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Classification of cellular therapy and gene therapy (CGT) products:

How regulators are working with industry.

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Introduction

Advanced therapy medicinal products (ATMPs)/cellular therapy and gene therapy (CGT) products are a rapidly growing innovative class of biopharmaceuticals due to their potential to offer therapeutic breakthroughs for many ailments, especially life-threatening cancers and rare serious inherited disorders for which conventional medicine and various other modalities have not been completely effective. Due to their unique ability to address the unmet needs, health authorities across the globe are actively encouraging their development. The 2019 Annual Report published by the Alliance for Regenerative Medicine (ARM), mentioned worldwide 1078 ongoing clinical trials and over 1000 regenerative medicine and advanced therapy companies worldwide, including gene, cell, and tissue-based therapeutic developers. Of these, over 500 developers are based in the United States and over 200 are based in the European Union [1]. In both EU and US regions, advanced therapies fall under the regulatory framework of biological products that determines the legal basis of their development [2]. Considering the nature and complexity of these products, appropriate classification of advanced therapies is very crucial for regulatory oversight, quality assurance, and patient safety. In the European Union, the classification of ATMPs involves categories such as somatic cell therapy products (SCTMP), tissue-engineered products (TEP), and gene therapy medicinal products (GTMP), whereas in the United States, there are two major categories, i.e., CGT products under the broad classification of biological products. The terminologies and definitions of these product types differ or overlap across various regions and even regional determination of classification for each product is not as easy and straightforward as it appears. **Table 1 refers to the various terminologies referred in the EU and US regions**.

Table 1. Terminologies referred in EU and US.

(Adapted from: Regulation (EC) No.1394/2007, Directive 2001/83/EC & Directive 2009/120/EC, 21 CFR part 11, section 600.3, 21 CFR 1271.10, 1271.3, FDA Guidance for Human Somatic Cell Therapy and Gene Therapy. March 1998 and weblink: www.fda.gov.)

Terminologies used in the EU	Terminologies used in the US
ATMP[a] means any of the following medicinal products for human use: ▪ a GTMP ▪ a SCTMP ▪ a TEP	**CGT/ Somatic cell therapy and gene therapy products[b]** This group includes products that do not meet all the criteria in 21 CFR 1271.10[(a)] and are regulated as drugs and/or biological products. Examples include but are not limited to gene therapy products, human cells used in therapy involving the transfer of genetic material (cell nuclei, oocyte nuclei, mitochondrial genetic material in ooplasm, genetic material contained in a genetic vector), and unrelated allogeneic hematopoietic stem cells. Gene therapy product and somatic cell therapy products are explained in detail, including the differences between the two in the subsequent sections.
Biological medicinal product[c] a product, the active substance of which is a biological substance. Immunological medicinal products, medicinal products derived from human blood and human plasma, and ATMPs shall be considered biological medicinal products **Biological substance[c]** a substance that is produced by or extracted from a biological source and needs a combination of physicochemical-biological testing for its characterization and the determination of its quality, together with the production process and its control	**Biological product[d]** means a virus, therapeutic serum, toxin, antitoxin, vaccine, blood, blood component or derivative, allergenic product, protein, analogous product, arsphenamine or derivative of arsphenamine (or any other trivalent organic arsenic compound) applicable to the prevention, treatment, or cure of a disease or condition of human beings
GTMP[e] a biological medicinal product that has the following characteristics: (a) contains an active substance that contains or consists of a recombinant nucleic acid used in or administered to human beings with a view to regulate, repair, replace, add, or delete a genetic sequence (b) its therapeutic, prophylactic, or diagnostic effect relates directly to the recombinant nucleic acid sequence it contains or to the product of genetic expression of this sequence. (c) GTMPs shall not include vaccines against infectious diseases.	**Gene therapy product[f]** Gene therapy is a medical intervention based on modification of the genetic material of living cells. Cells may be modified ex vivo for subsequent administration to humans or may be altered in vivo by gene therapy given directly to the subject. When the genetic manipulation is performed ex vivo on cells which are then administered to the patient, this is also a form of somatic cell therapy. The genetic manipulation may be intended to have a therapeutic or prophylactic effect or may provide a way of marking cells for later identification. Recombinant DNA materials used to transfer genetic material for such therapy are considered components of gene therapy and as such are subject to regulatory oversight.

SCTMP[e]

a biological medicinal product that

(a) contains or consists of cells or tissues that have been subject to substantial manipulation so that biological characteristics, physiological functions, or structural properties relevant for the intended clinical use have been altered, or those cells or tissues that are not intended to be used for the same essential function(s) in the recipient and the donor.

(b) is presented as having properties for or is used in or administered to human beings with a view to treat, prevent, or diagnose a disease through the pharmacological, immunological, or metabolic action of its cells or tissues.

Somatic cell therapy[f]

The term somatic cell therapy refers to the administration of autologous, allogeneic, or xenogeneic living non-germline cells, other than transfusable blood products to humans for therapeutic, diagnostic, or preventive purposes.

The manufacturing of products for somatic cell therapy involves the ex vivo propagation, expansion, selection, or pharmacologic treatment of cells or other alteration of their biological characteristics. Such cellular products might also be used for diagnostic or preventive purposes.

HCT/Ps[g]

mean articles containing or consisting human cells or tissues that are intended for implantation, transplantation, infusion, or transfer into a human recipient. Examples of HCT/Ps include but are not limited to bone, ligament, skin, dura mater, heart valve, cornea, hematopoietic stem/progenitor cells derived from peripheral and cord blood, manipulated autologous chondrocytes, epithelial cells on a synthetic matrix, and semen or other reproductive tissue.[g]

These HCT/Ps are regulated solely as "361 products" under section 361 of the PHS Act if they meet all the criteria in 21 CFR 1271.10[h]

TEP[i]

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 regenerate, repair, or replace a human tissue. A TEP 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, biomolecules, biomaterials, chemical substances, scaffolds, or matrices.

ATMP: Advanced therapy medicinal product; CGT products: Cellular therapy and gene therapy products; GTMP: Gene therapy medicinal product; HCT/Ps: Human cells, tissues, and cellular and tissue-based products; SCTMP: Somatic cell therapy medicinal product; TEP: Tissue-engineered product.

[a] Article 2(1)(a) of Regulation (EC) No.1394/2007

[b] Available at: https://www.fda.gov. Accessed on 02 Feb 2021

[c] Directive 2001/83/EC, Annex 1, Part I, Section 3.2.1.1(b)

[d] 21 CFR part 11, section 600.3.

[e] Directive 2009/120/EC (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), Part IV of Annex I to Directive 2001/83/EC, as amended

[f] FDA Guidance for Human Somatic Cell Therapy and Gene Therapy. March 1998

[g] 21 CFR 1271.3

[h] 21 CFR 1271.10

[i] Article 2(1)(b) of Regulation (EC) No. 1394/2007

Combined ATMPs versus Combination Products

The combination products are also defined differently in both regions, with a broader classification in the United States, whereas these have a very specific meaning in the European Union (**Table 2**). For example, in the US drug/device, drug/biologic combinations, antibody–drug conjugates, etc. are classified under a blanket term of combination products. In the European Union, drug device combinations are classified separately as drug device combinations. For example, Autologous Cultured Chondrocytes on a Porcine Collagen Membrane (MACI) is an autologous implant consisting characterized cultured chondrocytes (biological component) seeded onto a resorbable Type I/III (ACI-MaixTM) collagen membrane (device component). In the United States, MACI comes under the definition of a combination product and has been approved since 2016 for the repair of single or multiple symptomatic, full-thickness cartilage defects of the knee with or without bone involvement in adults. The same was classified as combined ATMP and was first approved in the European Union in 2013, though the license was withdrawn in 2014, post manufacturing site closure, due to commercial reasons [3,4].

Table 2. Combined ATMP and Combination Product

(Adapted from: Regulation (EC) No.1394/2007 and 21 CFR 3.2(e))

cATMPs[a]	Combination Product[b]
A combined ATMP: (a) must incorporate, as an integral part of the product, one or more medical devices within the meaning of or one or more active implantable medical devices and (b) its cellular or tissue part must contain viable cells or tissues (c) or its cellular or tissue part containing non-viable cells or tissues must be liable to act upon the human body with action that can be considered primary to that of the devices referred to	**The term combination product[b] includes any of the following:** a) A product comprising two or more regulated components, i.e., drug/device, biologic/device, drug/biologic, or drug/device/biologic, that are physically, chemically, or otherwise combined or mixed and produced as a single entity. b) Two or more separate products packaged together in a single package or as a unit and comprising drug and device products, device and biological products, or biological and drug products. c) A drug, device, or biological product packaged separately that according to its investigational plan or proposed labeling is intended for use only with an approved individually specified drug, device, or biological product, where both are required to achieve the intended use, indication, or effect, and where, upon approval of the proposed product, the labeling of the approved product would need to be changed, e.g., to reflect a change in the intended use, dosage form, strength, route of administration, or significant change in dose. d) Any investigational drug, device, or biological product packaged separately that according to its proposed labeling is for use only with another individually specified investigational drug, device, or biological product, where both are required to achieve the intended use, indication, or effect.

cATMP: Combined advanced therapy medicinal product

[a] Article 2(1)(d) of Regulation (EC) No. 1394/2007

[b] 21 CFR 3.2(e)

Classification challenges

In the European Union, if a product falls within two or more definitions at the same time, the product will be classified under the most complex category for regulatory considerations. For example, if a product falls within the definitions of both SCTMP and TEP, it will be considered TEP. Similarly, if a product falls within the definitions of SCTMP or TEP and GTMP, the product will be considered GTMP [5]. For example, CAR-T cell therapies such as Kymriah (tisagenlecleucel) and Yescarta (axicabtagene ciloleucel) have been classified as GTMP in the European Union and cell-based gene therapy in the United States [6–9].

In the European Union, SCTMP and TEP are defined separately and are classified based on indication, whereas there is no specific definition or category of TEP in the United States. Human cells, tissues, and cellular and tissue-based products (HCT/Ps) is another terminology being used in the United States. HCT/Ps are the articles containing or consisting human cells or tissues intended for implantation, transplantation, infusion, or transfer into a human recipient and are not always classified as advanced therapies. To clarify this, 21 CFR 1271 has established a tiered, risk-based approach to the regulation of HCT/Ps, which is explained below [2,10,11]:

- Low-risk HCT/Ps that are the subject to a little oversight by the Food and Drug Administration (FDA).
- The 361 HCT/Ps are considered to pose moderate risk and are regulated under PHS Act 361 and Part 1271.
- The high-risk products (351 HCT/Ps) meet the criteria of "more than minimally manipulated" and "non-homologous use" and require full approval as new drugs, biologics, and/or medical devices under Public Health Service Act (PHS Act) 351 and/or the Federal Food, Drug, and Cosmetic Act (FDCA). These products are also called "human somatic cell therapy products" and are classified under advanced therapies.

The term minimal manipulation refers to processing that does not alter the original relevant characteristics of the tissue related to the tissue's utility for reconstruction, repair, or replacement for structural tissues. For cells or non-structural tissues, it refers to the processing that does not alter the relevant biological characteristics of cells or tissues [12]. In European Union, the term substantial manipulation is used if biological characteristics, physiological functions, or structural properties have been modified to be relevant for their intended function during the manufacturing process.

How regulators are working with industry?

In the United States, FDA is the legal authority to authorize human medicinal products. The responsibilities are distributed to specific centers. The Centre for Biologics Evaluation and Research (CBER) regulates a variety of biological products, including blood and blood products; vaccines; allergenic products; and cellular, tissue, and gene therapies as well as some related devices. Cell and gene therapies are considered biological products and fall under the jurisdiction of Office of Tissues and Advanced Therapies (OTAT), formerly known as Office of Cellular, Tissue, and Gene Therapies (OCTGT) that is located within CBER. Gene therapy, tumor vaccines, xenotransplantation, stem cells, human tissue for transplantation, combination products, bioengineered tissues, and certain medical devices are considered OTAT-regulated products. In the United States, the Tissue Reference Group (TRG) acts as the single reference point for product specific questions. Inquirers who do not agree with a recommendation provided by the TRG may submit a Request for Designation (RFD) or a pre-RFD to OCP, as described in 21 CFR part 3 [13].

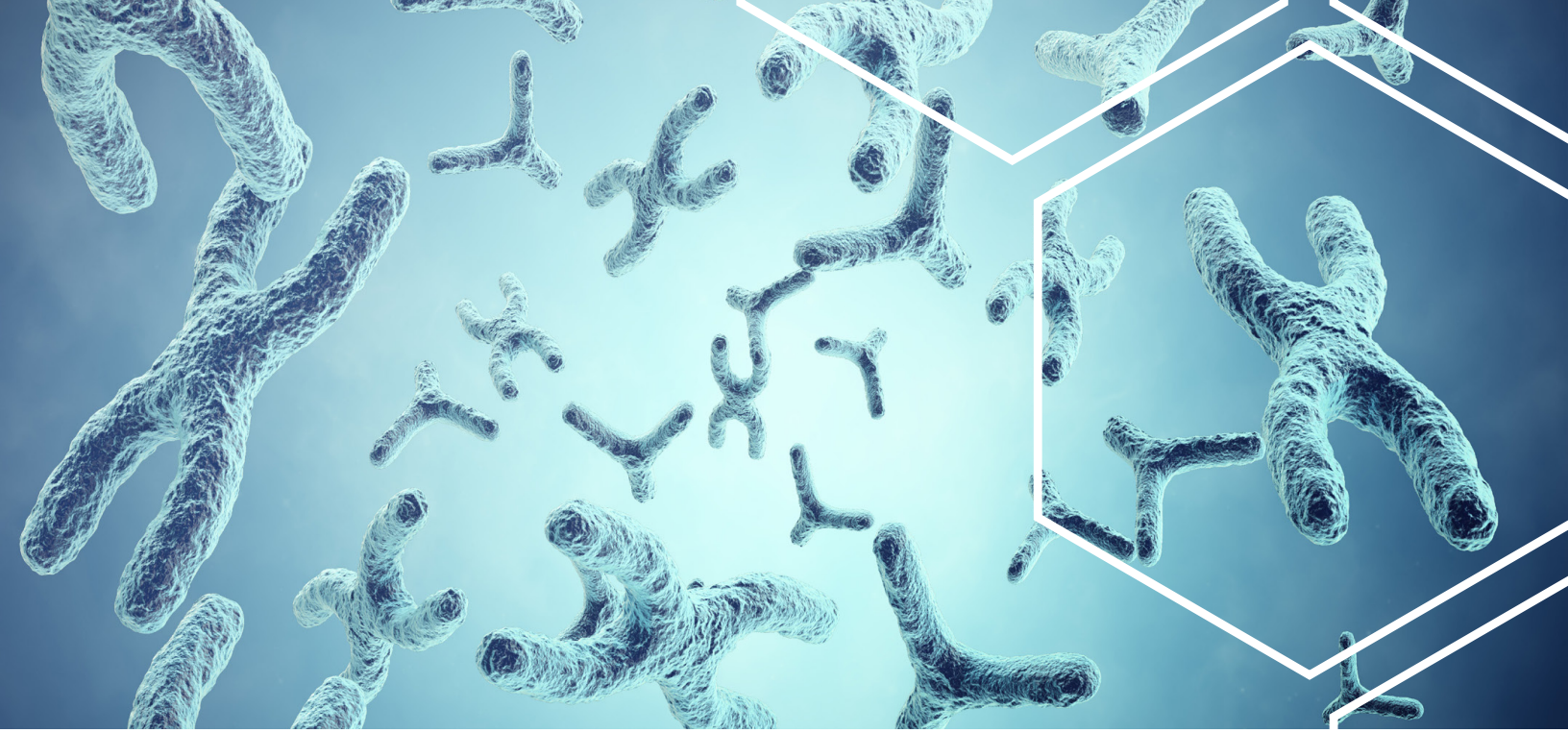
In the European Union, marketing authorization for advanced therapies must be applied for via the centralized procedure (CP) at the European Medicines Agency (EMA)[4]. The European Commission (EC) is the authorizing body for centrally authorized products (CAP) and takes legally binding actions based on EMA decision. The Committee for Medicinal Products for Human Use (CHMP) elaborates agency opinions on issues related to medicinal products. There is a multidisciplinary expert Committee for Advanced Therapies (CAT) that oversees quality, safety, and efficacy of ATMPs and reviews applications for marketing authorization, classification, certification, and scientific advice for ATMPs. The EMA guidance on reflection paper on classification of ATMPs (EMA/CAT/600280/2010 rev.1) should be referred to classify these products. To address questions on borderline classification, the EMA can be consulted by the companies to determine whether a medicine they are developing should be considered an ATMP or not. The outcome of the assessment of ATMP classification are published by the EMA as summary reports [14]. These summaries may include but are not limited to product description, proposed indication, classification outcome, and the rationale for classification of ATMPs. Over 200 such summaries have been published by the EMA since 2009 of which a few examples from each category have been illustrated in **Table 3**.

Table 3. ATMP classification of a few products after EMA review

(Adapted from the available summaries at EMA [15])

Product description	Proposed indication	Classification	Rationale
DNA plasmid vector encoding human IL-12	Advanced melanoma	GTMP	The product contains an active substance which consists of a recombinant nucleic acid administered to human beings with a view to add a genetic sequence, and its therapeutic effect relates directly to the product of genetic expression of this sequence.
Allogeneic mesenchymal stem cells suspended in cell supernatant	Osteoarthritis	TEP	It contains engineered cells that have been subjected to substantial manipulation, so that biological characteristics, physiological functions, or structural properties relevant for the intended regeneration, repair, or replacement are achieved, and it is presented as having properties for regenerating, repairing, or replacing a human tissue.
Human umbilical cord blood-derived mesenchymal stem cells	Atopic dermatitis	SCTMP	Consists of cells that have been subject to substantial manipulation so that biological characteristics, physiological functions, or structural properties relevant for the intended clinical use have been altered and is presented as having properties for or is administered to human beings with a view to treat atopic dermatitis through the pharmacological or immunological action of its cells
Autologous enriched CD31+ cell fraction from peripheral blood	Surgical care of bone fractures	not an ATMP	Does not contain cells that have been subject to substantial manipulation or cells that are intended to be used for the same essential function(s) in the recipient and the donor.

ATMP: Advanced therapy medicinal product; EMA: European Medicines Agency; GTMP: Gene therapy medicinal product; SCTMP: Somatic cell therapy medicinal product; TEP: Tissue-engineered product.



Brexit changes

Further in the United Kingdom, Medicines and Healthcare products Regulatory Agency (MHRA) has published Brexit guidelines on how these products will be regulated in relation to Great Britain and Northern Ireland. However, definitions and classification of ATMPs will remain unchanged, and the EMA guidance on reflection paper on classification of ATMPs (EMA/CAT/600280/2010 rev.1) can be referred. In case of further clarification about the classification of their products, sponsors can also contact MHRA by filling the ATMP advice form [16].

Discussion

The therapeutic products should be categorized per the regulatory definitions due to differences in applicable regulations for drugs, biologicals, and medical devices. Certain adverse effects may be specific to the product characteristics, such as inappropriate cell proliferation and/or cell differentiation for cell-based products, potential for insertional mutagenesis, or transgene-related concerns for the gene-based products. Depending upon the product category and persistence, post-marketing observational studies may be mandated by the regulators to evaluate the long-term safety and efficacy of these products. For example, in the United States, complex products such as cell-based gene therapy are usually approved with risk evaluation and mitigation strategies (REMS) in place along with stringent safety precautions also known as elements to assure safe use (ETASU). In the European Union, the risk management plan should include routine and additional risk minimization measures as applicable. Additionally, these products may fall under additional monitoring list, i.e., they are monitored more intensively than other medicines. Considering the nature and complexity of these products, appropriate classification of advanced therapies is very crucial for regulatory oversight and quality assurance and for monitoring safety and efficacy of these products.

References

1. Available at: https://alliancerm.org/. Accessed on 02 Feb 2021.
2. Iglesias-López C, Agustí A, Obach M, Vallano A. Regulatory framework for advanced therapy medicinal products in Europe and United States. Front Pharmacol. 2019 Aug 30;10:921.
3. Available at: https://www.fda.gov/vaccines-blood-biologics/cellular-gene-therapy-products. Accessed on 02 Feb 2021.
4. Available at: https://www.ema.europa.eu/en/medicines/human/referrals/maci. Accessed on 02 Feb 2021.
5. Directive 2009/120/EC (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).
6. Available at: https://www.ema.europa.eu/en/medicines/human/EPAR/yescarta. Accessed on 02 Feb 2021.
7. Available at: https://www.ema.europa.eu/en/medicines/human/EPAR/Kymriah. Accessed on 02 Feb 2021.
8. Available at: https://www.fda.gov/news-events/press-announcements/fda-approval-brings-first-gene-therapy-united-states. Accessed on 02 Feb 2021.
9. Available at: https://www.fda.gov/news-events/press-announcements/fda-approves-car-t-cell-therapy-treat-adults-certain-types-large-b-cell-lymphoma. Accessed on 02 Feb 2021.
10. Luria X. Handbook about Regulatory Guidelines and Procedures for the Preclinical and Clinical Stages of Advanced Therapy Medicinal Products (ATMPs). BIOREG (SOE3/P1/E750)- Co-financed by the INTERREG IVB SUDOE Program with ERDF funds.
11. Blumenfeld BAB. FDA sharpens its focus on regenerative medicine regulation. Available at: https://www.fdli.org/2017/08/fda-sharpens-focus-regenerative-medicine-regulation/#:~:text=FDA%E2%80%99s%20current%20HCT%2FP%20regulatory%20approach%20is%20based%20on,exceptions%20and%20are%20the%20subject%20of%20little%20FDA. Accessed on 02 Feb 2021.
12. 21 CFR 1271.3
13. Available at: https://www.fda.gov/vaccines-blood-biologics/tissue-tissue-products/tissue-reference-group. Accessed on 02 Feb 2021.
14. Advanced therapy classification | European Medicines Agency (europa.eu). Available at: https://www.ema.europa.eu/en/human-regulatory/marketing-authorisation/advanced-therapies/advanced-therapy-classification. Accessed on 02 Feb 2021.
15. Available at: https://www.ema.europa.eu/en/human-regulatory/marketing-authorisation/advanced-therapies/advanced-therapy-classification/summaries-scientific-recommendations-classification-advanced-therapy-medicinal-products. Accessed on 02 Feb 2021.
16. Available at: https://www.gov.uk/guidance/guidance-on-licensing-biosimilars-atmps-and-pmfs. Accessed on 02 Feb 2021.

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