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Original Article/Research

Unlocking the value of innovative medicines: Insights from the advanced therapy medicinal products (ATMP) innovation systems in Germany and Sweden

Piret Fischer [a,*], Thomas Reiss [a], Jörg Mahlich [b], Erwan Gicquel [b], Heike Aichinger [a], Liliya Pullmann [a], Tanja Bratan [a]

[a] Fraunhofer Institute for Systems and Innovation Research ISI, Breslauer Str. 48, Karlsruhe 76 139, Germany
[b] Miltenyi Biomedicine GmbH, Friedrich-Ebert Str. 68, Bergisch Gladbach 51 429, Germany

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ABSTRACT

Objectives: Generally low uptake in the advanced therapy medicinal products (ATMP) market and difficult patient access has been observed across Europe. The objective is to analyze the key challenges of the ATMP innovation ecosystem around R&D, entrepreneurial activities, framework conditions and legitimacy and to highlight how national level activities can impact on patient access to ATMPs in Sweden and Germany.
Methods: An exploratory case studies approach was applied for analyzing ATMP development and uptake in Sweden and Germany between 2010 and 2021. A mixed methods and multi-level approach was used to collect data, including desktop research and 17 expert interviews.
Results: Germany is performing well and apart from better patients' engagement has lower barriers for ATMP development and diffusion compared to Sweden. The main hindrances in Sweden include a lack of collaboration between stakeholders in translational research, conservative HTA assessment and lack of innovative payment models. Both countries could benefit from better streamlined regulation on different aspects around clinical trials (i.e. ranging from legislation on genetically modified organisms for gene therapy medicinal products and master file approach for raw materials).
Conclusions: Despite a number of hindrances around ATMP development and uptake, the evidence in terms of technological development on the one side and unmet patient needs on the other side, shows that ATMPs will play an important role in the future of modern healthcare systems. It is clear that further national level collaboration between academic, clinical and industrial players is necessary to overcome the existing hindrances and boost further development of ATMPs in Europe.

Introduction

Advanced therapy medicinal products (ATMPs) are a wide group of innovative medicines that offer the potential to improve health outcomes for often severely ill patients, whose current treatment options are limited or unsatisfactory [1]. They are characterized by a great heterogeneity, i.e. gene therapy medicinal products (GTMP), tissue engineered products (TEP) and cell therapy based medicinal products (CTMP) and variations in administration ranging from a single intravenous injection to a surgical placement [2].

ATMPs are regulated as medicinal products in the European Union (EU) and marketed either via the centralized authorization procedure or via hospital exemption (HE) pathway [1]. As is common in radical innovations and major technical breakthroughs, besides a number of technological challenges, there are nontechnical barriers and significant uncertainties associated with ATMPs, which are all aligned with the needs of existing technologies [3,4]. Therefore, radical innovations, such as ATMPs, cannot build on established routines and standards in reaching patients, and major system level changes are necessary to successfully adopt these highly innovative medicines by healthcare systems [1,2].

Therefore, this paper focuses on the following research questions:

* Corresponding author at: Fraunhofer ISI, 48 Breslauer Str, Karlsruhe 76139, Germany.
E-mail address: piret.fischer@isi.fraunhofer.de (P. Fischer).

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1) *What are the key barriers to, and facilitators of, innovation around ATMPs in Germany and Sweden?*
2) *What can other EU countries learn from them?*

In this study, we investigate the problems related to ATMP manufacturing and market access on a system level, by considering the innovation process around ATMPs as a whole. In order to do that, the article covers key issues along the entire value chain, starting with R&D (i.e. publications, clinical trials), entrepreneurial activities (i.e. ATMP companies, different business models and patenting activities), framework conditions (i.e. policy, regulation, availability of resources), stakeholder engagement and legitimacy. It enables a look at the "bigger" picture and includes all of the contributing factors for the overall ATMPs innovation system. The analysis is carried out on a national level, which enables us to develop insights from Sweden and Germany, but also includes insights on European level of various factors that have a major influence on the national level ATMP ecosystems developments. Both of these countries serve as positive examples in the EU when it comes to excellence in terms of academic research and the existence of dedicated SMEs and pharmaceutical companies [5]. However, in parallel, there are also significant differences and challenges with regard to market uptake and diffusion of ATMPs. In Germany there is relatively fast and good access to ATMPs once they are authorized in the EU [6]. While Sweden has a strong policy push, reimbursement decisions take long and only three ATMPs are currently available compared to nine in Germany [7,5]. Therefore, these two countries are interesting cases to compare and to draw key messages for other European countries from.

Methodology

In this study, we investigate the problems related to ATMP manufacturing and market access on a system level, by considering the whole ecosystem (i.e. actors, activities, artifacts, institutions and relations that are important for the innovative performance of the system, including the population of stakeholders) [8]. This approach allows to assess not only single elements (i.e. research or manufacturing) within the innovation system, but the innovation process around ATMPs as a whole.

Data collection and analysis

A mixed methods and multi-level approach was used to collect data: This included stakeholder mapping, document analysis, patent and bibliometric analyses, clinical trial information, as well as semi-structured expert interviews.

Document analysis

As a first step, relevant stakeholders, networks, collaborations and NGOs of ATMPs in Germany and Sweden were identified and mapped to get an overview of the ATMP sector in both countries. Empirical data on how the ATMP sector has evolved over the past years and what the main challenges for different stakeholders are was collected from various sources, i.e. from internet sites of ATMP companies, regulatory authorities (e.g. MPA, TLV, PEI, G-BA, BFARM) ,[1] industry organizations (e.g. LIF, BAH, VFA) ,[2] professional groups (e.g. ATMP-Sweden, CAMP,[3] German Lymphoma Alliance, German Cancer Consortium) and patient organizations (e.g. NORD, DEGETHA, ALAN) .[4] Additionally, “gray” literature such as professional journals, ATMP industry reports, ATMP market studies, press releases, EU and national level policy papers in Sweden and Germany was reviewed. The following keywords relating to ATMPs were used: ’ATMP’, ’advanced therapeutic medicinal products’, ’gene therapy’, ’DNA therapy’, ’cell therapy’, ’tissue engineering’, ’engineered cell’. These searches were conducted in English and in the respective national languages.

Patents, clinical trials and publications

To get an overview of academic publication activities, a bibliometric analysis was carried out using the Scopus database (www.scopus.com) for the period between 2010 and 2021 to map how research activities within the ATMP field have developed over the past decade. We searched for articles that used "ATMP", "advanced therapeutic medicinal products", "car-t" in their titles, abstracts or keywords. The search focus was narrower compared to the gray literature search, since the other keywords would have resulted in ten-fold higher results, with the majority of the publications not directly related to ATMPs. Information on ATMP-related clinical trials in Germany and Sweden was collected from the EU Clinical Trials Register (www.clinicaltrialsregiser.eu). A search strategy based on key words "gene therapy", "cell therapy" and "tissue-engineered" and "tissue-based" was designed and applied. Additionally, a patent analysis was carried out to identify the main patent holders in Sweden and Germany. A search strategy based on key words “cell therap*” OR “gene therap*” and on patent classifications (A61K35-12 and A61K48) was designed and applied to identify patents related to cell or gene therapies in Espacent.net, the European Patent Office database. The search was restricted to transnational patents to ensure a good comparability between different countries [9]. For bibliometric analysis, clinical trials and patent analysis duplicate results were removed and the results were verified by another researcher before the statistical analysis.

Interviews

In a second step, the narrative that emerged from these sources was complemented by 17 semi-structured interviews with experts from different stakeholder groups (e.g. industry, academia, nonprofit organizations, drug regulators, and policy makers) in Germany and Sweden (see Table 1). The experts were identified by snowball sampling, using the criteria of having profound knowledge and/or experience on either ATMPs development or uptake in Germany and Sweden. The interviews took place between February 2022 and April 2022. The interview guide was personalized and adapted for each expert based on their field of expertise, and the interviews lasted between 1 and 2 h. We anonymized all results in order to protect the identities of the interviewees. Interview data was triangulated and any contradictory statements between interview results were followed-up, leading to more precise questions and more detailed insights. In few cases, experts were re-contacted to clarify their responses. For remaining contradictions, additional information searches were conducted to include all the possible data sources in the analytic process.

[1] MPA(Swedish Medical Products Agency), TLV (Swedish Dental and Pharmaceutical Benefits Agency), PEI (Paul-Ehrlich Institute), G-BA (German Federal Joint Committee), Federal Institute for drugs and Medical devices (BFARM)

[2] LIF (Swedish Association of the Pharmaceutical Industry), BAH (German Medicines Manufacturer’s Association), VFA (German Association of Research Based Pharmaceutical Companies)

[3] Centre for Advanced Medical Products (CAMP)

[4] Swedish Association of Rare Disorders (NORD), Barncancerfonden (Swedish Childhood Cancer Fund), DEGETHA (German Society of Thalassemia and All Rare Diseases), ALAN (German Acute Leukemia Advocates Network)

Table 1
Overview of interviewees.

ID	Role	Country
A	Health economist	Sweden
B	Patient organization representative	Sweden
C	Cancer organization representative	Sweden
D	Industry organization representative	Sweden
E	Researcher, ATMP-sector expert	Sweden
F	Researcher, ATMP -sector expert	Sweden
G	Industry expert, consultant	EU
H	Regulatory authority representative	Sweden
I	Regulatory authority representative	Sweden
J	Industry organization representative	Germany/EU
K	Business developer	Sweden
L	ATMP organization representative	Sweden
M	Venture capital expert, funding organization representative	Germany
N	Patient organization representative	Germany
O	Regulatory authority representative	Germany
P	SME founder, clinician	Germany
R	Research director, clinician	Sweden

Results

The findings from this study are summarized in Table 2 and described in more detail below.

Table 2
Comparative insights of Germany and Sweden.

Category	Germany	Sweden
R&D Activities	- High level of research funding, activities and publications, the top performer on published research - Good level translational research - General increasing trend of CTs, approval time between 6 and 12 months.	- High level of research activities and publications, one of the top performers in the EU per capita - Translational research very problematic - Very attractive country for CTs per capita, AT approval time 2 months
Entrepreneurial activities	- Dominance of SMEs - Major focus on CTMP and GTMP - DM infrastructure in place, but scale-up needed - HE with one of the best uptakes in the EU	- Dominance of SMEs - Major focus on CTMP and GTMP - DM complicated to implement, due to small population and lack of necessary infrastructure - One HE treatment available, regulation unsupportive
Framework conditions	- Very strong supportive policy push - High access: 12 ATMPs reimbursed (June 2021) - Supportive regulation, PEI has taken initiative on ATMP regulation - CTA and GMO assessment handled both by PEI - VC well accessible	- No dedicated policies in place - Very low access: 3 ATMPs reimbursed (June 2021) - Regulation not up to the speed of the innovative medicines - Different authorities for CTA and GMO assessment - VC well accessible
End-User involvement and Acceptance	- Low patient involvement in research and regulatory issues - Supportive measures for higher patient involvement initiated	- General good level involvement - Patient organizations have difficulties gaining critical mass

(clinical trials (CT); small and medium size enterprises (SME); cell therapy medicinal products (CTMP); gene therapy medicinal products (GTMP); hospital exemption (HE); Paul-Ehrlich-Institute (PEI); clinical trial application (CTA); genetically modified organisms (GMO); venture capital (VC)).

Knowledge generation

Publications

In Germany, there is excellent R&D funding and access to resources (Interview P). There key funding bodies are the German Research Foundation and Ministry of Education and Research, from which the actors can benefit. Although, according to the interviewed experts, there is no ATMP specific funding in place (Interview M, P). Nevertheless, in absolute numbers, our bibliometric analyses in the Scopus database indicated that Germany was leading across different ATMP therapies based on the total number of ATMP related published research in the EU between 2010 and 2021. The number of publications was steadily increasing since 2016, reaching almost 300 publications in 2021 (Fig. 1), having an increasingly larger share of published research on GTMPs. The authors' affiliations of the publications indicate that the research groups focusing on ATMPs development are numerous and are scattered all over Germany, including key players from the German Cancer Research Centre and a number of University Hospitals, i.e. Würzburg, Tübingen, Cologne, Heidelberg, Munich, Hamburg, together with Charité in Berlin.

In Sweden, there is very good project- based R&D funding (Interview R). The key funding bodies include National Cancer Institute, Swedish Cancer Society, Karolinska Institute, Swedish Research Council and Vinnova (Interview L, R). There are currently around 17 research groups focused on ATMP research, Karolinska Institute being the biggest hub with 9 research groups, followed by Uppsala, Lund and Gothenburg University [10]. Sweden also has a strong position in terms of scientific productivity, as according to the search results in the Scopus database, the number of ATMP related publications from Swedish affiliations has been increasing constantly over the past decade, reaching 110 publication in 2021 (Fig. 1). When adjusted for country population size, based on the number of ATMP-related publications, Sweden is the most productive country among the countries compared between 2010 and 2021 in the Fig. 1.

Clinical trials

There are more than 1200 ATMP related clinical trials globally, out of which 90% are on gene therapies [5]. Over the past decade, the number of ATMP-related clinical trials has multiplied tenfold, owing to the increasing number of clinical trials in the gene therapy segment [11, 12]. The growth has however taken place outside of Europe (i.e. by 36% in North America and 28% in Asia), as in Europe the number of clinical trials with advanced therapies has stalled, growing below 2% in 2019 [13].

According to the search results in the EU Clinical Trials Register, over the period 2010 until 2021, 31 clinical trials were initiated in Sweden and 133 in Germany. The number of clinical trials in the field of ATMP had a moderate growth until 2019, followed by a rapid decrease, which is likely to be because of the COVID-19 pandemic (Fig. 2). Even though Germany initiated four times higher number of new ATMP clinical trials compared to Sweden, based on a number of new clinical trials by country relative to their size Sweden attracts proportionally significantly more new ATMP clinical trials per capita than Germany [12]. Our analysis also indicated that by product type, gene and cell therapy products (Sweden: 13 GTMP/13CTMP, Germany: 57 GTMP/46 CTMP) are dominating in both countries over tissue-engineered products (Sweden: 5, Germany: 30) and oncology is the key indication area in both countries.

Entrepreneurial activities

Companies

The global ATMP market was estimated to be worth 7.9 billion USD in 2020 and is expected to grow at a compound annual growth rate (CAGR) of 13.2% over the next years, reaching 21 billion USD by 2028 [14]. There is up to 5 trillion USD total potential market for gene

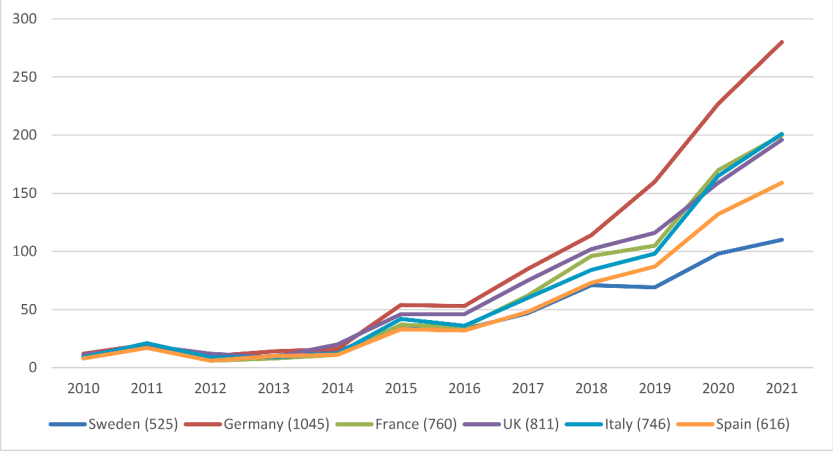

Fig. 1. Total published research within ATMP/year in six European countries (Source: Scopus database).

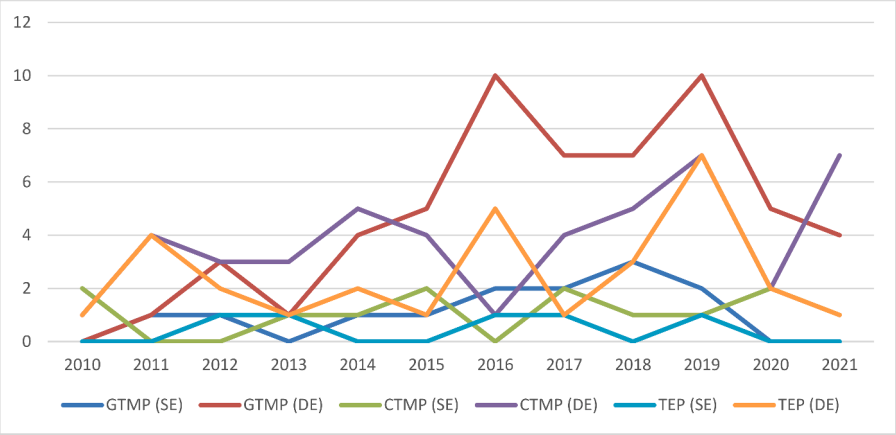

Fig. 2. Clinical trials on ATMP in Sweden and Germany (2010–2021).

therapies [15]. There are more than 1100 companies active in the field globally, with half being based in North America [5] and around 240 based in Europe [11]. The majority of these firms are SMEs (around 65%), which is significantly higher than in the traditional pharmaceuticals and biotechnology industry [5,15]. It is expected that as the R&D business model is changing as SMEs try to commercialize their inventions by themselves, as they are rather big and active on the stock market (i.e. Bluebird Bio) [5,15]. Based on the headquarter location, we identified 20 ATMP companies both in Sweden and Germany. In Germany, only four are focused on tissue engineering products and in Sweden two. In both countries, the majority specializes either on CTMP or GTMP development. In Sweden, the majority of the SMEs originate from publicly funded academic research, which has been transferred to a start-up firm in order to facilitate further R&D and commercialization [5]. In Germany, the identified ATMP companies are also mostly SMEs, but not explicitly originating from publicly funded research, as in Sweden. The main development of ATMP is a result of extensive work of academic hospitals/research centers and SMEs, without the involvement of the pharmaceutical industry [2]. In parallel, big pharma is increasingly moving into this field, as they see promising results with the strategy to buy the start-up companies and get high returns for their investments (Interview H, I). The involvement of pharmaceutical companies is mostly focusing on oncology [2]. Indeed, since 2017 the ATMP market has witnessed Gilead's acquisition of another CAR-T developer, Kite pharmaceuticals, Celgene's acquisition of Juno Therapeutics and Novartis's acquisition of AveXis [16]. Furthermore, Celgene has been acquired by Bristol-Myers Squibb and Spark Therapeutics by Roche, which demonstrates the desire of large players to have a presence in the ATMP market [16]. In parallel, there are also some opposite examples, with GSK selling its therapy portfolio of rare diseases ATMP to Orchard Therapeutics in 2018, as part of GSK's ongoing prioritization, with a focus on priority in two therapy areas - i.e. respiratory and infectious diseases together with oncology and immuno-inflammations [17]. This illustrates the difficulties of some players in the pharmaceutical industry to sustain their traditional business model. Despite high prices, ATMPs are not able to sustain the same level of revenues as therapies for chronic diseases did for pharmaceutical companies [18].

Patenting

ATMP development occurs to a greater extent in the public domain and in SMEs [15]. Despite a number of challenges (i.e. high development costs, complex and expensive manufacturing, reimbursement uncertainty) [19,15], it also brings along a great deal of new intellectual property (IP) [20] . For example, the patenting of CAR-T inventions resulted in a total of almost 2000 patent documents by 2017 [20]. Furthermore, the patentability is very restricted and more complex in the ATMP field compared to traditional pharmaceuticals business [21]. According to the European Patent Convention [22], terminology, i.e. whether the final product is marketed as a drug or medical treatment, can play an important role on ATMP IP. For example, therapies such as Kymriah and Yescarta (both are CART-T cell therapy products) are characterized as drugs in regulatory filings by their manufacturers and not as medical treatments, but in its essence they are more akin to medical treatments, which are not subject to patent protection [21]. For

companies, these details play a crucial role, as for example more than 80 countries globally, including the members of the European Patent Convention, prohibit the patenting of such methods of medical treatments. At the same time, patenting is necessary for drug developers to recoup R&D costs and avoid immediate competition [21]. Furthermore, unlike new small molecule drugs or biologics, for ATMP companies it is often challenging to patent their inventions, as the final product is a modified version of human's cells. Also, it can either already build on publicly existing knowledge or it is rather a component of the innovation process than the final product itself (i.e. a construct, used to deliver genetic material to the cells) (Interview L). There seems to be a dominating trend towards process patenting in the field of ATMPs (i.e. production, quality control methods) [23]. For example algorithms in manufacturing processes or selection of algorithms in terms of starting materials, i.e. a process constitutes a patented product (Interview L). Also, patenting different components, used in manufacturing processes (e.g. lamina in cell therapy or constructs) can be observed (Interview L). This is especially important in cell therapies, where a traceable human component has to be a part of the product, which is normally not even possible to patent. Therefore, ATMP companies have to find ways to patent parts of processes or as components that can be brought into the process (Interview L). The patent field of ATMPs is steadily growing and Europe is showing a strong performance in this area, with exponential growth in IP activity in CAR T-cell therapy, unsurprisingly [23]. Based on our research, in the European Patent Office database, 616 patent applications were filed from Germany and 230 from Sweden between 2000 and 2021. The affiliations with the highest numbers of filed patent applications in Sweden were Cellartis AB [17], Takara Bio EuropeAB [15], Biolamina AB [12]. In Germany, the highest number of patents in the same timeframe were submitted by Curevag AG [27], CSL Behring GmbH [18] and Bayer Shering Pharma [12].

Decentralized manufacturing

Successful ATMP uptake requires change in the overall structure of the market and change existing value chains and business models [24]. Decentralized manufacturing (DM) is ATMP manufacturing where it is carried out locally at hospitals or suitable manufacturing sites (i.e. as near to the patient as possible), opposite to being centrally manufactured in one location and then distributed globally [25–27]. DM is especially important for autologous products (i.e. CAR-T) over allogenic (Interview P).In such personalized products, based on living cells, manufacturing time and time to treat is a critical factor and DM would enable faster processes and logistics. In Sweden, the topic has been discussed extensively and large university hospitals are actively involved (Interview C). Currently for T-cells therapy, leukapheresis (i.e. white blood cells separation from a blood sample) of patients is done in the hospitals (Interview R). Thereafter the cells are frozen and sent abroad for manufacturing before being sent back to Sweden to treat the patients (Interview J). This "vein-to-vein" time varies depending on the drug, but on average it takes between three to six weeks [28].

In Germany, the DM topic has also been discussed intensively by different interest groups (Interview P). Currently for T-cells therapy, leukapheresis is done in 26 medical centres [29]. Thereafter the cells are frozen and sent to CAR-T manufacturing facilities. Currently in Germany mostly the existing infrastructure is used for CAR-T manufacturing [31]. It is taking place in collaboration between big pharmaceutical companies together with biotechnology companies and their different partners. The supply of cells comes normally from very highly qualified institutions [30]. For example, in the frame of collaboration between Fraunhofer Institute for Cell Therapy and Immunology IZI and Novartis, more than 500 CAR-T cells have already been produced. Germany is also one of the three European manufacturers for the overall global supply chain of Novartis' CAR-T technologies (i.e. Kymriah) [31].

Automation is considered as key for DM, as it would solve issues around manufacturing variations and quality and minimizes human errors [31,32]. Hospitals hold an increasingly important role in DM as part of the manufacturing process and also as storage facilities. However, there are also a number of problems. Firstly, setting up a pharmaceutical quality system is very expensive (Interview P). In Sweden as well as in Germany, there are only few hospitals that have the industry-like infrastructure and GMP in place (Interview P, R). At the moment only Karolinska University Hospital in Sweden would have the capacity for in-house ATMP manufacturing and has the necessary GMP licence (Interview E, R). Also, other larger hospitals, such as those in Lund and Gothenburg could develop the capacity if necessary and qualify to manufacture between 2 and 3 drugs due to different capacity constraints (e.g. licence by the competent authorities and sponsors) (Interview R). In Germany, Charité University Medicine Berlin is one of the hospitals with a capacity for in-house ATMP manufacturing, where the ATMP manufacturing to the department of transfusion medicine with a GMP license for conventional blood products (e.g. erythrocytes, thrombocytes) (Interview P). Therefore, using the infrastructure of transfusion medicine allows sharing the cost of the quality system and even covering the costs of ATMP manufacturing through revenues of conventional blood product manufacturing (Interview P). Another option is to establish GMP manufacturing sites by using public funding for experimental products in very specialized university hospitals, with a specific focus on immunotherapy or cancer (e.g. University Hospitals in Regensburg and Tübingen) (Interview P).

In both countries, even when DM is taken up at hospital sites with necessary GMP infrastructures, there limitations in terms of manufacturing capacities remain. Furthermore, many companies still see the advantage of being positioned centrally in bigger countries, such as Germany for CAR-T therapies by Novartis, as described above. In the case of Libmeldy, there are so few potential patients in Sweden (and neighbouring Nordic countries) that only one Nordic centre for treatment would be feasible (Interview H). As for Zolgensma, only three hospitals (in Stockholm, Gothenburg and Lund) will administer the drug to patients in Sweden. So even though the company agreement is only with few regions, the uptake is national, as all regions can send patients to these specialized centres and then these three regions will invoice others (Interview H).

Hospital exemption

As defined in Art 3(7) of Directive 2001/83/EC [33], amended by the ATMP Regulation 1394/2007 [34], ATMPs can be licensed under the Hospital Exemption pathway (HE) which is an exception to EU law: ATMPs that are licensed under the HE pathway are exempted from the requirements of Directive 2001/83/EC and, therefore, have no central marketing authorization (MA). However, HE still follows very strict standards, pharmacovigilance and quality. It is therefore an alternative pathway for ATMPs to reach patients in Europe, but under special conditions, which include treating only individual patients at a hospital setting on a non-routine basis and is limited to the same member state of the EU where it was developed [35]. Germany has been the leading country in Europe in authorizing products under HE. The Paul-Ehrlich Institute (PEI) grants temporary HE manufacturing licenses between three to seven years, depending of the product and there is no limit on how many patients can be treated with one HE product, neither how many HE can be approved per year (Interview O). According to the PEI homepage, as of April 2022 there are nine products available on the German market under HE scheme (Table 3), the majority being TEPs.

In Sweden, HE manufacturing must be authorized by the Swedish Medical Products Agency (MPA) ("Läkmedelsverket"). Currently, there is only one product available (Interview H, I). According to the interviewed experts, there are a number of reasons behind the low HE availability in Sweden. Over the past years, the interpretation of HE by the MPA has shifted and changed the unlimited manufacturing permit to 5-years (Interview L) and therefore some of the HEs is Sweden that did not manage to start a clinical trial in order to go for MA, had to stop (e.g. Gothenburg University Clinic and Karolinska Hospital (Interview L). Also, certain HE needed to undergo criminal investigation, because

Table 3
ATMPs available in Germany under the hospital exception scheme (March 2022).

Product/MA holder	Category at PEI
Amesanar/RHEACELL GmbH	Somatic cell therapy
Cytokine-induced killer cells (CIK-Zellen)/Red Cross Blood Transfusion Service GmbH	Tumor Vaccine
BioSeed-C Autologes 3D-Chondrocyte Implant /BioTissue Technologics GmbH	Tissue engineered product
co.don chondrosphere, 1 /co.don AG, Teltow	Tissue engineered product
MukoCell/MukoCell GmbH	Tissue engineered product
NOVOCART 3D/TETEC AG	Tissue engineered product
NOVOCART Inject/TETEC AG	Tissue engineered product
Obnitix/medac GmbH	Tissue engineered product
t2c001/t2cure GmbH	Tissue engineered product

researchers used the HE scheme for not authorized research purposes (Interview R). One of the key issues seems to be GMP, as HE applications are often rejected by the MPA not because of the clinical profile, but because of manufacturing quality issues (Interview F).

Framework conditions

Sweden

Discussions around ATMP within the scientific community took off in Sweden around 5 years ago (Interview B). After this, the pharmaceutical industry reacted to it and initiated a number of seminars and media outreach (Interview J). Over the past years, a number of ATMP supporting initiatives have been set up, most relevant are ATMP Sweden, which span from basic discovery to hospital readiness. The Swedish National Life Science Strategy has defined precision medicine and ATMPs as priority fields [7]. Furthermore, the national ATMP-Sweden network (www.atmpsweden.se) has been set up and funded by Vinnova to promote collaboration and communication of the Swedish ATMP sector. However, none of these initiatives has so far successfully addressed one of the major issues related to difficulties in term of translational research and funding (Interview C). This is partly due to the Teacher's Exemption law, which prohibits universities from obtaining the IP rights of employed researchers. Due to this, the researchers have to secure their own funding to patent and bring their inventions to clinical trials (Interview C). Researchers therefore start their own companies and try to attract venture capital (VC) to develop their innovation further. However, as the VC companies want their investments back, the companies are sold with low influence on the innovation and a low likelihood that the innovation is developed further (Interview R). If this happens very early in the development phase, it is not always in the best interest of the invention/product, when the company is sold with a very early stage IP, as firms benefit most from VC funding when they have been in operation for a few years, but have not yet matured completely [36] Therefore, the likelihood of success of a ATMP SME can be reduced together with the likelihood to reach the patient (Interview R).

Secondly, the conditions for medical doctors to engage in research activities have been assessed by the interviewed experts as not being favorable (Interview B, C). Firstly, clinicians have less access to financial and other resources for R&D than the private sector (Interview C). Also, in Sweden there have been some recent regulations with the goal of separating doctors and pharmaceutical industry, so that the companies are not able to influence clinicians on what kind of medicines to use. That has resulted in healthcare professionals being extremely careful to work with companies, to avoid conflict of interest (Interview B, C). Compared to Germany, the Swedish healthcare system is more cost driven and extremely defensive, where doctors are not encouraged by the system to look for new treatments and innovative approaches. Last, but not least, doctors often are also under massive workload pressure and their time for doing research is therefore simply limited (Interview C).

Besides problems with translational funding and innovation, access to ATMPs in Sweden remains low and there is only one product available under HE scheme. As there is value based pricing in Sweden, the focus of the HTA is on the value of the ATMPs, which, combined with very high prices and weak evidence, has led to the situation that in May 2022 only Yescarta, Kymriah and Zolgensma are available to Swedish patients out of all the 15 authorized ATMPs in the EU (including the ATMPs withdrawn from the market). There is a big mismatch between facilitated processes in terms of regulation and in terms of access to R&D funding versus payer perspective (Interview I). This mismatch is highly relevant to SMEs, which so far do not take into account sufficiently that they need to demonstrate added value in order to get reimbursed later on. Recently, the CAR-T therapies triggered the discussion around reimbursement models of these onetime extremely expensive medicines, in terms of how to better evaluate them (Interview I). The Dental and Pharmaceutical Benefits Agency (TLV) was given an assignment by the Swedish government in 2019 to analyze the particular challenges that relate to ATMPs (i.e. analysing current HTA assessment, proposing innovative payment models, better evaluation of the value of ATMPs) to improve access to the Swedish market [37]. This tension around low access to ATMPs has led to a lot of activities, but at the same time, there are no specific measures proposed or implemented (Interviews J, L).

Also, Sweden has a smaller amount of each type of patient, compared to the bigger EU countries, such as Germany. Therefore, for each cell therapy for example, there needs to be a dedicated center, which requires setting up regional centres to give treatment to the patients, which poses a significant economic challenge. This has been recognized by the community and the development of ATMP centres in different parts of Sweden is high up on the agenda to improve access to ATMPs (Interview F).

Germany

The German Research Foundation (DFG) has recently started an initiative in order to establish inter-medical university infrastructures across Germany [38]. These translational hubs would serve as platforms for interdisciplinary collaboration of public and private stakeholders to advance ATMP therapeutics [38]. In Germany the situation on collaboration is also better than in Sweden, as clinicians are more open to participating in trials and clinical trials are heavily incentivized (Interview M). When clinicians participate in clinical trials, they can use the money received to fund their research group in whatever they find necessary, whereas in Sweden all the fees from companies go to the central administration (Interview H). Therefore, the clinical researchers in Germany are interested in participating in as many trials as possible and furthermore, it makes the industry support to a large extent the infrastructures at hospitals (Interview M).

Germany also has one of the best uptakes of ATMPs in Europe and there is direct market access after EMA approval, as the manufacturers had to submit their dossiers to receive decisions on pricing and reimbursement within 12 months, which is reduced to 6 months of free pricing from 2022 onwards [6,39]. This means that unlike in other countries, there is no delay until the HTA process is completed (Interview N). As of April 2022, 12 ATMPs were approved and reimbursed in Germany through the European Centralized Approval and 9 through HE. In Germany, unlike in Sweden, the Federal Joint Committee (G-BA) first categorizes the ATMP either as a medicine or a medical procedure and undergoes the HTA according to the AMNOG (*Arzneimittelmarktneuordnungsgesetz*, Medicine Market Reorganization Act), where discounts on list prices are negotiated after 12 months on the German market with the producer, based on various factors, such as added value [19]. Alternatively, if the ATMP is categorized as a medical

procedure, it is assessed by the PEI [19]. All the ATMPs have been categorized as medicines, apart from Spherox and Holoclar [19]. Rebates are applied and installment plans with annual payments are set up, if the treatment is successful (i.e. Zynteglo) [19]. Also additional funds (i.e. under the new examination and treatment method "NUB" scheme) are provided to hospitals managing new drugs, including ATMPs, if the price is not covered by an existing diagnosis-related group (DRG) fee [19]. Additionally a Risk Pool fund has been initiated in Germany, to reduce financial burden of expensive ATMPs for the payers. The fund will cover 80% of the costs for each patient exceeding 100,000 EUR per year via solidarity financed German Health Fund, redistributing the aggregate burden among different payers [40]. Until the availability of CAR-T technologies, the reimbursement had been less of an issue in Germany, as ATMP treatments were so rare that the system was able to afford it. Now, with a number of new technologies in the pipeline and the number of potential patients increasing, the question how healthcare systems can afford to pay for ATMPs becomes more urgent (Interview O).

Clinical trials & GMO legislation

The current Clinical Trials legislation in Europe involves a lot of back and forth, i.e. EMA evaluates the results of clinical trials, data obtained in the clinical trials and approves the drugs [38]. The clinical trial study protocol approval, evaluation and monitoring is taking place in individual EU member states (MS) [38], including requirements on testing donors and starting materials, which can lead to diverging opinions, causing delays for companies. In Germany, after ATMP clinical trials authorization by the national competent authority (NCA) "Paul-Ehrlich Institut" (PEI), approval from the local ethics committees within the state the principle investigator is located is required in addition to manufacturing license authorization from the respective local competent authority ("Landesbehörde"). In Sweden, the clinical trials are authorized by the Medical Products Agency (MPA), followed by the Swedish Ethical Review Authority (EPM) [41]. At the beginning of 2022, a new Clinical Trials Regulation entered into force, with a transition period for clinical trial submission. The new legislation is expected to centralize and facilitate clinical trials evaluation and approval processes [42].

An additional hurdle for gene therapies is the GMO legislation, as gene therapies are considered genetically modified organisms in Europe and must therefore comply with GMO regulation, which, depending on the country, belongs to environmental or agriculture legislation, meaning that the companies need to apply for double authorization [43]. In case a company wants to conduct multinational CTs, they have to multiply the number of authorisations, and the applications and procedure are different in every country. Furthermore, the decisions of the authorities can be different, meaning the CTs have to be carried out differently, depending on the GMO regulation in the country [44]. This is especially complicated for rare disease, as the choice of CT locations is limited. Many companies choose where to do CTs just because of the GMO legislation and it definitely gives a disadvantage to Europe compared to the US and China (Interview G).

Lately there have been some efforts at the EU level to streamline and create a more consistent process for the assessment of the environmental risks for medicines containing GMOs for both CT applications and MA applications, to support ATMP developers on at the EU market (e.g. coordinated assessment of the clinical trial application between the involved Member States, with one MS leading the procedure [44]. This also includes common forms endorsed in a number if EU countries for CAR-T products, which are valid in all the countries in case of multinational trials [45].

Nevertheless, national documents (i.e. informed consent forms), will still need to be submitted, to respective countries, the exact mechanisms between the Clinical Trial Regulation and the GMO legislation is not in place, neither is there a procedure for submission of a GMO application as part of the new single submission as defined by the new Clinical Trial Regulation [44].

Germany and Sweden are among the leading countries in Europe where this issue is dealt within one data package, i.e. in Germany the PEI is next to Clinical Trial Assessment also responsible for environmental risk assessment in consultation with the Federal Office for Consumer Protection and Food Safety ("Bundesamt für Verbrauchschutz und Lebensmittelsicherheit") [46]. In Sweden, also only one application to regulatory authorities in needed [47], but the data package, is treated by two different regulatory authorities: MPA and Swedish Environmental Authority that are still in the process of deciding regarding who grants permits and how exactly it should be done (Interview L).

Master file approach

There is a need to extend the ASMF to include raw materials and critical starting materials that are used for the manufacturing of cell & gene therapies (e.g. cytokines, media, reagents, viral vectors), as it already exists in other jurisdictions like the US (Interview G), [48]. This would reduce red tape for regulators and developers by avoiding multiple assessments by every single National Competent Authorities (NCA) each time an application is submitted by a developer for a cell & gene therapy product using these materials (Interview G). It would also preserve confidentiality of commercial information (e.g. exact composition, manufacturing details) by being available to EMA/NCAs only and not to competitors. [48]

Venture capital

In terms of availability of venture capital (VC), until CAR-T were first introduced to the market, the ATMPs sector was heavily underfunded (Interview O). CAR-T technologies proved that ATMPs can be sustainable products with good clinical outcomes, and this exponentially triggered VC companies' interest in the field (Interview O). Typically, VC companies are not country specific unlike some country specific funding agencies, such as the Federal Agency for Disruptive innovation SPRIN-D and GO-BIO funding program of the Ministry of Education and Research in Germany (Interview M). In Sweden, the key funding player is the Innovation Agency Vinnova (Interview J). The main classical seed investors in the field include Germany based High-Tech Gründerfonds (HTGF) for high tech start-ups and in Sweden-based HealthCap that is a family of venture capital funds investing globally in the life sciences. Long-term investors in the field include Forbion European Acquisition Corporation, EQT Life Sciences and Sofinnova Partners SAS and Flerie Invest that all have broad(er) focus on healthcare and life sciences (Interview J, M). The latter one recently invested 52 million USD in an innovation hub and a large scale production site for advanced therapeutics NorthXBiologics in Sweden [49]. Also big pharma is an important stakeholder in this category, as most of the companies support R&D that fits with their own portfolio, such as Roche, NovoNordisk, Merck. The strategy is often to fund the pre-clinical stage, in order to have full exclusivity over clinical trials afterwards (Interview M).

End-user involvement and acceptance

Germany

In Germany patient involvement in research and regulatory discussions does not have much of a tradition and research is dominated by institutional actors and the clinical community [50]. For ATMPs, patient involvement is highly important though, as there is lack of data available on how patients respond during and after the treatment (Interview N). This is also a significant worry for the ATMP patient community, because they do not know what to expect (i.e. what are the side effects, how long do they last) when they undergo very invasive therapy, such as CAR-T (Interview N). Often, clinical specialists might consider specific side effects manageable, but patients who receive treatment actually find the side effects too severe to continue treatment. Therefore, knowing what is ahead of them and how long it will last, might help them to persevere. But available data is currently very limited and

patients are not sufficiently engaged in the research [50]. This problem has been acknowledged by policy makers and there are some initiatives trying to address the issue. For example, the Federal Institute for Drugs and Medical Devices (BfArM) started a pilot on patient involvement, partly as a rapporteur to EMA the organization was requested to have patient representatives involved and there was no systematic process in place on how exactly it should be done (Interview N). Also, the BMBF has started the initiative "Decade Against Cancer" that is trying to bring all relevant stakeholder groups together in the fight against cancer and to also keep patient participation on the agenda [51]. Furthermore, BMBF has made patient participation obligatory in their funding calls, which is a major improvement (Interview N).

Sweden

In Sweden, patient involvement in different processes can be regarded positive (Interview C). However, experts pointed out that manufacturers should listen and collaborate more with patients and patient advocates in order to better align R&D with actual patient needs. More interactive ways of collaboration would also be beneficial for companies (Interview B, C). However, how well patients groups are represented seems to depend highly on the profile of the disease and how many patients are affected. This puts patients with orphan diseases or rare cancers in a particularly weak position in terms of making their voices heard, compared to e.g. breast cancer patients. Also, relevant NGOs seem to be unaware that new and innovative treatments exist, even though patients have access to them in Sweden. Therefore, one of the experts notes that the main Swedish cancer organizations are not driving the discussion in terms of access to advanced therapies and the main focus is often on meeting more traditional objectives, such as access to wheel chairs or personalized care instead of innovative therapies (Interview B).

Discussion

Based on the high number of publications and available R&D funding, there is a lot of basic research on ATMP both in Sweden and Germany, and the beginning of the value chain can be considered excellent in both countries (Table 2). However, there is a major gap in translating all early-stage research into actual medicines and a lot more translational research is needed in academia compared to what is eventually translated into knowledge and concrete products, which seems to be especially problematic in Sweden. One of the reasons is the Teacher's Exemption law, which forces the inventors to involve VC at a very early stage of research and therefore decrease the chances of the innovation eventually reaching the patients.

The other reason seems to be the two distinct "paths" of research - academia and industry going about their research differently and not collaborating enough for different reasons, such as healthcare professionals and companies considering each other as competitors and healthcare professionals being reluctant to work with companies to avoid having their independence questioned. In parallel in Germany, the situation on translational R&D and collaboration is better than in Sweden, as clinicians are more open to participating in clinical trials, which is a heavily incentivized system due to the industry supporting the infrastructures at participating hospitals.

As for ATMP companies, both in Sweden and Germany the sector has similar profile: it is dominated by SMEs, who focus mostly on CTMP and GTMP development and the big pharmaceutical sectors' involvement is currently still low. The experts' opinion from both countries is in line with previous studies that found that the current pharmaceutical industry business models need to be better adapted for ATMP development. The different options for big pharma in terms of revenues, would be addressing either the largest markets within the ATMP field, such as hemophilia, or tackle high incidence disorders (i.e. spinal muscular atrophy). An additional alternative would be to carry on investing in constant portfolio expansion in order to treat for example various retinal diseases [18]. Opinions on whether in the future there will be more allogenic or autologous products on the market differ between experts. However, the dominant view is that decentralized manufacturing is inevitable for autologous products, but the implementation is lengthy, as it requires many resources and drastic changes in the way how healthcare is delivered. This includes major technical changes, such as a high level of automation in order to guarantee the quality of produced products. Furthermore, it will also require hospitals to become manufacturers in addition to being healthcare providers. This, as described above, is a very challenging task for which very few hospitals would currently be capable of in Sweden. In Germany the number of hospitals is higher in terms of necessary resources and qualifications. Furthermore, Germany is already one of global supply hubs for CAR-T production, which has a positive impact on the overall ATMP sector development in the country.

HE is regarded as a legitimate alternative for access to innovative drugs when there are no officially approved alternatives available nor clinical trials that the patient would be eligible for however problems are also associated with it. HE enables patients to receive new ATMPs faster and cheaper compared to a product that goes through a centralized MA process. In Germany, the process is coordinated by PEI, which has a very flexible and innovative attitude towards HE, resulting in 9 ATMPs available for German patients, which is the highest number in the EU. Sweden, contrary to Germany, serves as an opposite example with only one HE available for Swedish patients. The key problem is that there is no solid assessment and no transparency in terms of safety and efficacy. Different MSs have different regulations, leading to different quality and standards, which can be detrimental to patients, who are often in a very vulnerable situation and have extremely limited treatment options available. There is some confusion regarding what is allowed and what not and rules are not applied homogeneously across the EU, meaning that an increased pan-European harmonized approach and regulated HE environment would be necessary to foremost increase patient safety.

In terms of a number of aspects around clinical trial design and execution (i.e. GMO legislation, misalignment regarding data requirements between regulators and payers), it becomes evident that there are various barriers at both, national and EU level. A better aligned innovation climate is necessary in terms of better advising and supporting companies. Especially, as the ATMP field is dominated by SMEs in both countries under study, who, compared to big pharma, have a lot less competences in planning and carrying out clinical trials. With higher coordination, clinical trials could be better aligned from the beginning with regulatory requirements and be more beneficial for all stakeholders involved. Therefore, the whole process should be more aligned and streamlined instead of the current step-by-step approach. Germany is already ahead of Sweden in this aspect, as the CTA and GMO assessment procedures are both handled by the same organization, i.e. PEI. This kind of streamlining also in other countries, i.e. Sweden, would make Europe more attractive for companies as clinical trial sites in comparison to other regions such as the US and Asia with currently better streamlined processes. There are some improvements to be expected from the adoption of the new Clinical Trial Regulation [52], which came into force in January 2022, but issues around GMO and master file approach on raw materials were not addressed in the new regulation and will still remain an issue [44].

Also, regulation would need to be adopted for DM, as the fact that the current GMP guidelines are tailored largely to large patch/volume production can be restrictive for some ATMPs, where the patch could be a one patient dose only [53], and this poses an additional hindrance for small scale DM.

In terms of HTA and reimbursement, the example of Germany shows that sooner or later all EU countries should adapt their HTA models in order to accurately define the value of ATMPs regardless of high upfront costs and unclear economic value. Also, innovative payment models to overcome the uncertainty of the full value of ATMPs and affordability is

an important topic for regulators and policy makers in order to enable equal access to advanced therapeutics to all EU patients needing them. In Sweden, the topic is being intensively discussed and investigated (i.e. see the recent report by The Swedish Institute for Health Economics from 2020) [54], and novel payment methods, i.e. outcome-based payment system, have been recommended for Sweden, without any further steps of implementation so far.

Last but not least, improvements are needed in terms of patient involvement and advocacy around ATMPs, especially in the research part at the beginning of the value chain. The current challenges seem to be driven by two main problems — first, ATMPs are an extremely wide therapeutics area, so there is no single patient organization and they are scattered between different disease groups, ranging from neurodegenerative diseases to specific childhood cancers. Therefore, in Sweden for example it is very complicated for patient representatives, especially in the field of rare diseases, to gain a critical "voice" in order to be heard. Also for large associations, the approach is more conservative and less effort has been dedicated towards improved access to advanced therapeutics. In Germany the key issue seems to be lack of collaboration between different organisations and also there are some important cultural issues, related to the role of patient advocacy in society (i.e. focus mostly on primary care) and the domination of the clinical community in any kind of decision making involving patients wellbeing. This also used to be a like this in Sweden, but the country has made significant progress over the years to change the role of patient organizations in Sweden.

This study is among the first in peer-reviewed literature that provides deeper insights and evidence on a number of problems related to ATMP manufacturing and market access on a system level in Sweden, where a number of problems exist in comparison with Germany, where the ATMP innovation system faces less hindrances. This approach allows to assess not only single elements (i.e. research or manufacturing) within the innovation system, but the innovation process around ATMPs as a whole. However, it also has a number of limitations. Since this research is based on two countries, its transferability to other EU countries is limited. Including further countries would increase the generalizability and validity of the conclusions. Also, as this work has a system level perspective, any deeper insights on the internal (business) strategies of the companies involved in the ATMP sector, are not included. These type of internal insights could provide valuable understanding why the companies in the sector have chosen specific strategies in developing and diffusing ATMPs. We hope that our analysis and findings can offer new research paths along which different hurdles in ATMP development and diffusion can researched further in greater detail.

Conclusions

As illustrated in this article, the ATMP innovation ecosystem is still facing a number of national and EU level hindrances around R&D, manufacturing or regulation. However, the evidence in terms of technological development on the one side and unmet patient needs on the other side shows that ATMP have the potential to play an important role in the future of modern healthcare systems in both countries. It is clear that further collaboration between academic, clinical and industrial players is necessary to boost further development of ATMPsIn terms of manufacturing, the currently limited capacity of pharmaceutical industry with a centralized manufacturing approach, is by far not enough to meet the market demand. This gives an opportunity for other stakeholders and manufacturing practices (i.e. DM) to gain a competitive position on the ATMP market. It foremost requires the development of sufficient GMP decentralized manufacturing infrastructure in both countries and re-evaluating the role of academic medical centers from becoming solely teaching institutions and treatment providers to manufacturing sites with required infrastructure and competences, such as large academic hospitals (e.g. Karolinska University Hospital in Sweden or Charité in Germany). In terms of framework conditions, the key observations of this study suggest that the biggest issues for the ATMP community are a combination of national and EU-level framework conditions regarding streamlining CT and GMO assessments for facilitating the clinical trials process for companies and better harmonized approach and regulated HE environment together with better streamlined ATMP HTA, to enable equal access to innovative medicines in Europe. At the country level, conservative HTA assessment and lack of innovative payment models in Sweden or setting up decentralized manufacturing facilities both in Sweden and Germany need to be considered. At EU level, the lack of regulation on HE and alignment of the requirements on different aspects around clinical trials (i.e. ranging from GMO legislation for GTMPs and master file approach for raw materials) create additional barriers. These hurdles are often ATMP specific, but there are also a number of aspects that are not unique to the ATMP sector and seem to apply to broader radically innovative fields. These include the need to consider the needs of patients already at the beginning of the R&D phase to better address their unmet needs or lack of R&D collaboration between industry and academia. The authors believe that the results can contribute to a higher level of awareness of different challenges related to ATMPs development and uptake in Europe and support the policy makers in creating a more innovation friendly climate for advanced therapies not only in Sweden and Germany, but also in the whole of Europe.

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Supplementary materials

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References

[1] Coppens DGM, Hoekman J, de Bruin ML, Slaper-Cortenbach ICM, Leufkens HGM, Meij P, et al. Advanced therapy medicinal product manufacturing under the hospital exemption and other exemption pathways in seven European Union countries. Cytotherapy 2020;22(10):592–600.
[2] Goula A, Gkioka V, Michalopoulos E, Katsimpoulas M, Noutsias M, Sarri EF, et al. Advanced therapy medicinal products challenges and perspectives in regenerative medicine. J Clin Med Res 2020;12(12):780–6.
[3] Bergek A, Jacobsson S, Sandén BA. 'Legitimation' and 'development of positive externalities': two key processes in the formation phase of technological innovation systems. Technol Anal Strategic Manag 2008;20(5):575–92.
[4] Fischer PK, Hekkert MP, Hüsing B, Moors E. Individual versus collective strategies in system building - the case of point-of-care diagnostics in Germany. Technol Forecast Soc Change 2022;177:121474.

[5] Lund J., Lausmaa J. A national infrastructure for development, manufacturing and commercialization of advanced therapy medicinal products (ATMP); 2021. Available from: URL: https://atmpsweden.se/wp-content/uploads/2021/04/20210406-ATMPInfrastructure-final.pdf.

[6] Dietrich Eva Susanne Bower David. Prospective measures to combat rising drug prices in Germany; 2022 [cited 2022 Jun 13]. Available from: URL: https://www.pharmexec.com/view/prospective-measures-to-combat-rising-drug-prices-in-germany.

[7] Government Offices of Sweden. Sweden's national life sciences strategy; 2020. Available from: URL: https://www.government.se/4abc0d/contentassets/a8cdfafc39444985973d729ecb95ed63/swedens-national-life-sciences-strategy.pdf.

[8] Granstrand O, Holgersson M. Innovation ecosystems: a conceptual review and a new definition. Technovation 2020;90-91:102098.

[9] Frietsch R, Schmoch U. Transnational patents and international markets. Scientometrics 2010;82(1):185–200.

[10] MSC. Nordic ATMP landscape and implications for the scale of an infrastructure for process development and manufacturing. MSC strategy and communication; March 2021 [cited 2022 Apr 14]. Available from: URL: https://atmpsweden.se/wp-content/uploads/2021/03/Report-infrastructure-RISE_v4.pdf.

[11] Hubert A. ATMPs in Europe: state of play. Alliance for regenerative medicine; 2020. Available from: URL: https://alliancerm.org/wp-content/uploads/2020/02/CBX-Meeting-7-Feb-2020-FINAL.pdf.

[12] Alliance for Regenerative Medicine. Getting ready: recommendations for timely access to advanced therapy medicinal products (ATMPs) in Europe; 2019. Available from: URL: http://alliancerm.org/wp-content/uploads/2019/07/ARM-Market-Access-Report-FINAL.pdf.

[13] Fernandez C. EU regulations are holding back gene and cell therapy clinical trials: labiotech; 2019 [cited 2022 Apr 14]. Available from: URL: https://www.labiotech.eu/trends-news/eu-regulations-cell-gene-therapy-trials/.

[14] Grand View Research. Advanced therapy medicinal products market size, share & trends analysis report by therapy type (CAR-T, Gene, Cell, Stem cell therapy), By Region (North America, Europe, APAC, ROW), And Segment Forecasts, 2021 - 2028; 2021 [cited 2022 Apr 15]. Available from: URL: https://www.grandviewresearch.com/industry-analysis/advanced-therapy-medicinal-products-market#:~:text=The%20global%20ATMPs%20market%20size,USD%209.5%20billion%20in%202021.

[15] RMT Ten Ham, Hoekman J, Hövels AM, Broekmans AW, Leufkens HG, Klungel OH. Challenges in advanced therapy medicinal product development: a survey among companies in Europe. Mol Ther - Methods Clin Dev 2018;(11):121–30.

[16] Synthace. The cell and gene therapy market: why it matters [cited 2022 Jun 13]. Available from: URL: https://www.synthace.com/the-cell-and-gene-therapy-market-why-it-matters/.

[17] GSK. GSK signs strategic agreement to transfer rare disease gene therapy portfolio to orchard therapeutics; 2018 [cited 2022 Jun 13]. Available from: URL: https://www.gsk.com/en-gb/media/press-releases/gsk-signs-strategic-agreement-to-transfer-rare-disease-gene-therapy-portfolio-to-orchard-therapeutics/.

[18] Miglierini Giuliana. The sustainability of the business model for advanced therapies; 2018. Available from: URL: https://www.pharmaworldmagazine.com/the-sustainability-of-the-business-model-for-advanced-therapies/.

[19] Ronco V, Dilecce M, Lanati E, Canonico PL, Jommi C. Price and reimbursement of advanced therapeutic medicinal products in Europe: are assessment and appraisal diverging from expert recommendations? J Pharm Policy and Pract 2021;14(1):30.

[20] Picanco-Castro V, Gonçalves Pereira C, Swiech K, Ribeiro Malmegrim KC, Tadeu Covas D, Silveira Porto G. Emerging CAR T cell therapies: clinical landscape and patent technological routes. Hum Vaccin Immunother 2020;16(6):1424–33.

[21] Abinader LG, Contreras JL. The patentability of genetic therapies: CAR-T and medical treatment exclusions around the world. Am Univ Int Law Rev 2019;(34):707–56.

[22] European Patent Convention, Article 53(c) [cited 2022 Nov 18]. Available from: URL: https://www.epo.org/law-practice/legal-texts/html/epc/2020/e/ar53.html.

[23] Roberts C., Bell R. UK at the forefront of advanced therapies; 2021. Available from: URL: https://www.europeanpharmaceuticalreview.com/article/161176/uk-at-the-forefront-of-advanced-therapies/.

[24] Slocum Rubin. Understanding radical technology innovation and its application to CO2 capture R&D: interim report, volume one—literature review. Carnegie Institute of Technology; 2008.

[25] Wilson A, Cockroft A. Regulatory considerations for decentralized manufacture of ATMPs. Cell Gene Therapy Insights 2019;5(10):1213–24.

[26] Maschan M, Caimi PF, Reese-Koc J, Sanchez GP, Sharma AA, Molostova O, et al. Multiple site place-of-care manufactured anti-CD19 CAR-T cells induce high remission rates in B-cell malignancy patients. Nat Commun 2021;12(1):7200.

[27] Dropulic Boro O.R. Decentralized CAR-T manufacturing reduces costs & complexity, expands access; 2022 [cited 2022 Dec 6]. Available from: URL: https://www.cellandgene.com/doc/decentralized-car-t-manufacturing-reduces-costs-complexity-expands-access-0001.

[28] Geethakumari PR, Ramasamy DP, Dholaria B, Berdeja J, Kansagra A. Balancing quality, cost, and access during delivery of newer cellular and immunotherapy treatments. Curr Hematol Malig Rep 2021;16(4):345–56.

[29] Versorgung mit CAR-T-Zellen in Deutschland [cited 2022 Nov 18]. Available from: URL: https://www.dgho.de/aktuelles/presse/pressemeldungen/versorgung-mit-car-t-zellen-in-deutschland.

[30] Vucinic V, Quaiser A, Lückemeier P, Fricke S, Platzbecker U, Koehl U. Production and application of CAR T cells: current and future role of Europe. Front Med (Lausanne) 2021;8:713401.

[31] Harrison RP, Rafiq QA, Medcalf N. Automating decentralized manufacturing of cell & gene therapy products. Cell Gene Therapy Insights 2016;2(4):489–97.

[32] Raper V. Decentralized manufacturing of advanced therapies; 2022 [cited 2022 Jun 13]. Available from: URL: https://www.genengnews.com/topics/bioprocessing/decentralized-manufacturing-of-advanced-therapies/.

[33] The European Parliament and the Council of the European Union.; 2001.

[34] The European Parliament and the Council of the European Union; 2007.

[35] Juan M, Delgado J, Calvo G, Trias E, Urbano-Ispizua A. Is hospital exemption an alternative or a bridge to European medicines agency for developing academic chimeric antigen receptor T-Cell in Europe? Our experience with ARI-0001. Hum Gene Ther 2021;32(19–20):1004–7.

[36] Rosenbusch N, Brinckmann J, Müller V. Does acquiring venture capital pay off for the funded firms? A meta-analysis on the relationship between venture capital investment and funded firm financial performance. J Bus Venturing 2013;28(3):335–53.

[37] ATMP Sweden. Payment models for ATMPs - what happens?; 2018. Available from: URL: https://atmpsweden.se/events/betalningsmodeller-for-atmp-vad-hander/.

[38] Pizevska M, Kaeda J, Fritsche E, Elazaly H, Reinke P, Amini L. Advanced therapy medicinal products' translation in Europe: a developers' perspective. Front Med (Lausanne) 2022;9:757647.

[39] Deutscher Budestag, editor. Finanz-reform der gesetzlichen Krankenversicherung beschlossen [cited 2022 Dec 6]. Available from: URL: https://www.bundestag.de/dokumente/textarchiv/2022/kw42-de-gkv-finanzierungsstabilisierungsgesetz-916742.

[40] Schurz Stephan, Lieverscheidt Lisa. ATMPs – prepare for successful access in a changing environment: Simon Kucher & partners. Available from: URL: https://www.simon-kucher.com/en/blog/atmps-prepare-successful-access-changing-environment.

[41] Clinical Studies Sweden. Applying for an ethical review [cited 2022 Nov 21]. Available from: URL: https://kliniskastudier.se/english/research-process/application.

[42] Clinical trials - Regulation EU No 536/2014 [cited 2022 Nov 21]. Available from: URL: https://health.ec.europa.eu/medicinal-products/clinical-trials/clinical-trials-regulation-eu-no-5362014_en.

[43] Tajima G, Huh S, Schmidt NA, Macdonald JC, Fleischmann T, Wonnacott KM. Impact of genetically modified organism requirements on gene therapy development in the EU, Japan, and the US. Mol Ther Methods Clin Dev 2022;26:74–83.

[44] Lambot N, Awigena-Cook J, Reimer T, Persson A, Romanetto J, Friedeberg B, et al. Clinical trials with investigational medicinal products consisting of or containing genetically modified organisms: implementation of Clinical Trials Regulation EU 536/2014. Cell Gene Therapy Insights 2021;7(9):1093–106.

[45] Whomsley R, Palmi Reig V, Hidalgo-Simon A. Environmental risk assessment of advanced therapies containing genetically modified organisms in the EU. Br J Clin Pharmacol 2021;87(6):2450–8.

[46] BVL. Homepage [cited 2022 Apr 14]. Available from: URL: https://www.bvl.bund.de/EN/Home/home_node.html;jsessionid=BCA27EF4EB711A8781C385B4A7F0430C.2_cid351.

[47] Gorman A. Environmental risk assessments: EU clinical trials with GMO-based ATMPs.; 2016 [cited 2022 Nov 21]. Available from: URL: https://www.ema.europa.eu/en/documents/presentation/presentation-environmental-risk-assessments-eu-clinical-trials-gmo-based-atmps-ann-gorman_en.pdf.

[48] Salazar-Fontana LI. A regulatory risk-based approach to ATMP/CGT development: integrating scientific challenges with current regulatory expectations. Front Med (Lausanne) 2022;9:855100.

[49] Globe Newswire. Flerie invest AB leads $52 m acquisition of Swedish biopharma facility from Charles River [cited 2022 Apr 16]. Available from: URL: https://www.globenewswire.com/news-release/2021/10/15/2314743/0/en/Flerie-Invest-AB-leads-52m-acquisition-of-Swedish-Biopharma-Facility-from-Charles-River.html.

[50] Geißler J, Isham E, Hickey G, Ballard C, Corbett A, Lubbert C. Patient involvement in clinical trials. Commun Med (Lond) 2022;2:94.

[51] BMBF. National Decade Against Cancer [cited 2022 Apr 19]. Available from: URL: https://www.dekade-gegen-krebs.de/en/home/home_node.html.

[52] European Parliament; 2021. Available from: URL: https://eur-lex.europa.eu/legal-content/EN/ALL/?uri=CELEX%3A02001L0020-20090807.

[53] Newbould C. Annex 21: importation of medicinal products. EJPPS 2020.

[54] Persson Ulf NJ. Opportunities and challenges of an innovative payment model for advanced therapy medicinal products in Sweden. The Swedish Institute for Health Economics; 2020 IHE Report 2020:3. [cited 2022 Apr 20]. Literature Cited.