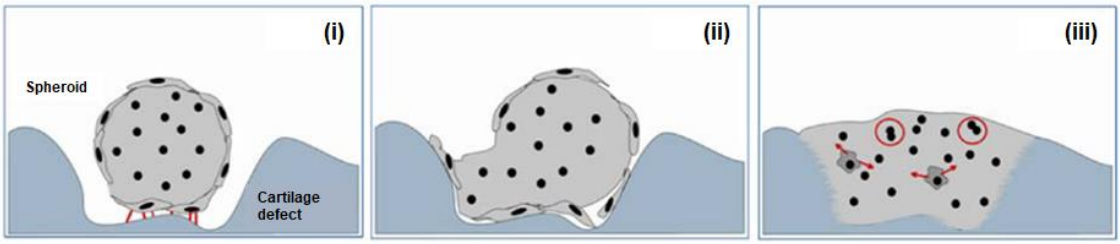


Figure 11: Representation of adhesion and integration of spheroid to the defect (image taken from EMA CHMP assessment report on Spherox, 2018[52])

(i) Adhesion of a cartilage cell spheroid to the defect ground through adhesion points (red lines). Followed by (ii) widening of the spheroids and its integration into the adhesion area by migration of surface chondrocytes along the irregular surface of the defect ground. (iii) the spheroid is completely integrated into the cartilage defect. Red arrows indicate synthesis and secretion of cartilage-specific proteins into the defect cavity with structural and regulating function. Red circles indicate putative cell proliferation, which leads to a formation of new chondrocytes within the defect[52].

3.4 Combined ATMPs

Combined ATMPs (cATMPs) comprise an ATMP plus one or more medical devices. The EMA defines combined ATMPs as follows: "Combined ATMPs incorporate a cellular part consisting of cells or tissues and one or more medical devices or one or more active implantable medical devices as an integral part of the product"[5,53].

An example of a cATMP is cells embedded in a scaffold, which is often used in tissue engineering. Scaffolds provide the structural support for cell attachment and subsequent tissue development.

3.5 Product overview

The following overview provides information on ATMPs with a valid marketing authorization in the EU (provided by EMA, license codes starting with "EU"). In addition to products with a centralized EU approval, we have listed medicines with individualized approval in Germany by the Paul-Ehrlich-Institut (PEI), license codes starting with "PEI" (grey fields in tables below). In terms of licensing, it can be observed that GTMPs all hold Europe-wide licenses, whereas especially TEPs available in Germany are mainly holding local approvals.

The list is based on information accessed in January 2023 and therefore is valid for this period[54,55].

3.5.1 Overview GTMPs

Table 3: Approved GTMPs (EU / Germany) as of January 2023

Name of product	Brief product description	Marketing authorization holder	Licensed since	License number
Abecma	***Ex vivo* GTMP** CAR-T cell therapy indicated for the treatment of adult patients with relapsed and refractory multiple myeloma (MM). It includes an immunomodulatory agent, a proteasome inhibitor and an anti-CD38 monoclonal antibody.	Celgene	18.08.2021	EU/1/21/1539
Breyanzi	***Ex vivo* GTMP** CAR-T cell therapy indicated for the treatment of relapsed or refractory diffuse large B-cell lymphoma (DLBCL), primary mediastinal large B-cell lymphoma (PMBCL) and follicular lymphoma grade 3B (FL3B). It is a CD19-directed genetically modified autologous cell-based product consisting of purified CD8+ and CD4+ T cells that have been separately transduced using a replication incompetent lentiviral vector expressing an anti-CD19 chimeric antigen receptor.	BMS	04.04.2022	EU/1/22/1631/001
Carvykti	***Ex vivo* GTMP** CAR-T cell therapy indicated for the treatment of adult patients with relapsed and refractory multiple myeloma (MM). It includes an immunomodulatory agent, a proteasome inhibitor and an anti-CD38 monoclonal antibody.	Janssen-Cilag	25.05.2022	EU/1/22/1648
Imlygic	***In vivo* GTMP** Oncolytic immunotherapy derived from Herpes Simplex Virus type-1 (HSV-1). The virus is genetically modified to replicate in cancer cells and to produce the immune stimulatory protein granulocyte-macrophage colony-stimulating factor (GM-CSF). As a consequence, anti-tumor responses are promoted. Imlygic is indicated for the local treatment of unresectable cutaneous, subcutaneous, and nodal lesions in patients with melanoma recurrent after initial surgery.	Amgen	16.12.2015	EU/1/15/1064
Kymriah	***Ex vivo* GTMP** CD19-directed CAR-T cell therapy indicated for the treatment of B-cell	Novartis	23.08.2018	EU/1/18/1297

	acute lymphoblastic leukemia (ALL), diffuse large B-cell lymphoma (DLBCL) and follicular lymphoma (FL).			
Libmeldy	***Ex vivo* GTMP** Autologous CD34+ cells transduced with a lentiviral vector encoding ARSA cDNA. Used in children with metachromatic leukodystrophy (MLD) who have mutations in the ARSA gene.	Orchard Therapeutics	17.12.2020	EU/1/20/1493
Luxturna	***In vivo* GTMP** Uses the adeno-associated viral vector serotype 2 (AAV2) to carry a functional copy of the RPE65 gene into the retinal pigment epithelial (RPE) cells to compensate for the RPE65 mutation. RPE65 mutation causes loss of vision due to retinal dystrophy.	Novartis	22.11.2018	EU/1/18/1331
Roctavian	***In vivo* GTMP** Indicated for the treatment of severe hemophilia in adult patients presenting with a mutation in the gene responsible for producing Factor VIII protein. Roctavian consists of a non-replicating recombinant adeno-associated virus (AAV) based vector containing the cDNA of the B-domain deleted SQ form of human coagulation factor VIII gene.	BioMarin	24.08.2022	EU/1/22/1668/001
Strimvelis	***Ex vivo* GTMP** An autologous CD34+ enriched cell fraction containing CD34+ cells transduced with retroviral vector encoding for the human adenosine deaminase (ADA) cDNA sequence from human hematopoietic stem/progenitor (CD34+) cells. Strimvelis is indicated for the treatment of patients with immunodeficiency due to adenosine deaminase deficiency (ADA-SCID), for whom no suitable human leukocyte antigen (HLA)-matched related stem cell donor is available.	Orchard Therapeutics	26.05.2016	EU/1/16/1097
Tecartus	***Ex vivo* GTMP** CAR-T cell therapy based on autologous anti-CD19-transduced CD3+ T cells for the treatment of adult patients with relapsed or refractory mantle cell lymphoma (MCL).	Kite Pharma	14.12.2020	EU/1/20/1492
Upstaza	***In vivo* GTMP** Indicated for the treatment of patients with aromatic L-amino acid decarboxylase (AADC) deficiency based on a mutation in the corresponding gene. This defect causes severe developmental and movement disorders. Upstaza is based on an AAV vector, expresses the human AADC enzyme and is directly administered in a certain region of the brain.	PTC Therapeutics	18.07.2022	EU/1/22/1653/001

Yescarta	***Ex vivo* GTMP** CAR-T cell therapy based on autologous anti-CD19-transduced T cells for the treatment of relapsed or refractory diffuse large B-cell lymphoma (DLBCL) and primary mediastinal large B-cell lymphoma (PMBCL) as well as relapsed or refractory follicular lymphoma (FL).	Kite Pharma	23.08.2018	EU/1/18/1299
Zolgensma	***In vivo* GTMP** Zolgensma expresses the human survival motor neuron (SMN) protein. It is a non-replicating recombinant adeno-associated virus serotype 9 (AAV9) based vector containing the cDNA of the human SMN gene. It is indicated for use in patients with spinal muscular atrophy (SMA) originating from a mutation in the SMA1 gene.	Novartis	18.05.2020	EU/1/20/1443

3.5.2 Overview sCTMPs

Table 4: Approved sCTMPs (EU / Germany) as of January 2023

Name of product	Brief product description	Marketing authorization holder	Licensed since	License number
Alofisel	Human allogeneic mesenchymal adult stem cells extracted from adipose tissue (expanded adipose stem cells - eASC) for the treatment of complex perianal fistulas.	TiGenix	23.03.2018	EU/1/17/1261
Amesanar	Allogeneic ABCB5-positive mesenchymal stromal cells produced from human donor skin for the local treatment of chronic venous ulcers due to chronic venous insufficiency (CVI).	RHEACELL	27.09.2021	PEI.A.12060.01.1
Ebvallo	First authorised allogeneic T-cell immunotherapy approved for patients with relapsed or refractory Epstein-Barr virus positive post-transplant lymphoproliferative disease.	Atara Biopharmaceuticals	16.12.2022	EU/1/22/1700/001

3.5.3 Overview TEPs

Table 5: Approved TEPs (EU / Germany) as of January 2023

Name of product	Brief product description	Marketing authorization holder	Licensed since	License number
co.don chondros-phere	Human autologous matrix-associated chondrocytes for implantation. Indicated for the repair of symptomatic articular cartilage defects of the femoral condyle and the patella of the knee.	co.don AG	12.12.2013	PEI.A.11507.01.1
Holoclar	*Ex vivo* expanded autologous human corneal epithelial cells containing stem cells. Designed for the treatment of corneal lesions.	Holostem Terapie Avanzate (HTA) S.r.l.	17.02.2015	EU/1/14/987
MukoCell	Autologous cell transplant from cells of the oral mucosa for the treatment of urethral strictures. Urethral stricture is a narrowing of the urethra, mainly caused by injury and infection.	Muko-Cell GmbH	23.12.2013	PEI.A.11491.01.1
NOVOCART 3D	Autologous matrix-associated chondrocytes for the reconstruction of articular cartilage damage.	TETEC AG	29.08.2014	PEI.A.11511.01.1
NOVOCART Inject	Autologous matrix-associated chondrocytes for the reconstruction of articular cartilage damage.	TETEC AG	27.06.2016	PEI.A.11763.01.1
Obnitix	Human allogeneic mesenchymal stromal cells (MSC) used in acute graft-versus-host disease (aGvHD). Obnitix is used in addition to conventional therapy with immunosuppressants.	medac Gesellschaft für klinische Spezialprä-parate mbH	24.08.2016	PEI.A.11748.01.1
Spherox	Spherox contains spheroids of autologous matrix-associated chondrocytes. It comes as a cell suspension for implantation and is indicated for the repair of symptomatic articular cartilage defects of the femoral condyle and patella of the knee.	co.don AG	10.07.2017	EU/1/17/1181
t2c001	Autologous bone marrow-derived pro-genitor cell preparation for cardiovascular tissue regeneration.	t2cure GmbH	31.03.2014	PEI.A.11517.01.1

4 Regulatory considerations for ATMPs

The regulatory framework for ATMPs is complex and encompasses multiple legal prerequisites, which come along with the various steps of their development and application. The first step of any regulatory consideration is the correct classification of the corresponding medicinal product. This might start with answering the question whether it is an ATMP at all and if yes, in which of the ATMP categories it falls up to the final steps to gain market authorization.

In Germany, the Paul-Ehrlich Institut (PEI) is responsible for all regulatory aspects of ATMPs. Besides all fundamental regulatory tasks of the authorization process, the PEI offers so-called “scientific advices”, which can be booked in order to get answers to specific scientific questions. Such advices are recommended at different stages in the process of ATMP development, for example for the determination of specific preclinical experiments (e. g. toxicological studies), which will deliver data and/or during the preparation of clinical trials[56].

On a European level, regulatory issues are in the hand of the European Medicines Agency (EMA). The tabulated summary of approved ATMPs (at the time of writing this document) in section 3.5 shows that the majority of products obtain a Europe-wide market authorization (MA) and therefore undergo the regulatory steps defined by the EMA. Also, any national legislation in reference to medicinal products, follows the current European legislation. Specifications published by the EU are classified into different levels of bindingness, which determine to what extent these specifications must or must not be integrated into national legislation. The short Excursus 1 below provides a corresponding overview for better understanding.

Excursus 1 - EU legislation definitions[57]:

EU Regulation
A "regulation" is a binding legislative act. It must be applied in its entirety across the EU. For example, when the EU wanted to make sure that there are common safeguards on goods imported from outside the EU, the Council adopted a regulation.

EU Directive
A "directive" is a legislative act that sets out a goal that all EU countries must achieve. However, it is up to the individual countries to devise their own laws on how to reach these goals. One example is the EU consumer rights directive, which strengthens rights for consumers across the EU, for example by eliminating hidden charges and costs on the internet, and extending the period under which consumers can withdraw from a sales contract.

EU Decision
A "decision" is binding on those to whom it is addressed (e. g. an EU country or an individual company) and is directly applicable. For example, the Commission issued a decision on the EU participating in the work of various counter-terrorism organizations. The decision related to these organizations only.

EU Recommendation
A "recommendation" is not binding. When the Commission issued a recommendation that EU countries' law authorities improve their use of videoconferencing to help judicial services work better across borders, this did not have any legal consequences. A recommendation allows the institutions to make their views known and to suggest a line of action without imposing any legal obligation on those to whom it is addressed.

EU Opinion
An "opinion" is an instrument that allows the institutions to make a statement in a non-binding fashion, in other words without imposing any legal obligation on those to whom it is addressed. An opinion is not binding. It can be issued by the main EU institutions (Commission, Council, Parliament), the Committee of the Regions and the European Economic and Social Committee. While laws are being made, the committees give opinions from their specific regional or economic and social viewpoint. For example, the Committee of the Regions issued an opinion on the clean air policy package for Europe.

4.1 General regulatory framework in the EU

Medicinal products for human use in the EU are generally governed by Directive 2001/83/EC[18] and Regulation 726/2004/EC[20]. Biological products comprise various product types, including immunological products, medicinal products derived from human blood and plasma, biotechnology and ATMPs. ATMPs consist of products that contain recombinant nucleic acids or engineered cells and/or tissues. In the EU, there is a clear differentiation between cell-based products considered as advanced therapies, and cell-based therapies covered by other legal frameworks such as the blood system or transplant laws, in the context of which these cells are not considered a medicinal product, and the active substance (i. e., human cells and tissues), cannot be commercialized or manufactured on an industrial scale[58–61]. Therefore, the classification of an ATMP as a biological product will determine the wider regulatory framework by which the requirements of the development and the marketing authorization application are defined.

Directive 2001/83/EC[18] and Regulation 726/2004/EC[20] must be considered together with Regulation 1394/2007/EC[9], which provides the overall framework on ATMPs in the EU Member States. Subsequently, Directive 2009/120/EC[19] updated the definitions and detailed scientific and technical requirements for these products. On a side note, because of their combined nature, cATMPs are not only regulated under the guidelines of medicinal products but also of medical devices[61].

Overall, the key elements of ATMP regulation in the European context can be summarized as follows:

- First of all, a given product must be identified or defined as an ATMP and classified as one of the three possible product categories or as a combined product.

- In the process towards marketing authorization, the quality, safety, efficacy and benefit-risk profile of the product must be assessed and demonstrated in both preclinical as well as clinical studies.
- Marketing authorization can obtained through a centralized procedure at EMA leading to the obtention of one license being valid in entire EU.
- There are two committees responsible for the validation and scientific evaluation for product approval of ATMPs:
    - The Committee for Advanced Therapies (CAT) and
    - The Committee for Medicinal Products for Human Use (CHMP).

  Both are involved in the scientific assessment of all ATMPs being brought to EMA in the process towards marketing authorization.
- Furthermore, there are post-authorization measures in place at EMA to ensure efficacy and safety of ATMPs.

4.2 Committee for Advanced Therapies (CAT)

The CAT is EMA's committee responsible for classifying ATMPs and for assessing their quality, safety and efficacy and for following scientific developments in the field[62]. The CAT has specifically been created for the class of ATMPs in 2009.

In terms of identification and classification the CAT has published a reflection paper[63], which supports applicants with classifying their products. Especially the decision trees for each of the ATMP types are useful tools (see Appendix). The CAT's main responsibility is to carry out scientific evaluations on ATMPs in terms of their quality, efficacy and safety, including environmental impact and to prepare a draft opinion on each ATMP application submitted to the EMA in order to support the final decision by the CHMP. Furthermore, the CAT:

- Participates in certifying quality and non-clinical data for small and medium sized enterprises developing ATMPs
- Participates in providing scientific recommendations on the classification of ATMPs
- Contributes to scientific advice
- Takes part in any procedure delivering advice on the conduct of efficacy follow-up, pharmacovigilance or risk-management systems for ATMPs
- Advises the CHMP on any medicinal product that may require expertise in ATMPs for the evaluation of its quality, safety or efficacy
- Assists scientifically in developing any documents relating to the objectives of the regulation on ATMPs
- Provides scientific expertise and advice for any community initiative related to the development of innovative medicines and therapies that requires expertise on ATMPs
- Supports the work programs of the CHMP working parties

4.3 Committee for Medicinal Products for Human Use (CHMP)

The CHMP plays a pivotal role in the authorization of medicines in the EU. In the framework of the centralized authorization procedure, the CHMP is responsible for[64]:

- Conducting the initial assessment of EU-wide marketing authorization applications
- Assessing modifications or extensions/variations to an existing marketing authorization
- Considering the recommendations of EMA's Pharmacovigilance Risk Assessment Committee (PRAC) on the safety of medicines on the market and, when necessary, recommending to the European Commission changes to a medicine's marketing authorization, or its suspension or withdrawal from the market

Furthermore, the CHMP and its working parties contribute to the development of medicines and medicine regulation, by:

- Providing scientific advice to organizations researching and developing new medicines
- Preparing scientific guidelines and regulatory guidance to help pharmaceutical organizations prepare marketing authorization applications for human medicines
- Cooperating with international partners on the harmonization of regulatory requirements

Hence, the CHMP is not an ATMP-specific committee but nevertheless a central player for all types of medicines and their way to market authorization.

Figure 12 represents CAT and CHMP in terms of constitution and interplay.

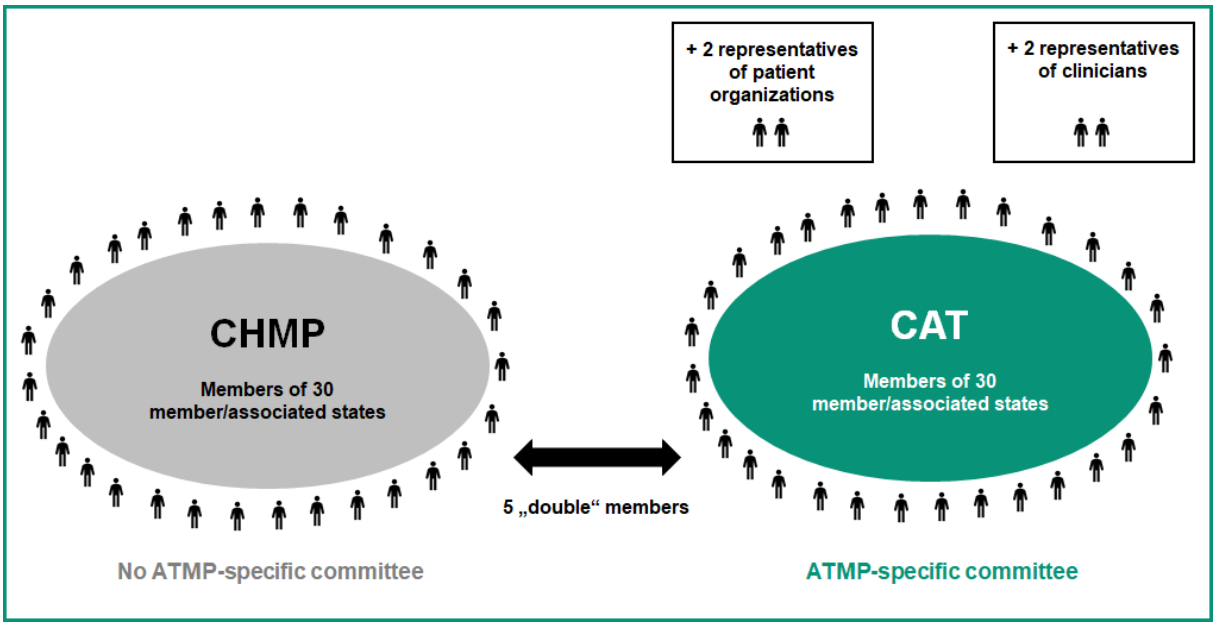


Figure 12: Members and interplay of CAT and CHMP

Scientists and physicians from all European regulatory bodies as well as delegates of the medical professions and patient representatives constitute the members of these European committees. Germany is represented in the CAT by experts of the Paul-Ehrlich-Institut (PEI)[65].

4.4 The ATMP pathway to marketing authorization

Under the EU regulatory framework for medicinal products, a marketing authorization (MA) is required to place medicinal products on the pharmaceutical market. Marketing authorization applications (MAAs) are addressed to the EMA, which is responsible for their evaluation and after a successful evaluation procedure, the MA is granted by European Commission. Being granted a MA for an ATMP generally entails the same regulatory principles as for other medicinal products. Developers must demonstrate in preclinical efforts that the quality of the starting material and all manufacturing steps of the product follow the appropriate standards and regulatory requirements and that the product is safe and effective in patients.

However, even if the general criteria for the benefit-risk assessment and the recommendation for or against the approval of a specific product are the same, some particularities for ATMPs can be noted. For instance, in the context of the pharmaceutical development of these complex products, changes in manufacturing and testing with the aim of optimizing the manufacturing process often take place as far as into the pivotal clinical testing phase. In consequence there is a possibility that, contrary to the regulatory standard, the ATMP used in the pivotal clinical trial is not, or at least not entirely, identical with the product that is brought to market after approval[65]. Based on the close linkage between quality and clinical data in the ATMP setting, it

may be questioned as to how representative the data for a given clinically tested product are in terms of efficacy and safety for the finally approved “version” of the ATMP. Concerns about the comparability of the final medicinal product, which might be manufactured based on different processes, are addressed to the applicant during the approval procedure as major objections (MO). These MOs must be solved before final approval[66]. An MO also arises if the commercial manufacturing process is lacking the corresponding manufacturing license. In this context, the absence of mutual recognition of ATMP manufacturing licenses between the EU and the US can be of concern. Since most ATMPs are still being manufactured in the US at the time of European approval, an inspection carried out in the US by national inspectors under the umbrella of the EMA is required for being granted a corresponding manufacturing license. Delays in the approval process arise when on-site inspections cannot be carried out, e.g. based on travel restrictions during the COVID pandemic. The introduction of "remote inspections" has helped to avoid or at least reduce such delays[65].

In terms of clinical development in general, authorities may accept a deviation from the classical phase I to phase III trial progression for ATMPs based on their specific complexity and the target patients groups, which might be rare and in great need of therapy. But such deviations must be well justified.

Once the clinical development is accomplished, CAT and CHMP assess the product in the way described above and in the case of a positive CAT/CHMP opinion, a Europe-wide license can be granted via the European Commission (EC)[65].

Also, once market authorization has been granted, regulatory procedures can vary from the approaches taken for conventional medicines, for which usually only classical phase IV studies are carried out in order to further monitor effects and safety in a big group of patients or specific subgroups.

Figure 13 summarizes some of the differences that might apply on the way to marketing authorization and beyond for ATMPs vs. conventional medicines.

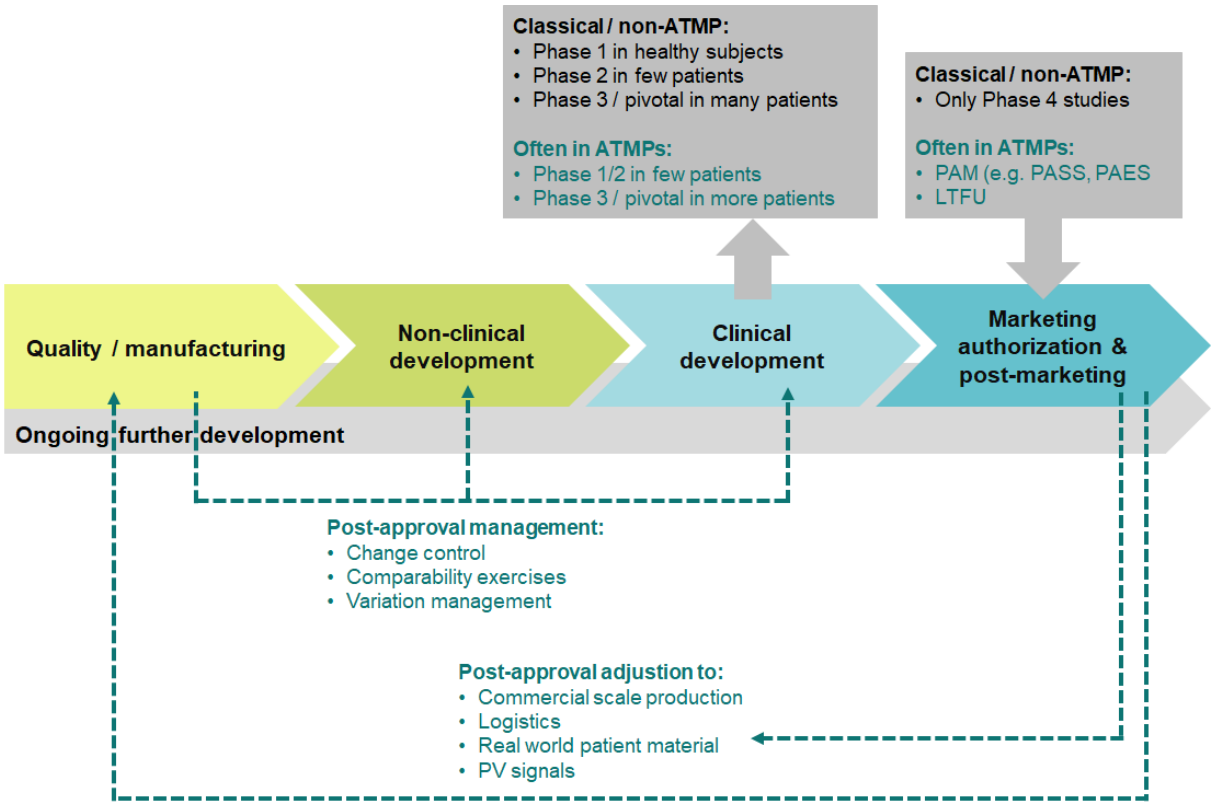


Figure 13: ATMP specificities on the way to marketing authorization

PAM: Post-authorization measures, PASS: Post-authorization safety studies, PAES: Post-authorization efficacy studies, LTFU: Long-term follow-up

Excursus 2 - clinical trial regulation in the EU - what's new with EU-CTR:

Since 2004, the EU Clinical Trial Directive 2001/20/EC (EU-CTD)[67] has governed the conduct of clinical trials in the EU and, by this, tried to standardize the corresponding rules. This attempted standardization, however, was limited by the fact that the EU-CTD has been formulated as a "directive" (as opposed to a "regulation"), resulting in reduced mandatory weight and in individual implementation of the corresponding requirements within the different national legislative frameworks (for reference also see "Excursus 1" above). Hence, multinational clinical trial applications had to be organized in a fragmented process with the necessity to submit different application packages to the competent authorities in each of the participating countries based on their individual requirements. Feedback was received from each of the authorities without them communicating on the content so that there even was a risk to obtain conflicting answers and requests for changes. This had the potential to delay study start, create challenges in creating uniform essential document for all countries and to significantly increase costs in terms of both regulatory fees as well as required manpower to prepare the submission packages.

The new EU Clinical Trial Regulation 536/2014 (EU-CTR)[68], effective since January 31st 2022, addresses the aforementioned challenges and provides a more harmonized environment for the regulatory aspects of clinical trials in the EU. As a "regulation", EU-CTR is binding for all EU member states in its entirety and helps to reduce the administrative burden and to streamline workflows. From the date of effectiveness (January 31st 2022), its implementation is organized in a transition period lasting three years and with the following steps:

- 31st January 2022 to 31st January 2023: sponsors may submit clinical trials under the legal framework of EU-CTD or EU-CTR.
- Starting from 31st January 2023: all clinical trial applications are subject to EU-CTR. However, trials approved under EU-CTD before 31st January 2023 can continue to be regulated under EU-CTD until 31st January 2025.
- 31st January 2025 onward: all clinical trials must be regulated under EU-CTR.

EU-CTR comes with a number of updates compared to EU-CTD that sponsors need to be aware of and need to address:

- The main difference, especially in a practical manner, is certainly the newly created centralized electronic database. EU-CTR has created a new portal and database called the Clinical Trial Information System (CTIS), which enables a centralized, single electronic submission in the case of EU multinational trials - instead of the prior multiple submissions with different dossiers. Sponsors must upload and submit all required data and documents to CTIS.

- In congruence with CTIS, coordinated assessments will take place in the framework of EU-CTR. This coordination happens at different levels.
    - On the one hand, national competent authority (NCA) and ethics committee (EC) assessments will now be merged in one decision. Under EU-CTD two separate submissions were necessary in each country.
    - Furthermore, EU-CTR offers a coordinated assessment throughout all involved countries in the way that one reporting member state will lead the assessment throughout the clinical trial's life cycle. For this, sponsors can request a specific reporting (i .e. leading) member state, however, this request can be overruled by the system and another state may be assigned as reporting.

  The reporting member state has great responsibility. It drives the assessment process for those aspects considered scientifically harmonized, including moderating discussions and preparing the draft assessment report. For instance, if a reporting member state refuses the scientific/technical application, it will be refused for all member states. Sponsors should therefore carefully choose the reporting member state for their trial.

- Another new aspect of EU-CTR is the increased transparency for the public. Data and documents (with a few exceptions) will be made publicly available once a decision has been taken for a given trial.

- Also, new definitions have been implemented. The concept of "low intervention clinical trials" has been introduced. This refers to studies that harbor minimal risks for patients, for instance in the context of investigational medicinal products (IMPs) that are already approved and on the market. These trials may require simpler submission dossiers and overall less stringent rules for some aspects of their conduct.

- The new submission procedure has also defined novel timelines for both applying sponsors as well as the reporting bodies. Overall, these timelines are tighter than before so sponsors should be well-prepared when it comes to potential questions and request that might result from assessments.

To determine the correct product classification in the context of ATMPs, the EMA offers a specific classification procedure administered by the CAT as described above. If a product is classified as an ATMP, it must, as any other medicine in the pipeline, undergo clinical trials to demonstrate safety and efficacy before a MA application (MAA) can be submitted. If the ATMP is planned to be used on a non-routine basis only within the hospital environment, the so-called hospital exemption scheme may be followed[3].

Overall, a MA may be granted in three ways:

- Standard MA
- Conditional MA or
- MA under exceptional circumstances

The type of MA applied for depends on the extent of clinical data obtained during the development and/or how big the unmet medical need in the corresponding indication is. If the product is intended to be used in children, it is mandatory that the clinical development comprises pediatric studies[3].

Medicines for which sufficient clinical data can be provided at the time of MAA will go through the **standard MA procedure**.

Products for which comprehensive clinical data are not expected to be obtained can go through the MA under the **exceptional circumstance procedure**.

Medicines that qualify as orphan medicinal products (based on the rarity of the therapeutic indication), and medicines under an accelerated development program, may go through the **conditional MA (CMA) procedure** initially until the MA can be converted to a standard MA at a later stage. An initial CMA may also be sought for medicines for which a standard development program is not achievable and for which an adaptive licensing route is appropriate.

Finally, **accelerated assessment** (expedited review) of standard and CMAs may be possible for priority medicines (in the PRIME scheme, details see Excursus 3 below) or other medicines addressing an urgent unmet need[3].

The procedures described above are summarized in Figure 14 below.

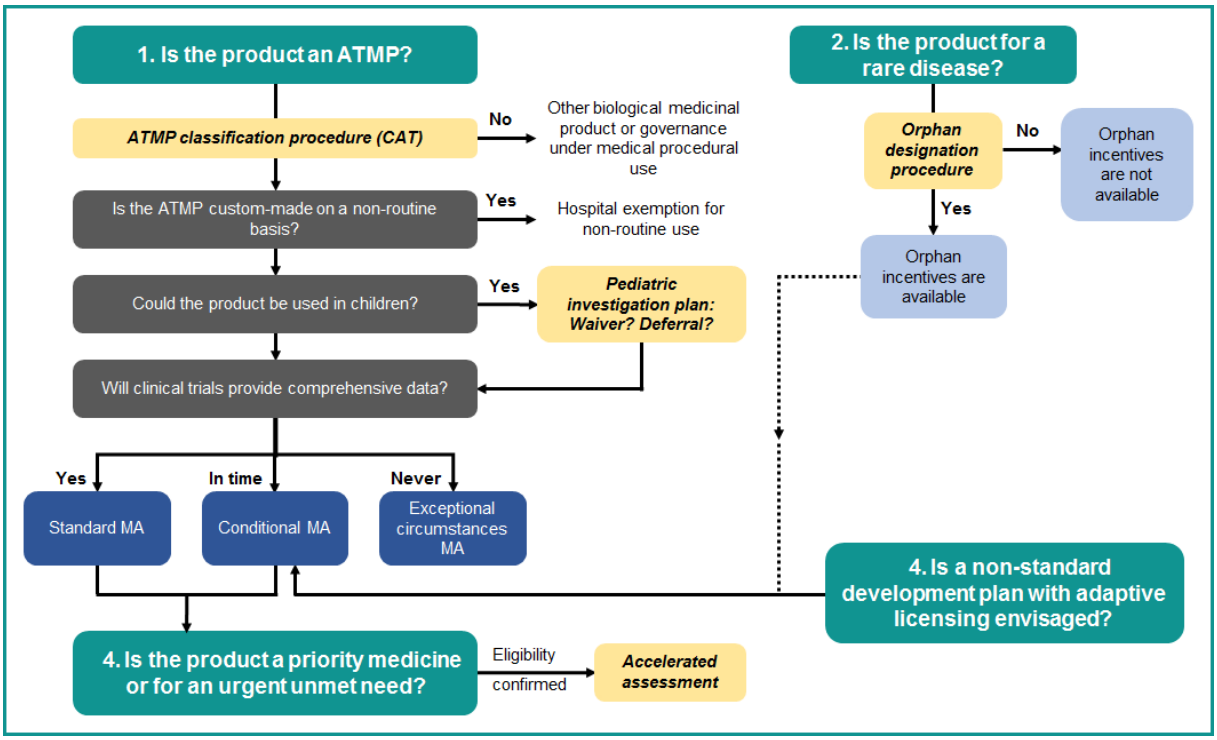


Figure 14: Regulatory pathways to marketing authorization for ATMPs
(adapted from Detela & Lodge, 2019[3])

The actual regulatory process for obtaining an ATMP-based marketing authorization application (MAA) under the centralized procedure can take up to 210 days, not counting clock stops when applicants have to provide additional information for instance. On request, the CHMP can reduce the timeframe to 150 days if the applicant provides sufficient justification for an accelerated assessment. The process is represented in Figure 15.

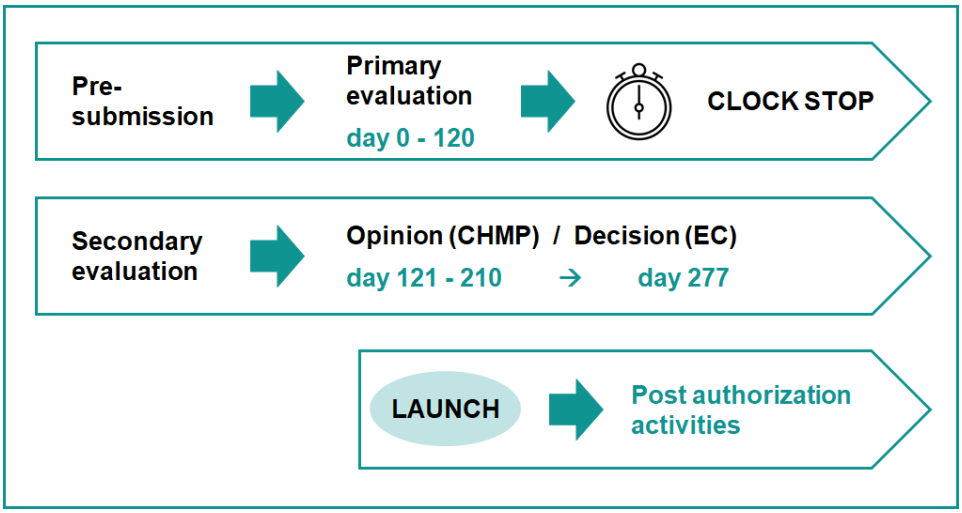


Figure 15: Timeframes for ATMP marketing authorization
(adapted from Celis, 2018[69])

Excursus 3 - the PRIME scheme:

PRIME ("**PRI**ority **ME**dicines") is a scheme launched by the EMA to enhance support for the development of medicines that target an unmet medical need. PRIME is a voluntary scheme, which is based on enhanced interaction and early dialogue with developers of medicines that may offer a major therapeutic advantage over existing treatments, or benefit patients without treatment options. PRIME was designed to optimize development plans and speed up evaluation in order to make these medicines available for patients as soon as possible[70].

The PRIME scheme was introduced in March 2016 and it uses already existing tools of the EU regulatory framework, e. g. scientific advice, conditional approval and accelerated assessment[3].

In March 2022, EMA has published a report presenting results from the first 5 years of its PRIME scheme[71].

The report reveals that in the last five years a total of 18 medicines that had PRIME support were approved in the EU. Of these, 10 received a conditional marketing authorization (CMA), enabling them to access the market earlier, seven are ATMPs and 16 aimed at rare diseases.

According to EMA, enhanced interaction with EU regulators through PRIME is particularly useful for developers of more complex products and for applications relying on smaller datasets, i. e. ATMPs and orphan diseases which are especially facing scientific and regulatory challenges.

The analysis also showed that the support for PRIME products throughout the development resulted in a reduction of clock-stops, i. e. the time required by the applicant to answer questions from EMA during the evaluation. This resulted in faster reviews and faster patient access to PRIME products.

At the time of publication of the report, 98 medicines had been accepted into the scheme. This also includes a first academia-led development, an ATMP intended to treat relapsed or refractory acute lymphoblastic leukemia in adults over 25 years old, which was granted PRIME eligibility in December 2021 (ARI-0001, chimeric antigen receptor T cells targeting CD19 developed by a Spanish group from Barcelona).

The report also states several recommendations for improvements to the scheme in three areas:

- Timing for entering the PRIME scheme
- Flexibility of scientific advice procedures for PRIME medicines
- Leveraging the knowledge built during development for more robust marketing authorization applications that can be assessed in an accelerated manner

5 ATMPs in the academic setting

To date, nearly 1.800 ATMPs have been investigated in clinical studies for various applications and indications. However, despite this large number of investigational projects, the number of ATMPs with a marketing authorization is still low. Overall, the rate of newly authorized products is considered significantly lower than for other types of medicinal products[72].

As elaborated in this paper, ATMP development is a complex matter, explaining this low ratio between investigational projects and actually marketed products. The sharp regulatory setting and requirements around ATMPs shape the innovation trajectory in many ways. Especially GMP- and clinical trial related requirements have an impact on which institutions are in a position to take on ATMP development projects. Developers must shoulder the burden of maintaining GMP manufacturing facilities, of coordinating complex clinical trials and to meet all bureaucratic requirements[73]. But not only infrastructure-related issues are determinants for ATMP development decision making.

Academia and industry have, naturally, diverging motivations in the context of drug development. Whilst both "worlds" certainly consider patient benefit as the top priority, industry-based developers are acting under the pressure of stringent milestone- and financial assessment. The products in their pipeline must be able to not only demonstrate clinical efficacy but also a prospect in terms of highly likely and sufficient profit margins over a certain period of time. In the field of ATMP development, a robust forecast in terms of efficacy and financial output is, however, difficult and the corresponding projects are considered of high risk. This might explain the reluctance observed through the still rather low numbers of ATMP marketing authorizations.

Academic groups, on the other hand, have a natural interest in complex and orphan indications and the institutions harboring these groups aim at providing an environment where specialized clinicians and scientists integrate best patient care with fundamental research and clinical development[74]. Fulfilling this aim is a challenge as the acquisition of funding for complex and therefore costly research projects and clinical studies is a real challenge, especially from public funding bodies. Long timelines, insufficient funding amounts and administrative restrictions imposed by the public providers are some of the challenges. Creating an environment for the development and clinical testing of ATMPs goes along with huge administrative, regulatory, financial and logistic requirements. The centers must have enough and accordingly trained staff, reliable GMP facilities, adequate logistic processes and well-equipped clinical trial units with ideally a phase I facility. To maintain and sustainably run such an infrastructure, comprehensive core funding is needed by the academic centers, especially in the start-up phase when labs, units, staff and processes need to be designed and built according to the stringent regulatory environment of ATMP handling.

However, the set-up and maintenance of academic ATMP-focused infrastructures and associated GMP facilities is not only an investment in terms of scientific opportunities and output. Centers with a proven track-record in preclinical and clinical ATMP involvement are very sought after for the participation in industry-sponsored clinical trials. Such collaborations can help sustaining the infrastructure and, by this, secure the possibility to make use of the environment for projects with less or no funding in for instance rare diseases, which might be unattractive for the pharmaceutical industry.

5.1 Hospital Exemption (HE)

Purely academically driven product developments, or those initiated by SMEs, are typically limited in terms of financial resources. Preclinical and clinical development are lengthy and costly processes and academia is usually not in a position to meet the requirements of a central European MA.

In this context the so-called Hospital Exemption (HE) can be a valuable alternative to allow patients to benefit from innovative developments which still lack a formal central MA. The exemption is included in Article 5 of the EU Directive 2001/83/EC[18] and the German AMG (Arzneimittelgesetz) has implemented it in § 4b[75]. The HE is a national procedure and represents an option to allow for use of specific products under certain circumstances, which are (exemplary for Germany):

- The product is an ATMP
- The product is prescribed by a physician as an individual preparation for an individual patient
- The product is manufactured in Germany according to specific quality standards
- The product is not routinely manufactured in Germany
- The product is used in Germany in a specialized health care facility
- The product is used in Germany under the professional responsibility of a physician

In order to be administered under these conditions, HE-ATMPs must be approved by the national competent authority (the PEI in the case of Germany). Manufacturers of HE-ATMPs must inform the authorities in regular time intervals about the manufacturing volumes and they must report any new insights, which are relevant for a comprehensive and continuous assessment of the product[16].

The quality, efficacy and safety of HE-ATMPs is being assured through the specific approval procedure for HEs in the corresponding market (according to § 4b Abs. 3 AMG in Germany). For this, a manufacturing license is required for the site producing the HE-ATMP and they must fulfil specific requirements regarding quality assurance and control. In terms of pharmacovigilance the usual reporting standards apply and the use of the product is bound to regulations and legislations regarding the traceability of medicinal products that are manufactured from human tissues and cells[16].

The definition of “non-routine manufacturing” can be broken down to meeting one of the following criteria:

- The product is manufactured in small quantities and there are deviations in the manufacturing procedure, which are based on medical reasons for the individual patient
- The product has not yet been manufactured in sufficient quantity so that there are not yet sufficient findings in order to perform a comprehensive product assessment

Especially based on the limited data and knowledge regarding the HE-ATMP at the time of approval, HEs can be of temporary nature. The time horizon for the duration of approval is individually determined by the authorities.

Overall, the HE is a good opportunity, especially for academic centers, to develop their own ATMPs in a more manageable setting than the process of a central European MA. HE helps to develop products in close contact with clinical practice, with the quality and rapid access needed by patients and at a lower cost compared to regular MA.

6 Q&As on ATMPs

ATMPs as a distinct product category are quite new and the delimitation of certain aspects in the context of their definitions can be challenging. We have therefore collected a number of potential questions and answers (Q&As) in order to address these. The Q&As presented below are mainly based on a corresponding summary provided by ATMP Sweden, the Swedish national network of activities within ATMPs in Europe, which offers good reading on the topic[13].

Why are cell-based ATMPs different to traditional transplants?

Traditional transplant cells or tissues are not considered to be substantially manipulated outside the body and are used for the same essential function in the donor and the patient. Both autologous and allogeneic cells used in conventional transplantation procedures are only processed in ways that are not deemed to change their behavior and when delivered to the patient will continue to perform the function they performed in the donor. For a cell based ATMP, the cells from a donor are either deemed to behave differently in the patient due to substantial manipulation steps outside the body and/or due to a different essential function in the patient compared to their original role in the donor[13].

Can the same cells be an ATMP in one context and not in another?

YES. If the cells are not substantially manipulated but are used for a different essential function in the patient they are classified as an ATMP. For instance, to transplant bone marrow from a donor to patient, the bone marrow cells are not considered an ATMP. However, to administer that same bone marrow to the patient's heart would fall in the ATMP definition (different function/purpose)[13].

Are synthetic oligonucleotide-based products ATMPs?

NO. Legally, synthetic oligonucleotide-based medicines are not classified as gene therapies. Only those products with active substances based on

recombinant DNA technologies that are delivered to patients to add or regulate gene sequences are considered gene therapies. Although synthetically produced oligonucleotides can widely be referred to as gene therapies, they are better described as complex small molecule medicinal products or nucleotide-based medicines[13].

Can recombinant mRNAs be ATMPs?

YES. If the mRNA is produced from a recombinant source, e. g. plasmids, and the resultant mRNA will be delivered to patients with a mechanism of action based on the mRNA or protein translated from it. Legally, synthetic oligonucleotide-based medicines are not classified as gene therapies[13,76].

Are mRNA vaccines, such as the recently developed anti-COVID-19 products, ATMPs?

NO. Vaccines are products with a mechanism of action intended to treat or prevent a viral infection. Therefore, even if produced from recombinant nucleic acid technologies these products are regulated as vaccines and do not fall under the ATMP regulation. Only if the recombinant nucleic acid product was intended to treat pathologies caused by the infection, for example malignancies, it would be classified as an ATMP[13].

Can recombinant bacteria being delivered to a patient be a GTMP?

YES. For example, bacteria genetically engineered and delivered to a patient to secrete a recombinant therapeutic protein are regulated as a GTMPs. The classification in this case is that the recombinant nucleic acid administered to human beings adds a genetic sequence that has a direct therapeutic effect[13,77].

Are extracellular vesicles (EVs) ATMPs?

IT DEPENDS. If the product consists of EVs that are purified from non-modified or genetically modified cells, but the vesicles only contain functional transgenic protein, they are not classified as ATMPs but as biologics. If the EVs contain functional transgenic mRNAs that will perform the intended therapeutic function in the patient they fall under the ATMP classifications (i. e. as GTMPs)[13,78].

Are de-cellularized tissues delivered to patients ATMPs?

IT DEPENDS. If de-cellularized tissue is transplanted back to a patient without addition of cells, it is regulated as a medical device. If it is re-cellularized with cells that have not been substantially manipulated and if the tissue is to be used for

the same essential function in the patient as in the donor it is not an ATMP either. However, if de-cellularised tissue is re-cellularized with cells that are substantially manipulated, it falls under the ATMP classification (as a TEP). If de-cellularized tissue is re-cellularized with cells that have not been substantially manipulated but the tissue is to be used for a different essential function in the patient compared to the donor it is also considered a TEP[13].

7 Appendices

7.1 Product classification overview

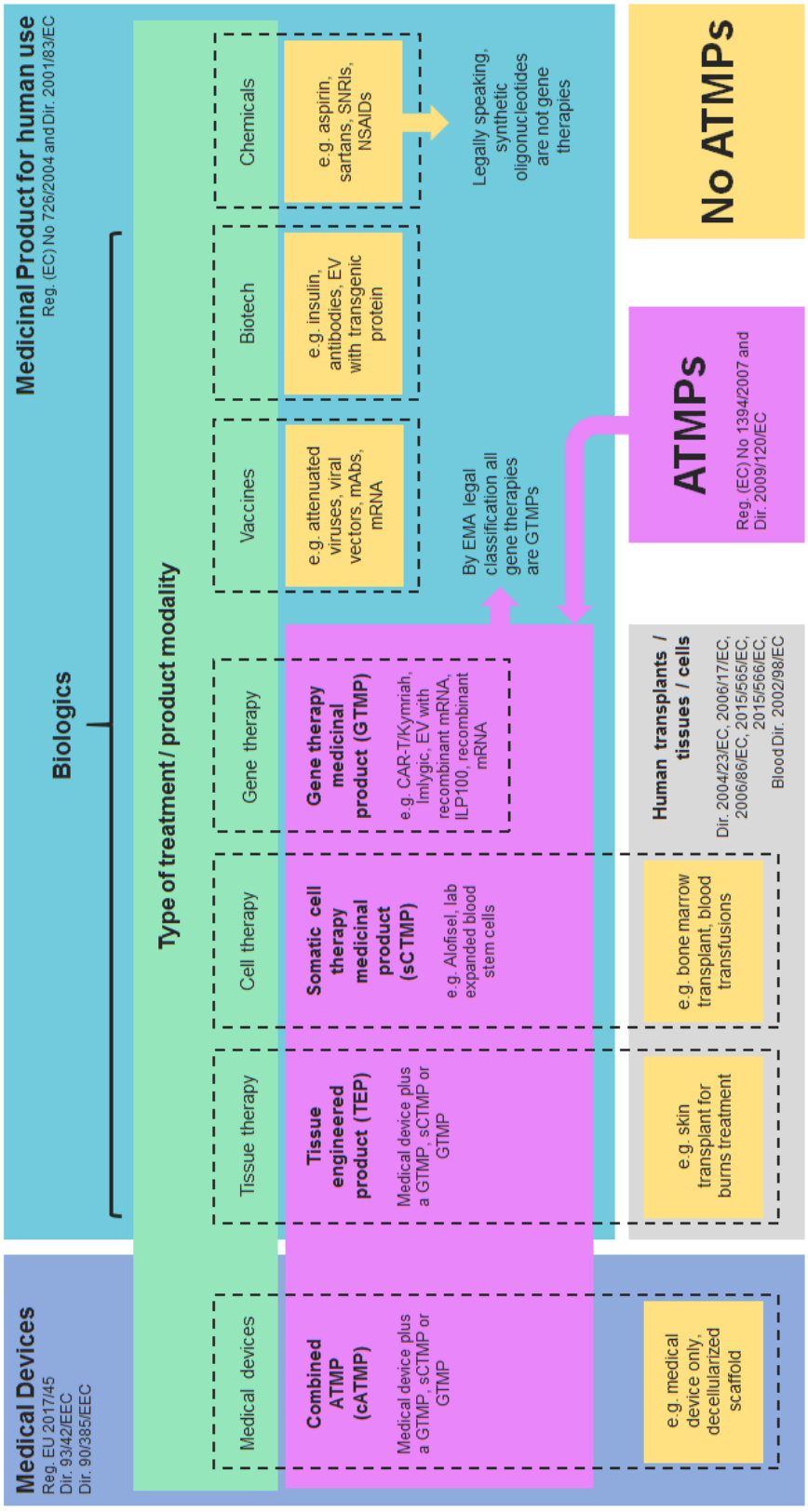
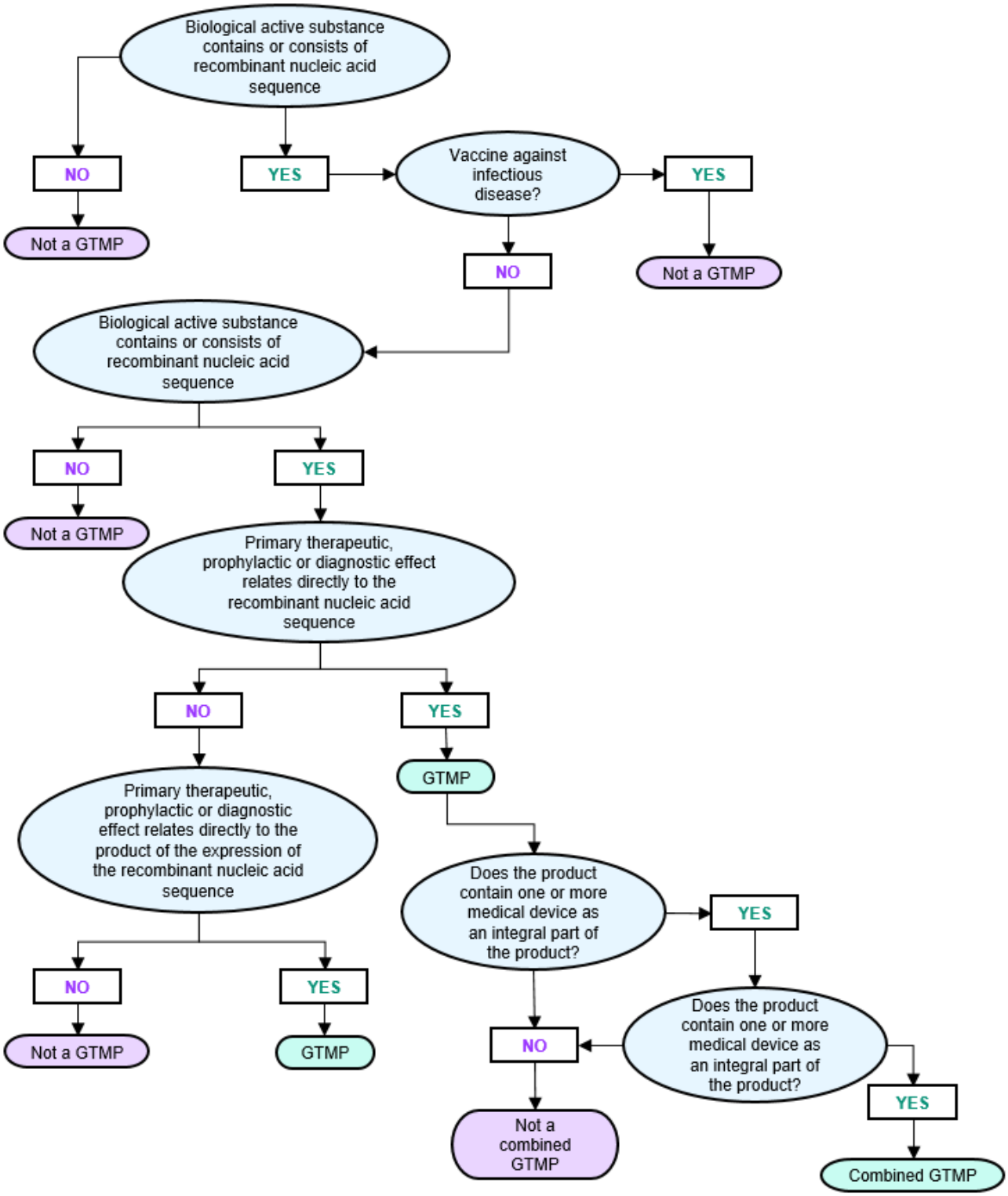
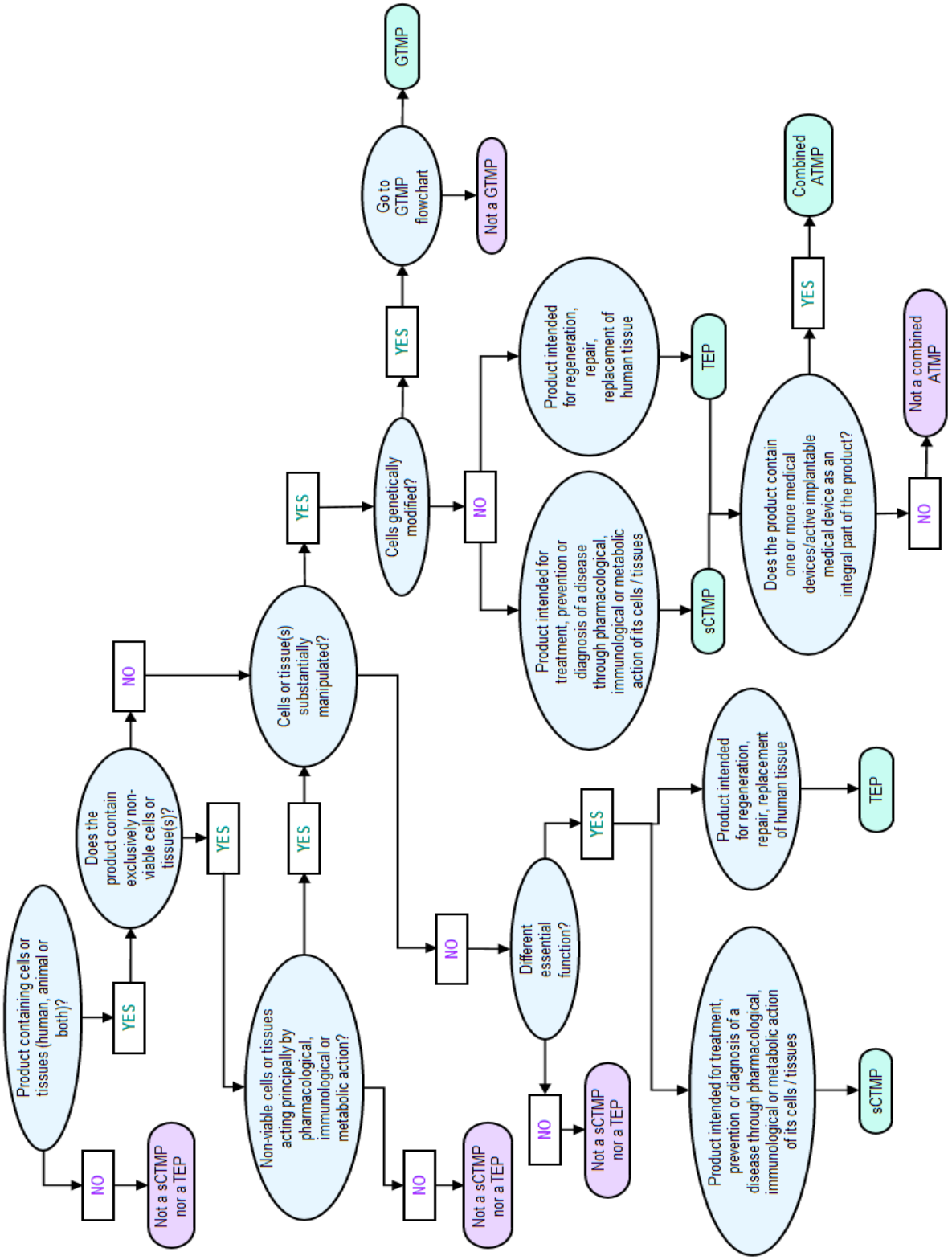


Figure 16: Overview medicinal classifications and regulatory frameworks (adapted from Hoogendoorn & Main, 2020[79])

7.2 EMA / CAT decision tree for GTMPs[63]



7.3 EMA / CAT decision tree for sCTPMs and TEPs[63]



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