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Update ATMP situation Belgium

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Business oriented EU human cell and tissue product legislation will adversely impact Member States' health care systems

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Table 2 Belgian establishments of human body material accredited (as published in Ministerial Decrees) for "advanced therapy" (with reference to the ATMP regulation 1394/2007/EC) under the EUCTDs, until 30 December 2012 (FAMHP 2012a)

Name	ATMP	Accredited by the Belgian Ministry of Health since
Public		
Liège University Hospital	Dendritic cells	4 December 2007
	Mesenchymal stem cells	4 December 2007
	Pre-osteoblastic cells	30 December 2008
South Luxemburg Hospital	Proliferative tissue	11 July 2011
Saint-Luc University Hospital	Hepatocytes	13 February 2006
	Hepatic stem cells	2 June 2008
	Islets of Langerhans	30 December 2008
	Adipose stem cells	25 August 2009
Institute Jules Bordet	Dendritic cells	30 December 2008
	Mesenchymal cells	30 December 2008
	Lymphocytes	1 December 2009
Antwerp University Hospital	Dendritic cells	30 December 2008
	Mesenchymal cells	30 December 2008
	Epithelial cells	30 December 2008
Brussels University Hospital	Beta cells	18 December 1997
Vrije Universiteit Brussel	Dendritic cells	30 December 2008
Ghent University Hospital	Dendritic cells	21 September 2010
	Keratinocytes	18 December 1997
Leuven University Hospital	Mesenchymal stem cells	1 September 2011
	Dendritic cells	5 August 2010
	Keratinocytes	17 February 2000
Queen Astrid Military Hospital	Keratinocytes	18 December 1997
Private		
Bone Therapeutics	Bone marrow stem cells	30 June 2010
Cardio 3 BioSciences	Cardiac progenitor cells	1 April 2011
TiGenix	Autologous chondrocytes[a]	1 December 2009

[a] ChondroCelect®, the first EC authorized ATMP on the EU market

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Current state-of-play of the EU advanced therapy medicinal product (ATMP) field, with an emphasis on Belgian human cell and tissue products

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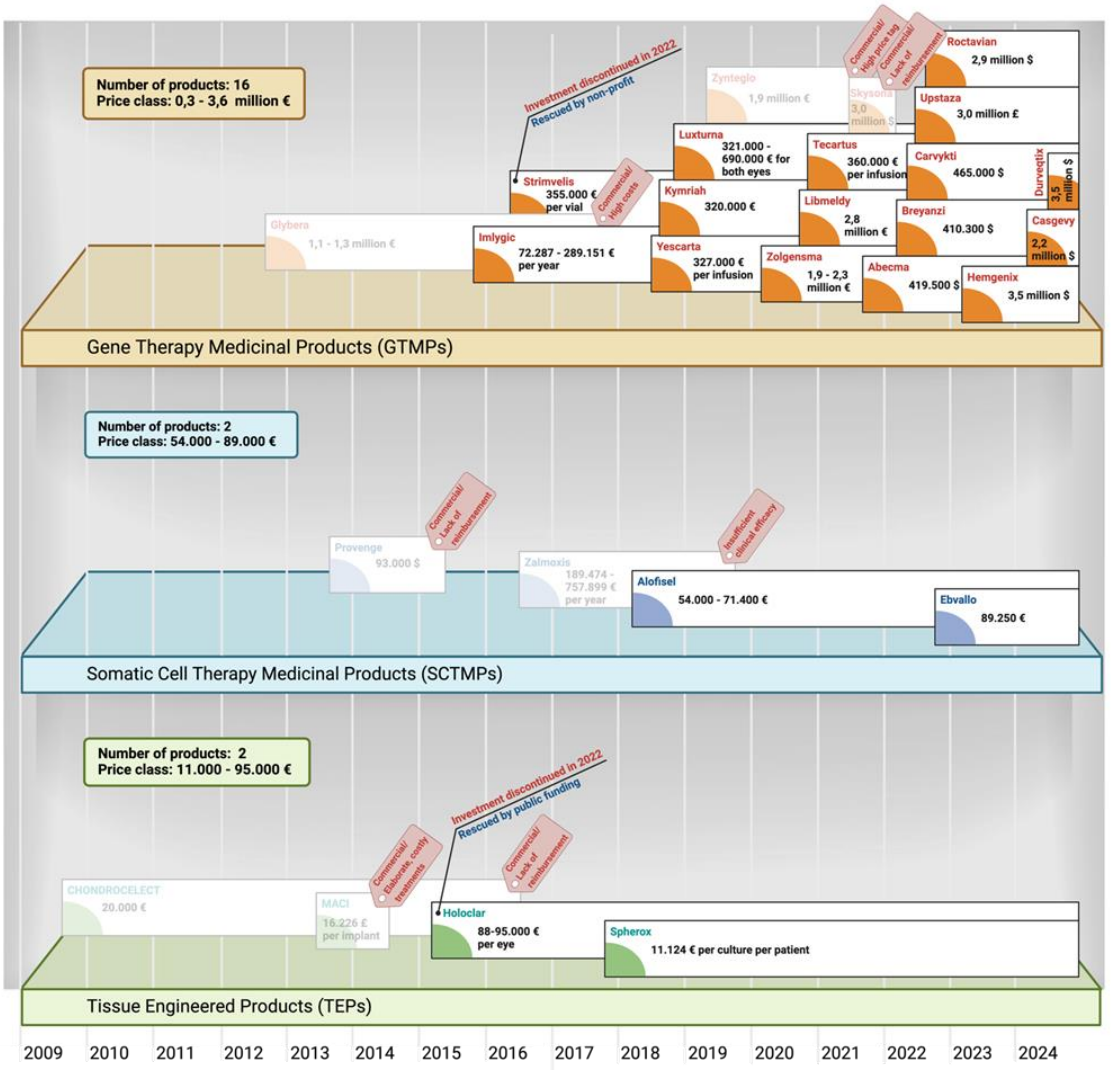
Table 1. Telling examples of established therapies that struggled or failed to reach the patients since their advanced therapy medicinal product (ATMP) classification.

Tissue Establishment	Human tissues and cells	Accredited by the Ministry of Health since	Current status (September 2024)	Comments
Public				
Liège University Hospital	Dendritic cells	December 4, 2007	Suspended	
	Mesenchymal stem cells	December 4, 2007	Investigational medicinal product	Produced by Liège University Hospital and the intra-tissular Injection of mesenchymal stem cells in Crohn Disease Patients is evaluated in clinical trials (NCT03901235 and NCT06317818)
	Pre-osteoblastic cells	December 30, 2008	Discontinued	
South Luxemburg Hospital[a]	Proliferative tissue	July 11, 2011	Discontinued	
Saint-Luc University Hospital[a]	Hepatocytes	February 13, 2006	Discontinued	
	Hepatic stem cells	June 2, 2008	Discontinued	
	Islets of Langerhans	December 30, 2008	Available	Not classified as ATMP
	Adipose stem cells	August 25, 2009	Investigational medicinal product	Produced by a private company and a clinical trial is in preparation
Institute Jules Bordet	Dendritic cells	December 30, 2008	Discontinued	
	Mesenchymal cells	December 30, 2008	Discontinued	
	Lymphocytes	December 1, 2009	Discontinued	
Antwerp University Hospital	Dendritic cells	December 30, 2008	Investigational medicinal product	Produced by a spin-off of the Antwerp University Hospital and of the University of Antwerp, and evaluated in clinical trials, which are sponsored by the Antwerp University Hospital
	Mesenchymal cells	December 30, 2008	Discontinued	
	Epithelial cells	December 30, 2008	Discontinued	
Brussels University Hospital	Beta cells	December 18, 1997	Available	Not classified as ATMP
Vrije Universiteit Brussel	Dendritic cells	December 30, 2008	Discontinued	
Ghent University Hospital	Dendritic cells	September 21, 2010	Investigational medicinal product	Produced by the Ghent University Hospital, and clinical trials evaluating dendritic cell vaccines in patients with non-small cell lung cancer are ongoing (NCT04078269 and NCT04082182)
	Keratinocytes	December 18, 1997	Discontinued	
Leuven University Hospital	Mesenchymal stem cells	September 1, 2011	Discontinued	
	Dendritic cells	August 5, 2010	Discontinued	
	Keratinocytes	February 17, 2000	Discontinued	
Queen Astrid Military Hospital	Keratinocytes	December 18, 1997	Discontinued	
Private				
Bone Therapeutics	Bone marrow stem cells	June 30, 2010	Discontinued	Bone Therapeutics was rebranded BioSenic, which in 2023 discontinued its bone marrow stem cell product (ALLOB) to focus its resources on its autoimmune disease platform (Adams 2022; No author 2023a)
Cardio 3 BioSciences	Cardiac progenitor cells	April 1, 2011	Discontinued	Cardio 3 BioSciences became Celyad Oncology, which in 2017 discontinued the cardiac progenitor program (C-Cure) and transferred the research data and intellectual property rights to the Walloon Region (Celyad Oncology 2023)
TiGenix	Autologous chondrocytes	December 1, 2009	Discontinued	The autologous chondrocyte product ChondroSelect®, the first approved ATMP on the EU market, was discontinued (marketing authorization withdrawal) in 2016 (EMA 2024)

Figure 1. Advanced Therapy Medicinal Products (ATMPs) approved in the EU (2009-2024). Notified prices, per treatment unless otherwise stated, are indicated on the medicine boxes and were extracted from scientific papers (Abou-El-Enain et al. 2016; Ronco et al. 2021; Iglesias-López et al. 2023; Wilkins et al. 2023) and trade magazines (Liu 2022; Shapiro 2023; No author 2023b and 2024; Buntz 2024). Faded boxes indicate that these ATMPs do no longer possess a marketing authorization (MA), while pink labels indicate the reason for the withdrawal or not renewal of the products' MAs.



Abstract

- In 2013, we demonstrated that industry's successful (ATMP) lobbying on key areas of regulatory and policy processes led to excessively business-oriented legislation.
- We predicted that the ATMP regulation would adversely impact Member States' health care systems and would threaten the sustainability of many HCTPs provided by public health institutions.
- To assess the current ATMP state of play and investigate whether these predictions ultimately came true, we consulted relevant scientific and trade literature, corporate websites sites, and official reports from the competent authorities, and surveyed the former Belgian HCTP producers.
- A hospital exemption (HE) scheme was enacted to assure the access of patients to ATMPs not intended for commercial exploitation. In Belgium, regulatory policies made HE utilization virtually impossible.
- As a result, 25 Belgian HCTPs (22 produced by hospitals, three by private companies) did not survive the implementation of the ATMP Regulation.
- We conclude that the ATMP Regulation indeed negatively impacted the universal access to healthcare, especially in Belgium where many valuable established HCTPs are no longer available to patients.

Conclusion

- The ATMP Regulation was supposed to improve the access of patients to innovative therapies. Fifteen years after its implementation, 20 ATMPs hold a MA, 80% of them GTMPs.
- Their very high prices (up to 3,6 million € per treatment) challenge the Member States' public reimbursement systems and the universal access of patients to healthcare, sometimes resulting in unethical solutions for the few (crowdfunding and lotteries).
- In addition, the classification of established HCTPs for transplantation as SCTMPs and TEPs often heralded their disappearance, especially in Belgium where a stringent regulatory pathway discouraged HE utilization.
- Therefore, we suggest to increase the weight of patient-based risk-benefit approaches in the ATMP approval process, and to include the assessment of the products' anticipated prices and reimbursement landscapes in the EU R&D and innovation funding decision process.
- Finally, we also call for a revision of the EMA standards on which ATMP classification decisions are made, and for a uniform and pragmatic HE framework, allowing for the survival of meaningful, but commercially non-viable HCTPs.