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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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ABSTRACT

The late 1980s saw the emergence of experimental therapies based on human cell and tissue products (HCTPs) within academic and hospital settings, several of them wound healing related. In 2008, the European Commission introduced the Regulation on advanced therapy medicinal products (ATMPs), defining many of these HCTPs as ATMPs, and more specifically as somatic cell therapy medicinal products (sCTMPs) or tissue-engineered products (TEPs). In 2013, 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 and official competent authority reports and surveyed the former Belgian HCTP producers. We found that the ATMP Regulation produced 19 authorised ATMPs, with 16 of them (84.2%) belonging to the gene therapy medicinal product (GTMP) class and only 3 HCTPs (15.8%), 2 TEPs and 1 sCTMP. List prices varied according to the ATMP class, with public health insurances struggling to reimburse ATMPs, especially the exuberantly priced GTMPs. This led to marketing authorization withdrawals, and crowd funding approaches and lotteries to determine who would receive lifesaving treatments. A hospital exemption (HE) scheme was enacted to protect ATMPs not intended for commercial exploitation. Whilst limited financial resources generally hampered HE utilisation by public actors, stringent regulatory policies made it virtually impossible in Belgium, resulting in meaningful HCTPs no longer being available to surgeons and their patients.

Abbreviations: ACI, autologous chondrocyte injection; ADA, adenosine deaminase; AGORA, ATMP GMP Open Access Research Alliance; AIFA, Agenzia Italiana del Farmaco; ATMP, advanced therapy medicinal products; CAR T-cell, chimeric antigen receptor T-cell; CEESP, Commission d'Évaluation Économique et de Santé Publique; CNRS, Centre national de la Recherche Scientifique; DARE-NL, Dutch infrastructure for cancer-specific ATMP Research; EC, European Commission; EMA, European medicines agency; EU, European Union; EUTCDs, EU Tissue and Cell Directives; FAMHP, Federal Agency for Medicines and Health Products; FDA, Food and Drug Administration; GMP, Good Manufacturing Practises; GTMP, gene therapy medicinal product; HCTP, human cell and tissue product; HE, hospital exemption; INSERM, Institut National de la Santé et de la Recherche Médicale; KCE, Belgian Healthcare Knowledge Centre; KEI, Knowledge Ecology International; MA, marketing authorization; NIH, National Institutes of Health; QAMH, Queen Astrid Military Hospital; SCID, severe combined immunodeficiency; sCTMP, somatic cell therapy medicinal product; SEED, Shaping European Early Dialogues for health technologies; SHC, Superior Health Council; SMA, spinal muscular atrophy; SMEs, Small and Medium-sized Enterprises; SMN, survival motor neuron; TEP, tissue-engineered product; TerCel, Spanish Cell Therapy Network; US, United States; WHO, World Health Organisation.

1 | Introduction

Experimental therapies based on human genes, cells or tissues emerged about three decades ago within academic and hospital settings. Examples are gene therapies for immunodeficiencies and haemophilia, chondrocytes for cartilage repair, beta cells for patients with diabetes, and keratinocytes or skin equivalents for severely burnt patients. In 2008, the European Commission (EC) introduced a specific Regulation on advanced therapy medicinal products (ATMPs), i.e., Regulation (EC) No 1394/2007. This ATMP Regulation is implemented by the European Medicines Agency (EMA) and defines ATMPs as medicinal products belonging to either gene therapy medicinal products (GTMPs), somatic cell therapy medicinal products (sCTMPs), tissue-engineered products (TEPs), or combined ATMPs, the latter containing a medical device and human cells or tissues. Of note, human cells or tissues that have not been substantially manipulated during the manufacturing process—their biological characteristics, physiological functions, or structural properties have not been modified to be relevant for their intended function—are not classified as ATMPs. And so, in 2008, the small number of gene therapy products then developed, but especially the many established human cells and tissue products (HCTPs) for transplantation, were classified as ATMPs, the former as GTMPs, the latter as either sCTMPs or TEPs. Before the ATMP Regulation came into force, HCTPs were governed by the European Union (EU) Tissue and Cell Directives (EUTCDs). Many HCTPs were produced and transplanted in hospitals, some of them since the 80s, and most of them were not intended for commercial exploitation [1]. A hospital exemption (HE) scheme—not to be confused with compassionate use programmes—was enacted. One of the main goals of the HE was to ensure that these existing academic and hospital HCTPs—and the patients' access to them—would not be unnecessarily compromised. The HE is further regulated at the Member State level—it can be granted by national competent authorities for medicines, based on their opinions and interpretations—and applies to unlicensed products, manufactured on a non-routine basis, custom-made for an individual patient under the responsibility of the requesting physician, for use in a hospital setting within the same Member State in which they are manufactured [2]. The requirements for granting HE vary between EU Member States. Some countries require scientific (non-clinical) and/or clinical evidence to reach a decision, others do not [3]. In Belgium, most of the HE (application) dossier content is directly related to the quality data requirements for the product itself. Non-clinical data dossier requirements are related to pharmacological, pharmacokinetic and toxicological documentation. On what basis final decisions are made by the Belgian competent authority, the weight of scientific evidence included, is not known. Only the decision is communicated, and no public assessment reports are available [4].

In 2013, it was shown that industry's successful lobbying on key areas of regulatory and policy processes, in congruence with Europe's risk aversion and urge to promote growth and jobs, led to the elaboration of business-oriented HCTP/ATMP legislation [1]. We predicted that the ATMP Regulation would adversely impact EU Member States' health care systems, hampering the fair access and reimbursement of these therapies, and would threaten the sustainability of many established HCTPs provided by public health institutions. It was also pointed out that there was a lack of clarity about how social security systems would be able to pay the price of the increase in costs that would undoubtedly come with the ATMP Regulation and how priorities would be set regarding reimbursement decisions [1].

In this perspective article, we assess the actual impact of the ATMP Regulation, 15 years after its implementation, with special attention to the predicted ATMP pricing, reimbursement, and patient access issues. For this, we consulted the relevant scientific literature, official reports from the competent authorities for medicines, trade magazines and corporate websites. In addition, we surveyed all Belgian academic and hospital HCTP producers to analyse whether the ATMP HE rules saved their products from extinction. We report and discuss here the results of our searches and survey.

2 | ATMP Prices, Reimbursement and Fair Access

Today, 15 years after its implementation, the ATMP Regulation has led to 19 ATMPs authorised in the EU (Figure 1) [14]. Once granted by the European Commission, upon EMA recommendation, the centralised marketing authorization—which is mandatory for ATMPs—is valid in all EU Member States and in the countries of the European Economic Area (EEA), Iceland, Liechtenstein and Norway. The success rate for marketing authorization was found to be considerably lower for ATMPs compared to all drug applications combined (59% versus 76%) [15]. It was suggested that this was due to the specificities of developing products based on small batches of living cells with complex manufacturing processes, which are difficult to scale at low cost [4]. Of note, the fact that 19 ATMPs were granted a marketing authorization (MA) does not mean that all of them are actually and currently available and accessible to patients. After MA, the approved ATMP needs to go through a so-called "economic valley of death" with lengthy pricing and reimbursement negotiations with the competent authorities in each EU Member State, which can ultimately prevent its use in patients [16]. In 2023, in Spain, one of the largest economies in the EU, only five of the 18 (28%) then approved ATMPs were reimbursed for use in the national public health system [15]. According to a recent (30 January 2025) report of the Belgian Health Care Knowledge Center, only 8/19 authorised ATMPs are currently marketed and reimbursed in Belgium [17].

Most of the currently (February 2025) authorised ATMPs are GTMPs (16/19, 84.2%), and their share is growing steadily (Figure 1) [14]. In contrast, only three authorised ATMPs are HCTPs (15.8%)—two TEPs and one sCTMP—with no sign of a significant increase in the near future (Figure 1). The TEP Holoclar, consisting of limbal stem cells to treat a rare eye condition, was saved at the last minute, in 2022, by a government-sponsored investment fund after the Italian government had been pressurised to act (Table 1) [19]. The public funding came with many conditions, including the producer's commitment to attract new private investors. The other TEP is Spherox (Figure 1), an autologous chondrocyte implantation (ACI) product, consisting of spheroids of human autologous matrix-associated chondrocytes, to repair cartilage defects in the knee. The sCTMP Alofisel (since December 2024 no longer authorised, Figure 1) was a stem cell therapy product designed to

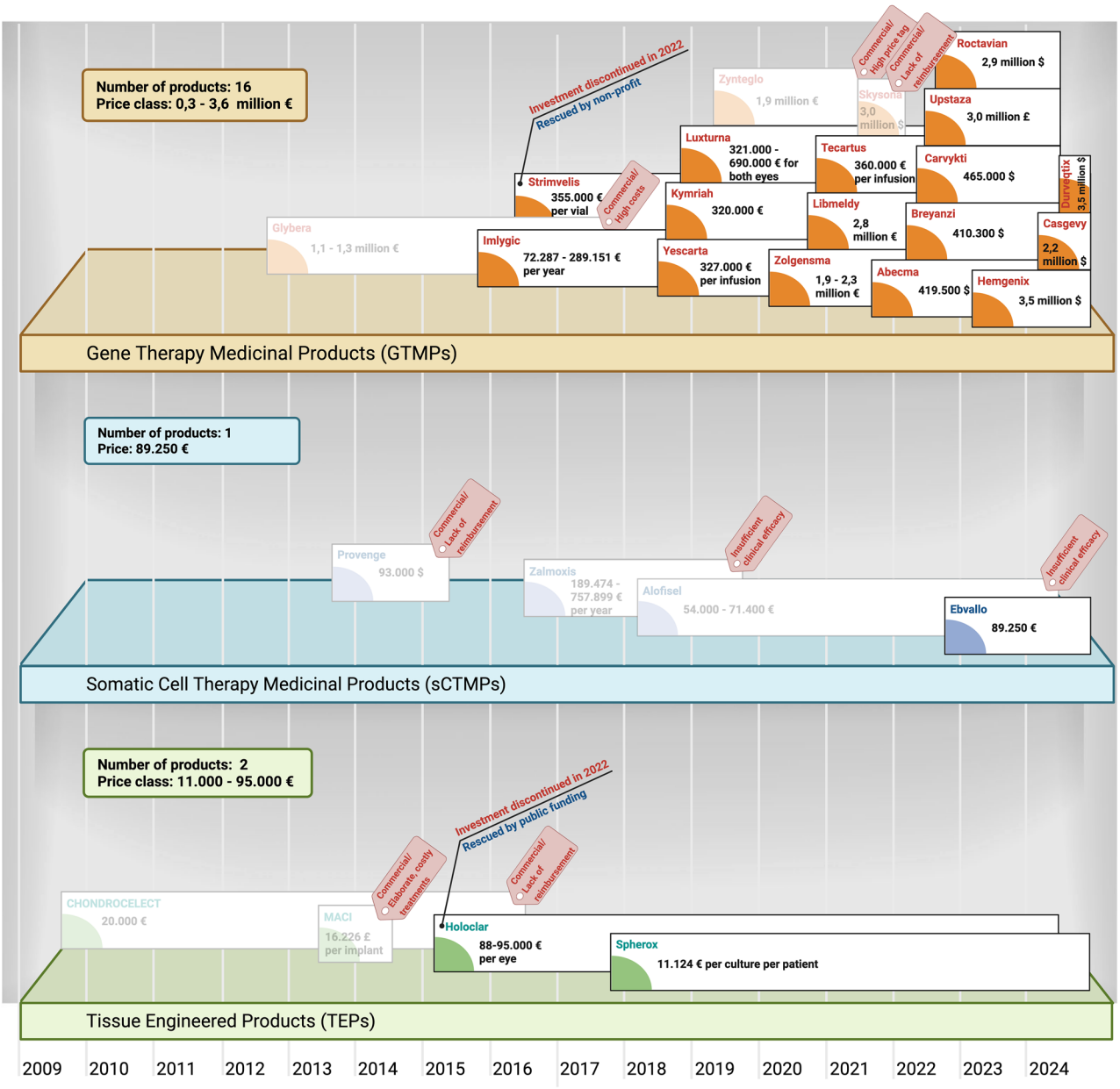

FIGURE 1 | Advanced Therapy Medicinal Products (ATMPs) approved in the EU (2009–2024). Notified prices, per treatment unless otherwise stated, are indicated on the medicine boxes and were extracted from scientific papers [5–8] and trade magazines [9–13]. Faded boxes indicate that these ATMPs do no longer possess a marketing authorization (MA), whilst pink labels indicate the reason for the withdrawal or not renewal of the products' MAs.

treat complex perianal fistulas, a debilitating complication of Crohn's disease. The last HCTP to obtain a MA was the sCTMP Ebvallo, an allogeneic T-cell immunotherapy (authorised since December 2022, Figure 1) [14].

List prices, extracted from scientific papers and trade magazines, vary considerably according to the ATMP class (Figure 1): 54–89 k€ for sCTMPs, 11–95 k€ for TEPs, and no less than € 0.3–3.6 million for GTMPs. The fact that GTMPs often address ultra-rare diseases with small numbers of patients, resulting in very high prices to balance the R&D and production costs, is often put forward as a reason for their exuberant prices [20]. However, most new cell- and gene therapies are developed with considerable support from non-profit entities, including charities. Persons who donate money can "benefit" from tax relief (e.g., in France, 66% tax reduction on the donation). However, the use of these donations varies. They can be used to help companies develop ATMP business activities (e.g., Généthon, France) or to enable the continuation of an ATMP that the concerned company decided to discontinue (e.g., Strimvelis, Italy).

Zolgensma, a GTMP for the treatment of spinal muscular atrophy (SMA), which is marketed by Novartis at a price of € 1.9–2.3 million, for instance. The storey of Zolgensma starts in France, in 2006, when Martine Barkats, group leader at Généthon, has the idea of testing gene therapy—a codon-optimised survival motor neuron (SMN) sequence delivered by the viral vector AAV9—in SMA mice, virtually curing these

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

Product name	Producer	Product description	Narrative
Holoclar	Holostem	Ex vivo expanded autologous human corneal epithelial cells containing stem cells	The University of Modena and Reggio Emilia (Italy) produced autologous tissue grafts grown from epithelial limbal to repair corneal damage, which were successfully used in a few hundreds of patients between 1998 and 2007 [18]. Upon the implementation of the ATMP Regulation, the Italian medicines agency, the "Agenzia Italiana del Farmaco (AIFA)," decided that the therapy needed to be licenced as an ATMP beyond 2012. As a result, the therapy was commercialised by Holostem Advanced Therapies as the ATMP Holoclar [18]. However, in 2022, Holostem came to the brink of bankruptcy when its main investor discontinued its investment due to poor financial results. The company was saved at the last minute by a government-sponsored investment fund after scientists, and patients and their families had been pressurising the government to take action [19]. However, the public funding comes on condition of a new industrial plan that includes a clear strategy to contain costs and increase revenues and Holostem's commitment to attract new private investors and partners.
Strimvelis	Orchard	Enriched autologous CD34+ cells transduced with retroviral vector that encodes for the human adenosine deaminase deficiency (ADA) cDNA sequence	In the 2000s scientists of the San Raffaele-Telethon Institute for Gene Therapy in Milan (Italy) developed a bone marrow stem cell-based gene therapy product that is the only available cure for the rare condition called Adenosine deaminase (ADA) deficiency with severe combined immunodeficiency (SCID) [20]. The product, Strimvelis, and the manufacturing and marketing rights went to the biopharma company Orchard. The subsequent ATMP was approved by EMA in 2016 and was distributed by Orchard until 2022, when it was concluded that the product was not economically viable. The Telethon Foundation, a non-profit organisation, then took over the licence to produce and distribute Strimvelis [20].
ChondroCelect	TiGenix	Ex vivo expanded autologous human cartilage cells expressing specific marker proteins	Autologous chondrocyte injection (ACI) was first proposed in 1994 [21], and is since then an established technique to repair joint cartilage defects that has been used in thousands of patients worldwide [22]. In Belgium, ACI products were prepared by university hospitals [23]. In 2009, ChondroCelect (autologous human cartilage cells expressing specific marker proteins), produced by the Belgian cell therapy company TiGenix, became the first approved ATMP on the EU market [14]. In 2016, ChondroCelect was discontinued (marketing authorization withdrawal) [14] due to commercial reasons together with the lack of reimbursement in key European countries [5]. Meanwhile, the two Belgian ACI products that were prepared in hospitals and were reimbursed by the National Institute for Health and Disability Insurance (price fixed by Ministerial Decree at € 2.068 per treatment) had been discontinued. A working group of the Belgian Senate concluded that it is not known whether this discontinuation is related to ChondroCelect coming onto the market [24].

(Continues)

TABLE 1 | (Continued)

Product name	Producer	Product description	Narrative
CryoCEAL	XCELLentis and QAMH	Ex vivo expanded allogeneic human keratinocytes	Since 1987, following earlier groundbreaking work in the US [25, 26], keratinocyte grafts were produced and used in the Queen Astrid Military Hospital (QAMH) in Brussels (Belgium) to stimulate wound healing in excised and grafted burns [27], autograft donor sites [28], and chronic wounds [29], in more than 1.000 patients without reported serious adverse reactions [30]. In 2001, the production and distribution of cryopreserved keratinocyte grafts (branded CryoCEAL) was outsourced to the biotechnology company XCELLentis. In 2005, the company decided not to continue commercial development—the anticipated market for meaningful applications, and associated profits, were considered too small—and the QAMH took over production. In 2012, the Federal Agency for Medicinal and Health Products (FAMHP) classified the keratinocyte grafts of the QAMH as ATMP, without recourse to the hospital exemption (HE) scheme. A period of tolerance, in which keratinocyte grafts were prescribed on a named patient basis and delivered by the QAMH hospital pharmacy, was followed by a series of formal discussions about possible solutions, such as the magistral preparation of keratinocyte grafts or a clinical trial sponsored by the Belgian Healthcare Knowledge Centre (KCE). Both possible salvage paths were rejected. The COVID-19 pandemic threw into disarray further discussions with the Belgian Federal Public Service of Health, Food Chain Safety and Environment regarding a proposed phasing out of the keratinocyte grafts over 5 years, the time needed to develop a next generation alternative. Finally, non-specialist representatives of the Cabinet of the Belgian Minister of Defence—against the advice of QAMH's experts—agreed to pursue the Belgian ATMP HE scheme, which was offered *in extremis* by the FAMHP. However, after evaluation by a specialised consultancy firm, it was decided that the required investments were too big and not compatible with a therapy applied to a few dozen of patients per year—the same conclusion XCELLentis had also reached previously—and the keratinocyte grafts were discontinued.

mice, which would normally die within 25 days [31]. Généthon is a non-profit organisation created and largely funded by the Muscular Dystrophy Association AFM-Telethon, a French patient association, which organises yearly Telethons (televised fundraising events) gathering around 90 million euros per year (approximately 75% of which goes to Généthon) [32]. To pursue its SMA project, Généthon forms partnerships with public research institutions, in particular with the "Institut National de la Santé et de la Recherche Médicale" (INSERM) and the "Centre national de la Recherche Scientifique" (CNRS) [32]. In 2018, the AAV9-SMN-based GTMP, named "onasemnogen abeparvovec", is finally ready for clinical trials in humans [33]. Faced with the near impossibility of financing these particularly expensive clinical trials, Généthon concludes a licencing agreement with AveXis, granting the American company, which specialises in the clinical development of gene therapies, exclusive worldwide rights to its treatment for SMA [33]. Généthon and CNRS, the patent owners, would receive a royalty rate of 5% on the turnover generated by the possible marketing of the GTMP. One month later, Novartis acquired AveXis for $ 8.7 billion and became the decision-maker for all matters affecting the GTMP, starting with its name (rebranded to Zolgensma) and setting its price [33]. In addition, Knowledge Ecology International (KEI), a not-for-profit non-governmental organisation, found that the United States (US) National Institutes of Health (NIH) RePORTer database lists nearly a half billion dollars in grants, when the search term "spinal muscular atrophy" is used, and that several US charities, such as Sophia's Cure, Cure SMA and Miracle for Madison, raised millions of dollars to advance SMA research [34]. In France, the Economic and Public Health Evaluation Committee (CEESP—"Commission d'Évaluation Économique

et de Santé Publique") analysed the economic impact of the inclusion of Zolgensma on the list of approved medicines and subsequent reimbursement by the public health insurance system [35]. They concluded that the approval and reimbursement of Zolgensma would be associated with an increase in health insurance expenditure—for the care of the population concerned by the approval request—of 257%. The CEESP added that the budgetary impact is likely underestimated considering the published French epidemiological data, which show a higher incidence of the disease than that used by the manufacturer. The use of French data could increase the size of the target population by 50%–100%. In view of the extremely high level of the price claimed, the CEESP expressed its wish that the fixing of drug prices be carried out within the framework of the principles set out in the World Health Organisation (WHO) resolution of 28 May 2019 [36] on the economic accessibility and improving the transparency of markets for medicines, vaccines and other health products in order to guarantee affordable and equitable access to these products [35]. The KEI suggests that companies seeking to obtain MA for novel treatments should provide an accounting of the role of charities and government agencies, in the US and in foreign countries, that have subsidised relevant research, thus giving effect to one of the provisions in the WHO resolution regarding the transparency of R&D subsidies [32].

Public health insurance institutions, whose budgets are already stretched to the limit by growing and ageing populations [37], are struggling to reimburse these ATMPs, and especially the very highly priced GTMPs. And this is just the beginning. Recently, the US Food and Drug Administration (FDA) approved the haematopoietic stem cell GTMP Libmeldy with a record price of $ 4.25 million per treatment and it is predicted that the cost price of Vyjuvek, the first GTMP for dystrophic epidermolysis bullosa, could be as high as $ 15–22 million per patient [9]. Six ATMP MAs were withdrawn or not renewed due to commercial issues (i.e., high treatment costs and lack of reimbursement), including ChondroCelect, the first ATMP to reach the market (Table 1 and Figure 1) [14]. One ATMP, Zalmoxis, was withdrawn due to insufficient clinical efficacy (Figure 1) [38]. Two authorised ATMPs were discontinued by the companies, to be rescued at the last moment; the abovementioned TEP Holoclar [19] and the GTMP Strimvelis [20], which was taken over by the non-profit Telethon foundation (Figure 1 and Table 1). As a result, Strimvelis is currently administered exclusively at the San Raffaele Hospital in Milan (Italy). Importantly, no non-substantially manipulated HCTPs (sCTMPs or TEPs) made it to an MA, indicating that these products should indeed keep their former human cell and tissue transplant classification [15].

For some lifesaving GTMPs, crowdfunding approaches were used to pay for the treatments, and lotteries were organised to determine who will receive these lifesaving treatments for free. In 2018, € 1.9 million was raised to get a Belgian baby girl with SMA type 1 treated with the GTMP Zolgensma [39]. Most babies with untreated type 1 SMA will die before they turn two. Notwithstanding the ethical issues it brings to the surface [39], medical crowdfunding has increased significantly since then [40, 41] and in 2020, Novartis launched a lottery-style access programme to choose babies who will receive Zolgensma for free (Dyer 2020), even though this practise was publicly condemned by several public health ministers [42].

Solving the price-reimbursement conundrum and increasing the number of TEPs and sCTMPs—many of them were prepared and transplanted in hospitals before the implementation of the ATMP Regulation—will not be easy and will require a multi-faceted approach. Some initiatives were launched to guide the development of innovative therapies in the EU, such as the academic-led "ATMP GMP Open Access Research Alliance (AGORA)" [15], or the "Shaping European Early Dialogues for health technologies (EU SEED)" programme [37], which initiates dialogues between European health technology assessment agencies and companies developing products. In addition, several EU Member States are evaluating national models which stimulate all stakeholders (public, private and regulatory actors) to collaborate from the embryonic stage of ATMP development, many of them focusing predominantly on new cancer therapies. Examples are the Spanish Cell Therapy Network (TerCel), the Dutch Oncode Accelerator Programme, and the Dutch infrastructure for cancer-specific ATMP Research (DARE-NL) consortium [43]. The Advanced Research Initiative (ARI, but the name was designed to honour the young girl Ariana Benedé, who was diagnosed with acute lymphoblastic leukaemia and passed away in 2016) of the Hospital Clinic of Barcelona produces chimeric antigen receptor (CAR) T-cell ATMPs under the HE scheme in compliance with pragmatic regulations set forth by the national regulatory agency [44]. They increased patient accessibility, with a lower reimbursement cost than commercial analogues, whilst achieving comparable clinical results [43]. Mandatory compliance with the provisions of the WHO resolution of 28 May 2019 on the economic accessibility and improving the transparency of markets for medicines could help keeping ATMP prices in control. In addition, we feel that there should be much more attention for health economics in the developing process of experimental therapies, and this from the very beginning. For instance, the evaluation process of EU research and innovation programmes, should ask developers to demonstrate the cost effectiveness and reimbursement potential of their proposed therapies.

3 | The Hospital Exemption Scheme in Belgium

HCTPs that were originally (since the 80s) provided by not-for-profit public actors (mainly hospitals) under a transplant legislation (mainly governed by the EUTCDs) were suddenly considered to be ATMPs (sCTMPs or TEPs). In the EU's masterplan, these products would be produced by for-profit actors from raw materials provided by not-for-profit, mainly hospital-based players [1]. It was anticipated, to a certain extent, that industry would show little to no willingness to take on the production of some HCTPs that are commercially unviable. Therefore, the ATMP Regulation was designed to provide the possibility for EU Member States to set up national HE rules for ATMPs manufactured by public facilities to provide treatment for patients where the ATMPs were not considered suitable for commercial development.

Unfortunately, policy makers did not realise that the HE escape route would need to cater for the majority of the original HCTPs [1], which were produced by mainly hospitals and whose limited resources ultimately prohibited the utilisation of the HE pathway [45]. In addition, there are important variations in how EU Member States' competent authorities interpreted and implemented the HE scheme. In Belgium, the Superior Health Council (SHC) was asked to provide advice on a draft Royal Decree on the Belgian HE for ATMPs, which was drawn up by the Federal Agency for Medicines and Health Products (FAMHP). The SHC stated that the ATMP Regulation and the proposed HE, which sets higher requirements than Belgium's neighbouring countries, would have serious financial implications and could potentially hamper the patients' access to innovative therapies [46]. In addition, the SHC expressed its concern about the mandatory withdrawal of the HE as soon as a commercial analogue comes onto the market or is evaluated in a clinical study, thus nullifying the investments that hospitals and universities would have made to comply with the HE. The FAMPH and policy makers ignored the SHC advice, and the Royal Decree came into effect in 2017 [47]. The pursuit of a "level playing field" between industrial and hospital ATMP manufacturers led to the imposition of industry quality standards and stringent clinical data requirements, which hardly differ from those for a fully-fledged centralised MA (via EMA), on unlicensed products pursuing the Belgian HE framework [47].

In 2012, 23 HCTPs produced by Belgian hospitals in 2012, accredited by the Belgian Ministry of Health (some of them since 1997) and reimbursed by the public health insurance, were considered to be ATMPs by the FAMHP and the manufacturers were invited to apply for a centralised MA or a national HE for continued preparation and use [1]. Two hospital-based tissue banks had already stopped the production and distribution of their autologous chondrocyte grafts by then. It is not known whether this discontinuation was related to the marketing of ATMP ChondroCelect, expanded autologous chondrocytes expressing specific marker proteins, by the Belgian cell therapy company TiGenix (Table 1). TiGenix stopped its production and distribution of ChondroCelect in 2016, due to commercial reasons together with the lack of reimbursement in key European countries. The product Spherox could be an alternative to the use of ChondroCelect. Spherox contains spheroids (spherical aggregates) of chondrocytes, cells found in healthy cartilage, that have been prepared from the patient's own tissues. Spherox is market-authorised in Europe, but commercialization in Belgium was discontinued in 2024 [17]. Some Belgian surgeons now use platelet enriched autologous plasma to repair defects to the cartilage. Its production only involves "minimal—often peri-operative—manipulation performed in the margin of a single surgical procedure", thus bypassing the ATMP Regulation.

We surveyed the Belgian academic and hospital HCTP producers whose products were classified as ATMPs in 2012 to see how their products had fared (Table 2).

Two beta cell products (islets of Langerhans) prepared by hospitals were eventually not considered to be ATMPs. HCTPs are classified as ATMPs if their manufacture involves a process that involves substantial manipulation (and no genetic manipulation) of the starting material (human cells or tissues), or when the HCTP is not intended for the same essential function in the recipient and the donor [51]. Sometimes this classification can lead to "borderline" cases and the EMA set the standards on which classification decisions are based. For instance, the EMA decided that when enzymatic treatment is used to isolate cells, this is considered a substantial manipulation because the enzymatic digestion of the tissues results in a cell suspension, altering cell structure and functionality. However, when an enzymatic treatment is used to isolate cell islets (e.g., islets of Langerhans) and the digestion step is stopped just before the isolation of single cells, the structure of the islet is considered to have been maintained, and the subsequent product is not classified as an ATMP, as it is not considered to have been substantially manipulated [51]. The two Belgian beta cell products thus remained available as "tissues or cells for transplantation", covered solely by the EUTCDs and distributed for medical treatment by Belgian tissue establishments, as was the case before the ATMP Regulation came into force.

None of the 23 ATMP-classified HCTP producers, identified by the FAMHP in 2012, applied for an ATMP production licence, MA, or HE. To date, only one ATMP HE was granted in Belgium. In July 2019, the company Novadip Biosciences was granted a HE for its product NVD-003, which consists of differentiated stem cells in an extracellular matrix for tissue regeneration in critical size bone defects such as congenital pseudarthrosis of the tibia, a rare paediatric orthopaedic condition. This HE was withdrawn after the approval of a clinical trial with the same medicine in July 2022 [52]. For 4 ATMP-classified HCTPs formerly prepared in hospitals (two dendritic and two stem cell-based products) an MA for investigational products was obtained, and 3 of them are since then being evaluated in clinical trials (Table 2). Clinical trial authorizations (CTAs) are granted at a Member State level by national competent authorities. These HCTPs entered phase I/II clinical trials, where they have been residing for a considerable time now, and it does not seem unlikely that for some of them, MA will never be sought.

With not a single HE in place today, the HE measures implemented by the Belgian competent authority turned out to be a measure for nothing.

In total, 25 established HCTPs (including the two chondrocyte products that were discontinued for unclear reasons, before being classified as ATMP)—22 produced by hospitals, three by private companies—are no longer available to patients in Belgium (Table 2). The four HCTP-based ATMPs that possess a centralised MA and are currently (in principle) available on the Belgian market (Figure 1) are hardly compensating for that loss. Belgian production facilities indicated that the incapacity to deal with stringent provisions (mainly for clinical data), long timelines for HE applications, and compliance with Good Manufacturing Practises (GMP) (GMP for ATMP since November 2017) were the main reasons that had led to their decision not to manufacture under HE [45]. Hospitals particularly struggled with GMP compliance, which requires substantial financial and human capital [53]. In contrast, in other countries such as Finland, Italy, and the Netherlands,

TABLE 2 | Status (September 2024) of 25 human tissues and cell products (HCTPs) that were prepared and distributed for transplantation by Belgian hospital-based tissue establishments in 2012 [1], before their formal classification as advanced therapy medicinal products (ATMPs) by the Federal Agency for Medicinal and Health Products (FAMHP).

Tissue establishment	Human tissues and cells	Accredited by the Ministry of Health since	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	

(Continues)

TABLE 2 | (Continued)

Tissue establishment	Human tissues and cells	Accredited by the Ministry of Health since	Status (September 2024)	Comments
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 [48, 49]
Cardio 3 BioSciences	Cardiac progenitor cells	April 1, 2011	Discontinued	Cardio 3 BioSciences became Celyad Oncology, which in 2017 discontinued the cardiac progenitor programme (C-Cure) and transferred the research data and intellectual property rights to the Walloon Region [50]
TiGenix	Autologous chondrocytes	December 1, 2009	Discontinued	The autologous chondrocyte product ChondroCelect, the first approved ATMP on the EU market, was discontinued (marketing authorization withdrawal) in 2016 [14]

[a]Currently part of the Health Network of "Université Catholique de Louvain (UCL)".

regulatory aspects were shown to motivate utilisation of the HE schemes by public facilities [45]. Incapacity to comply is more prominent in countries with the most stringent quality and clinical data requirements for HE manufacturing, such as Belgium. Coppens et al. also reported that no HEs had been granted in Belgium, whilst seven were granted in Germany, and 11 in both France and the Netherlands [54]; neighbouring countries of Belgium.

The Belgian competent authorities opted for a level ATMP playing field with industry standards, but industry showed little to no willingness to take on the production of sCTMPs and TEPs for transplantation, which are often commercially unviable (e.g., keratinocyte grafts; Table 1), and public actors did not have the necessary resources to implement the stringent HE requirements.

Finally, we question whether some HCTPs should have been classified as ATMP in the first place. Even though this classification can be rather arbitrary–sometimes it comes down to the duration of an enzymatic treatment, resulting either in cell islets or single cells–it can have major consequences. In Belgium, beta cell grafts were not classified as ATMP and are still available, whilst keratinocyte grafts–used since 1987 to stimulate wound healing in severely burnt patients–were classified as ATMP and are no longer available.

4 | Discussion and Conclusions

The ATMP Regulation was introduced to improve patients' access to innovative therapies, but 15 years after its implementation, only 19 ATMPs hold an MA, with 16 of them (84.2%) GTMPs. Their exuberant 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 utilisation.

The reason for the observed overrepresentation of GTMPs could be deduced from the Commission's 2005 impact assessment of the proposal for the ATMP Regulation [55]. This document mentions that in 2003, no less than 113 tissue engineering companies were identified in the EU and 35 TEPs were available on the European market, 90% of which were autologous products, mainly skin and bone (cartilage) products [55]. In contrast, in 2003, no GTMPs were approved in the EU. The first GTMP to be approved was Gendicine, in China, in 2003, whilst we will have to wait until 2012 for the first GTMP to be allowed in the EU (Glybera) [56]. Today, 15 years after the implementation of the ATMP Regulation, the ratio of TEPs to GTMPs is completely reversed.

The Commission's impact assessment noted the following points:

1. The impact of the ATMP Regulation will be less significant for GTMPs, as they have been regulated for many years under the legislation of medicinal products. Indeed, before the ATMP Regulation, GTMPs were regulated by Directive 2001/83/EC on the Community code relating to medicinal products for human use, whilst TEPs were not regulated by Community Regulation. The technical requirements applying to GTMPs and sCTMPs, which were already laid down in Annex I to Directive 2001/83/EC, would not be changed by the ATMP Regulation [57].
2. Compliance with regulatory requirements (e.g., GMP) might entail increased costs for small and medium-sized enterprises (SMEs) producing TEPs, which might reduce their innovative capacity and their portfolio, focusing on fewer, more promising products. The increase in regulatory security and potentially higher revenues due to a large market would make TEPs more attractive for investors and would help new companies to enter the market.
3. Very few hospitals and tissue banks produce—or are planning to produce—TEPs. TEPs produced by hospitals and tissue banks will not be significantly impacted by the ATMP Regulation, as they are not manufactured on a large industrial scale.
4. The ATMP Regulation could have an impact on public expenditure through pricing and reimbursement of ATMPs, but these fall under the responsibility of national healthcare systems.

Today, it seems that the Commission was right about points 1 and 4 but underestimated the impact of the ATMP Regulation (and the national HE schemes) on SMEs and the many overlooked hospital-based tissue banks, producers of mainly autologous TEPs and sCTMPs (points 2 and 3). In contrast to what was reported in the impact assessment, many TEPs and sCTMPs were produced on a small scale and distributed by hospital-based tissue banks (22 in Belgium alone) [1]. The vast majority of these TEPs and sCTMPs have now disappeared, without ATMP alternatives.

An additional reason for the dramatic skew of the HCTP/GTMP ratio could be the fact that companies are able to negotiate higher prices for GTMPs—generously covering for ATMP compliance costs—than for TEPs or sCTMPs, falling back on their potential clinical benefit (e.g., life-saving therapies) and the costs, risks, and uncertainties of development [58].

To rectify the situation, as far as possible (several HCTPs have probably disappeared permanently), we suggest increasing the weight of patient-based risk–benefit approaches in the ATMP approval process, especially for lifesaving HCTPs, and including the assessment of the products' anticipated prices and reimbursement landscapes in the EU R&D and innovation funding decision process. 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. There is a need for a broad discussion on this subject, involving all interested parties to define possible strategies to deal with the problem of difficult access.

Conflicts of Interest

The authors declare no conflicts of interest.

Data Availability Statement

Data sharing is not applicable to this article as no new data were created or analyzed in this study.

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