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Combined advanced therapy medicinal products: European regulatory requirements, pathways and processes

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Abstract

Combined advanced therapy medicinal products (CATMPs), regulated in the European Union (EU) under the Advanced Therapy Medicinal Product Regulation, contain one or more medical devices as an integral part of the product. These products offer innovative new treatment and prevention opportunities for many diseases, dysfunctions and injuries to various parts of the human body. However, these products are associated with additional challenges compared to conventional products because each component of such products is often covered by distinct requirements, regulations and guidelines. New European legislation has ensured that expertise is available at the European Medicines Agency (EMA) to assess these state-of-the-art products. The current legislation offers incentives supporting continued research and development of CATMPs and future generations of therapies.

Introduction

Advances in cellular and molecular biotechnology have resulted in an emerging and rapidly growing segment of biological medicinal products and advanced therapy medicinal products (ATMPs). ATMPs are medicines for use in humans that are based on genes, tissues or cells incorporating one of the following advanced technologies: 1) technology modifying the patient's genome, 2) nucleic acids or genes that are recombinant (novel sequences not otherwise found in the genome), 3) substantially manipulated cells or 4) cells modified to function differently in the patient than they had in the donor. There are three different types of ATMPs:[1,2,3]

- Gene therapy medicinal products (GTMPs) or medicines which contain genes that elicit a therapeutic prophylactic or diagnostic effect and work by inserting "recombinant" genes (DNA that is created by bringing together DNA from different sources) into cells, usually to treat a variety of genetic disorders, e.g., cancer or chronic diseases

- Somatic cell therapy medicinal products (CTMPs) or medicines which contain cells or tissues that have been manipulated to change their biological characteristics and can be used to cure, diagnose or prevent disease, e.g., the use of a patient's manipulated immune cells (CAR-T, as an example) to fight the remaining cancer cells in their body
- Tissue-engineered products (TEPs) or medicines which contain cells or tissues that have been modified so they can be used to repair, regenerate or replace tissue, e.g., artificial skin used to treat patients with burns

The EU does not have a "combination product" class for medicinal products and most products combining a medicine with a medical device are regulated under either the medicinal product legislation or the medical device legislation, depending on the product's principal intended action;[3,4] however, for ATMPs containing one or more medical devices as an integral part of the medicine there is a "combined ATMP" (or CATMP) product classification regulated under the ATMP Regulation (EC) No. 1394/2007 [unless the cell/tissue component is non-viable and its action is ancillary to that of the device component(s)].[1] This article provides an overview of the European regulatory requirements, pathways and process options for CATMPs in particular.[1,2]

Regulatory framework for CATMPs

Directives and regulations relevant to the licensing of ATMPs fall under Directive 2001/83/EC,[5] Directive 2009/120/EC[6] and Regulation (EC) No 726/2004,[7] as well as Regulation (EC) No 1394/2007. Regulation (EC) No. 1394/2007 of November 13, 2007 on ATMPs came into force on December 30, 2008. This defines ATMPs, their authorization procedure, supervision and monitoring to ensure that they are safe and effective. It also provides incentives to encourage research and development (R&D) of these therapies by providing fee reductions for scientific advice (SA) and centralized marketing authorization applications (MAAs) via the EMA. The EMA monitors the safety and effectiveness of marketed ATMPs.

The Committee for Advanced Therapies (CAT) provides scientific expertise and plays a central role in the evaluation of ATMPs. During the assessment procedure, the CAT prepares a draft opinion on the quality, safety and efficacy of an ATMP, which is sent to the Committee for Medicinal Products for Human Use (CHMP). Based on the CAT opinion, the CHMP adopts a recommendation, and on that basis the European Commission (EC) may grant or refuse a marketing authorization (MA). The CAT also provides recommendations on the classification of ATMPs, reviews data of products developed, contributes toward SA on ATMPs, encourages the development of ATMPs and provides scientific expertise for any initiatives related to the development of innovative products and therapies at the request of the EC.[1]

For medicinal products with an integral delivery device element, the details of the device aspects are included in the Quality Module of the submission documentation, and it is the responsibility of the competent authority (CA) to assess this documentation. The device should comply with Annex I of the Medical Device Regulation (MDR).[8] In general, for medicinal products incorporating a device element, CAs accept the EC Declaration of Conformity for many drug delivery devices. ATMPs may incorporate medical devices or active implantable medical devices as defined in Regulation 2017/745.[8] A medical device evaluation is conducted in accordance with ATMP Regulation.[9,10] A notified body (NB) for medical devices may be involved in the assessment of the medical device element of a CATMP. As the CAT prepares the draft opinion on a CATMP, it is also the committee which primarily interacts with a NB in the context of the procedure described in Regulation 2017/745. Article 9 of the ATMP Regulation[10] provides that where a CATMP is concerned, the whole product shall be subject to final evaluation by the EMA and that MAAs for CATMPs shall include evidence of conformity with the essential and general safety and performance requirements as well as the results of the assessment by a NB.

The Applicant of a CATMP is the person legally responsible for submitting a MAA for the CATMP to the EMA. The Marketing Authorization Holder (MAH) shall be responsible for placing the CATMP on the market, in accordance with Article 2 of Regulation (EC) No. 726/2004.[7] Data supporting the scientific and technical specifications for a CATMP must be provided in accordance with Annex I, Part IV of Directive 2001/83/EC,[5] (as amended, specifically by Directive 2009/120/EC6, section 3.4.2), and other relevant EMA guidance.[11] The "Guideline on human cell-based medicinal products" in particular includes various sections regarding aspects of CATMPs.[12] Furthermore, the details of regulatory and procedural guidance for the development ATMPs can be found on the EMA website.[11]

Classification of CATMPs

Article 17 of the ATMP Regulation provides that companies can apply to the EMA to determine whether a product they are developing is an ATMP. The EMA established this procedure to address questions of borderline classification with other areas such as medical devices. The CAT delivers scientific recommendations on ATMP classification after consultation with the EC within 60 days after receipt of the request. If the product is not considered an ATMP by the EMA but contains human tissues or cells it will be regulated entirely by Directive 2004/23/EC for the donation, procurement, testing, processing, preservation, storage and distribution of human tissues and cells,[13] as transposed into national legislation. However, even if the product is an ATMP, Article 3 of the ATMP Regulation provides that Directive 2004/23/EC will still regulate the part of ATMP production involving sourcing and processing of any human tissues/cells used in the product. Typically, numerous national agencies/authorities regulate various aspects of ATMPs, and it is different in every Member State, but some Member States provide a single point of contact to ease the regulatory burden.

A product is classified as a CATMP when it fulfills the definitions provided in Article 2(1)(d) of the ATMP Regulation, i.e., incorporates a gene/cell therapy or tissue engineered product as the active substance and one or more medical devices as an integral part of the product. If cells or tissues are not viable these must exert the primary action of the combined product. The medical device should retain its intended purpose/mode of action in the combined product (i.e., its usual/normal device function as, e.g., scaffold/matrix/physical barrier) and be considered an integral part of the final product (even if temporary, e.g., biodegradable/resorbable) to qualify the product as a CATMP. The outcome of the assessment of the classification of all CATMPs to date by CAT is summarized in Table 1 below.[14]

Table 1: Scientific recommendations on classification of ATMPs – Combined ATMPs[a]

Date recommendation adopted	Description of active substance/product	Therapeutic area
Tissue engineered product - combined		
March 23, 2023	*Ex vivo* expanded allogeneic human corneal endothelial cells	Treatment of the diseases of the corneal endothelium
Aug. 12, 2022	*Ex vivo* expanded allogeneic human corneal epithelial cells containing p63 positively expressing cells	Treatment of persistent corneal epithelial defects
April 16, 2021	Autologous expanded mesenchymal stem cells and bone morphogenic factor 2	Treatment of osteochondral defects
Nov. 6, 2020	Islets of Langerhans, cultured endothelial cells and fibroblasts/fibrocytes	Late chronic pancreatitis
Nov. 6, 2020	Adipose tissue derived stem cells or induced pluripotent stem cells transformed into insulin and glucagon releasing cells, cultured endothelial cells and fibroblasts/fibrocytes	Brittle diabetes mellitus Type 1
March 28, 2019	Suspension of autologous skeletal muscle derived cells attached to poly (DL-lactide-co-glycolide) microparticles	Treatment of fecal incontinence and anorectal malformation
Feb. 6, 2019	Adipose-derived stem cells seeded into the polypropylene conduit mimicking the extracellular environment of the urinary tract	Intended for urinary diversion in patients requiring radical cystectomy for the treatment of bladder cancer
Dec. 20, 2017	Autologous adipose-derived stem cells obtained from a stromal vascular fraction seeded on a collagen matrix scaffold	Treatment of cancer-related lymphedema in breast cancer patients
Oct. 17, 2017	Allogenic adipose-derived stem cells differentiated in vitro toward the cardiovascular lineage and combined with carrier and implanting device	Intended to restore cardiac function post-myocardial infarction
Sept. 14, 2017	Viable chondrocytes cultured within a 3D hydrogel	Intended for the treatment of articular cartilage defects of the knee
Jan. 22, 2016	Cells seeded on transgenic porcine acellular dermal matrix	Treatment of deep and extensive burns, chronic wounds, skin donor sites
Oct. 28, 2015	Suspension of autologous expanded viable chondrocytes embedded in a cross-linked hydrogel	Treatment of articular cartilage defect

Table 1: *continued*

Date recommendation adopted	Description of active substance/product	Therapeutic area
Tissue engineered product - combined		
May 13, 2015	Suspension of autologous expanded viable chondrocytes combined with three-dimensional structure	Articular cartilage defect of the knee
May 28, 2014	Tracheal scaffold seeded with autologous bone marrow derived mononuclear cells	Reconstruction of trachea subsequent to damage or stenosis due to cancer, injury or infection
June 21, 2013	Adipose derived mesenchymal stem cells combined with beta-tricalcium phosphate	Treatment of bone defects
Dec. 18, 2012	Concentrate of autologous bone marrow seeded on a matrix consisting of cross-linked bovine type collagen, coated with hydroxyapatite	Increase new bone formation in critical area of atrophic non-union
March 22, 2012	Autologous oral mucosa cells seeded onto a membrane	Treatment of urethral stricture
April 4, 2011	Allogeneic human fibroblasts cultured onto a biodegradable matrix	Dermatology
Oct. 4, 2010	Adult skeletal muscle derived cells	Treatment of female stress urinary incontinence
Aug. 5, 2010	Frozen, cultured allogeneic keratinocytes on a silicone dressing material	Intended the treatment of acute burn wounds
Jan. 26, 2010	Autologous osteoprogenitor cells, isolated from bone marrow and expanded *in vitro*, incorporated, as an integral part, with 3D biodegradable scaffold	Repairing, regenerating and replacing bone defects in odontostomatology and maxillofacial surgery
Jan. 15, 2010*	Autologous cultured chondrocytes integrated in a scaffold	Repair of symptomatic cartilage defects in joints such as the knee and ankle
Oct. 16, 2009	Suspension of expanded autologous skeletal muscle derived cells (myoblasts)	Regeneration of the external urethral sphincter muscle (rhabdosphincter) in patients suffering from various levels of stress urinary incontinence

Table 1: *continued*

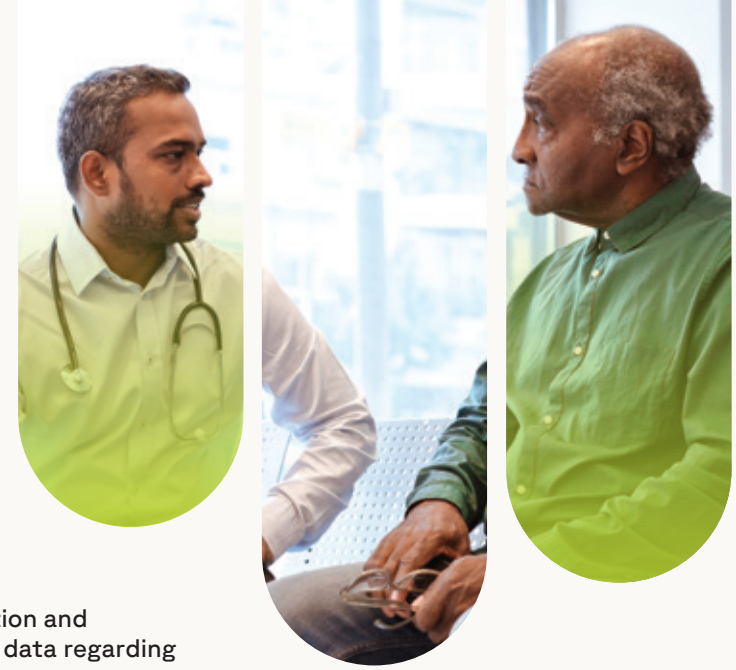
Date recommendation adopted	Description of active substance/product	Therapeutic area
Somatic cell therapy product – combined		
Nov. 25, 2015	Suspension of adipose derived regenerative cells encapsulated in hyaluronic acid	Treatment of articular cartilage and bone defects including osteoarthrosis or osteochondral lesions
Feb. 28, 2013	Alginate encapsulated porcine pancreatic islet cells	Treatment of Type 1 diabetes mellitus
July 2, 2010	Hollow fiber cartridges populated with C3A cells to be used with ancillary support equipment	Treatment of acute or chronic hepatitis
Gene therapy product – combined		
May 20, 2020	Plasmid encoding for the VEGF-A protein	Various bone healing indications (sinus lift, non-unions, spinal fusion, etc.)
Nov. 9, 2017	Encapsulated human retinal pigment epithelial cells genetically modified to express human factor IX protein	Treatment of Hemophilia B
Dec. 21, 2015	Human hepatoblastoma cells encapsulated in alginate, expanded to competence, and maintained in a fluidized bed bioreactor	Treatment of acute liver failure
Sept. 25, 2015	Encapsulated allogeneic cells secreting GM-CSF and irradiated autologous tumor cells	Treatment of malignant solid tumors
Oct. 4, 2012	Human ciliary neurotrophic factor	Reducing photoreceptor loss associated with degeneration of the cells of the retina
Oct. 16, 2009	Autologous tolerogenic dendritic cells derived from peripheral blood monocytes	Treatment of rheumatoid arthritis

*First CATMP approved in the EU April 25, 2013: MACI matrix applied characterized autologous cultured chondrocytes, for the repair of symptomatic, full-thickness cartilage defects of the knee in adults[b] – MA suspended 25 September 2014 due to transfer of ownership followed by closure of the only authorised manufacturing site.[c]

a) European Medicines Agency. 'Summaries of scientific recommendations on classification of advanced therapy medicinal products,' https://www.ema.europa.eu/en/human-regulatory-overview/marketing-authorisation/advanced-therapies-marketing-authorisation/scientific-recommendations-classification-advanced-therapy-medicinal-products (accessed April 14, 2024).

b) Summary of opinion (initial authorization): MACI Matrix applied characterized autologous cultured chondrocytes, EMA/54023/2013, April 25, 2013.

c) Assessment report: Procedure under Article 20 of Regulation (EC) No 726/2004: MACI Matrix applied characterized autologous cultured chondrocytes, EMA/671958/2014.



Certification of quality and non-clinical data

A procedure for pre-MAA scientific evaluation and certification of the quality and non-clinical data regarding an ATMP is available for those products being developed by organizations which qualify as micro, small and medium sized enterprises (SMEs), implemented by Regulation (EC) No 668/2009.[15] Article 4 of the ATMP Regulation specifically addresses the additional requirements in respect of the medical device component(s) of CATMPs, including involvement of a NB at this stage. The procedure is normally 90 days, but clock stops apply if site visits or NB consultation are required. Certification is a voluntary procedure intended to aid micro and SMEs in ATMP development.[16]

Issues and opportunities of CATMPs

All phases of the ATMP manufacturing process do not fall within the scope of the ATMP Regulation. The donation, procurement and testing of the human tissue or cells involved in the manufacture of the ATMP are instead governed by Directive 2004/23/EC on setting standards of quality and safety.[13] A 2018 survey of 68 CATMP/ATMP developers found that their most often reported challenges were related to country-specific requirements (16%), manufacturing (15%), and clinical trial design (8%). Of the survey respondents, 65% were micro, small or medium-sized enterprises (SMEs), 72% were in early clinical development, and 40% were developing gene therapies.[17,18]

From 2009 to October 2023, 38 MAAs for ATMPs had been submitted to EMA, of which 25 had successfully been granted positive draft opinion, one of which was a CATMP.[19] Refer to Table 2 on the following page for further information.

The EMA ATMP classification procedure is provided free of charge, and can foster development processes that maximize the chance of success in obtaining an MA; however, it is non-binding in nature so product developers may disregard it.[16]

The difficulty of ATMP classification, burdensome procedures for ATMP medical device combinations, uncertainties surrounding certification procedures, the lack of harmonization of import and export rules and the divergent procedures for ATMP development across different Member States, should be considered as these issues are compounded by the extra level of complexity involved with a CATMP. SMEs enjoy investment for the development of ATMPs.[18,20]

Table 2: List of approved ATMPs in the European Union

Name	Type of ATMP	Authorization date
Chondrocelect*	TEP	Oct. 5, 2009
Glybera**	GTMP	Oct. 25, 2012
MACI/*****	TEP, combined ATMP	June 27, 2013
Provenge*	CTMP	Sept. 6, 2013
Holoclar	TEP	Feb. 17, 2015
Imlygic	GTMP	Dec. 16, 2015
Strimvelis	GTMP	May 26, 2016
Zalmoxis*	CTMP	Aug. 18, 2016
Spherox	TEP	July 7, 2017
Alofisel	CTMP	March 23, 2018
Yescarta	GTMP	Aug. 23, 2018
Kymriah	GTMP	Aug. 23, 2018
Luxturna	GTMP	Nov. 22, 2018
Zynteglo*	GTMP	May 29, 2019
Zolgensma	GTMP	May 18, 2020
Libmeldy	GTMP	Dec. 17, 2020
Tecartus	GTMP	Dec. 14, 2020
Skysona*	GTMP	July 16, 2021
Abecma	GTMP	Aug. 18, 2021
Breyanzi	GTMP	April 4, 2022
Carvykti	GTMP	May 25, 2022
Upstaza	GTMP	July 18, 2022

*MA withdrawn; **MA not renewed; ***a combined ATMP for repair of symptomatic, full-thickness cartilage defects of the knee (grade III and IV of the Modified Outerbridge Scale) of 3-20 cm^2 in skeletally mature adults

Conclusion

CATMPs offer promising prospects for the treatment of disease, dysfunction and injury. These therapies have been developed mainly by academic laboratories, academic spin-offs, not-for-profit organizations, micro and SMEs or research units in hospitals, and are benefiting from the incentives offered in most cases. However, evaluating these novel products often requires specific expertise in their classification, development, manufacture and regulation compared to conventional products. Nevertheless, there is a need to balance between the requirement to ensure that CATMPs are made available to patients only after their quality, safety and efficacy have been demonstrated, and the requirement to enable early access for new products in cases of unmet medical needs. With the adoption of the ATMP Regulation, the EU is attempting to implement an open market for CATMPs, in which quality standards are adequately applied.[18,20]

In conclusion, as the knowledge of these products rapidly grows, there are many products with encouraging clinical trial results and the overall development of CATMPs continues to show rapid growth,[14,21] and remains one of the most exciting pharmaceutical sectors.

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