2025

EUCOPE White Paper on ATMP Manufacturing

A White Paper prepared by EUCOPE's Cell & Gene Therapy Working Group

EUCOPE
European Confederation of Pharmaceutical Entrepreneurs AISBL

White Paper on ATMP Manufacturing

Recommendations

To promote and facilitate ATMP manufacturing in the EU, a number of challenges must be addressed. Various opportunities exist, which can be addressed by both legislative and non-legislative solutions. Many solutions can address more than one barrier to ATMP manufacturing – thereby being mutually reinforcing. Therefore, EUCOPE puts forward a number of solutions that will address the 5 key areas where policy action is needed:

The 23 recommendations outlined in this paper can be captured in 5 buckets of action. Additional details can be found in the respective sections. The key issues are:

1. Access to Raw Materials;
2. Limited manufacturing and testing capacity and lack of an appropriate framework for a global manufacturing network;
3. Lack of or inappropriate regulatory standards for centralised and decentralised ATMP manufacturing, including the Point of Care framework;
4. Inconsistent implementation and limitations imposed by the GMO legislation;
5. Lack of sufficient manufacturing expertise and knowledge; immaturity of systems and equipment development to support ATMP manufacturing.

EUCOPE puts forward the below recommendations:

1. **Update regulatory and manufacturing guidelines** to ensure they are designed to reflect the technical and scientific needs of ATMPs. ATMPs should not be treated as 'just' another biologic;
2. Review the **EU GMO framework** to provide further, or even complete, derogations for therapeutic ATMPs based on a risk-benefit assessment;
3. Provide necessary financial and administrative **support** in the **training, educating, and upscaling of knowledge on ATMPs** and their manufacturing. The Union requires expertise across the value chain from development to regulatory, which includes manufacturing processes.
4. Support the **digitalization of the ATMP manufacturing and monitoring system** by promoting the use of electronic batch records and other digital and automation systems by developing harmonized and standardized guidelines.
5. **Facilitate cross-country manufacturing** of ATMPs **by removing legislative and administrative barriers** which are duplicative, inappropriate, or overly burdensome.
6. Strengthen the EU as a region for scientific and ATMP excellence by **facilitating the movement of experts and attracting global experts** by reviewing and **updating visa-schemes**.

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Introduction

In 2007, the European Union (EU) adopted a Regulatory framework to govern the authorisation of Advanced Therapy Medicinal Products (ATMPs)[1], a new class of therapies that are often seen as the next generation of medicine, bringing with them the promise of transformative approaches to treatment. Since the adoption of the ATMP Regulation (Regulation EC 1394/2007), 27 ATMPs have received a positive opinion from the CHMP[2]. This represents just the first 'wave' of ATMPs as developers continue to invest in the technology. Various predictions and horizon scanning initiatives are expecting the number of ATMPs heading for marketing authorisation to increase from current levels[3].

The EU's ATMP manufacturing footprint receives less attention in current debate, which instead focuses on other important discussions including the access and clinical trial context. However, the manufacturing landscape should not be ignored, as our ability to manufacture ATMPs will have a significant impact on the EU's competitiveness landscape, informing future access and security of supply discussions. The 2024 – 2029 European Commission mandate is the opportune moment to kick-off the discussions, and to implement needed changes. To date, most ATMP manufacturing still takes place in the US[4], and the EU has been lagging in terms of the number of clinical trials taking place, with the vast majority in the US and Asia Pacific[5].

The renewed focus on the EU's global competitiveness and the development of an EU Biotech Act and Life Sciences Strategy are unique opportunities to lay the foundation for a strong ATMP manufacturing sector to ensure that the EU remains a relevant and competitive world region. The 2024 Draghi report highlighted the importance of ATMPs, calling for dedicated EU policy to increase the block's competitiveness[6]. The need for the EU to cement itself and draw in ATMP manufacturing is also more relevant as the geopolitical environment becomes increasingly more complex and trade conflicts escalate. The potential Biotech Act and overarching Life Sciences Strategy can play an important role in shaping an environment that supports industry in successfully navigating the changes needed to facilitate the expansion of the ATMP industry. Ensuring a robust environment for ATMP manufacturing in the EU is also important as it will maintain existing research expertise and avoid further brain drain and transfer of expertise. The EU continues to have strong early stage research[7] and we must avoid losing this. Promoting a virtuous and mutually reinforcing cycle can play a role in that context. The importance of a robust ATMP research, development and manufacturing landscape is further underscored as we have witnessed a small downturn in the investment in ATMPs more generally and a number of failures in clinical trial programmes and failed commercialisations. While the potential of

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[1] ATMPs encompass a large range of different therapies that fall in the broad buckets of gene therapies, cell therapies, and tissue engineering. For the purpose of this paper, ATMPs will refer exclusively to cell and gene therapies.

[2] **European Medicines Agency (EMA), Committee for Advanced Therapies (CAT)**, "*CAT Quarterly Highlights and Approved ATMPs – November 2024*," EMA/CAT/511673. https://www.ema.europa.eu/en/committees/committee-advanced-therapies-cat.

[3] **Pharmaceutical Technology**, "*AIFA Horizon Scanning 2024: Influx of ATMPs*," analyst comment. https://www.pharmaceutical-technology.com/analyst-comment/aifa-horizon-scanning-2024-influx-atmps/.

[4] **Charles River Associates (for EFPIA)**, *Investment Location – Final Report* (2024). https://www.efpia.eu/media/676753/cra-efpia-investment-location-final-report.pdf.

[5] **Alliance for Regenerative Medicine (ARM)**, "*Sector Snapshot: December 2023.*" https://alliancerm.org/sector-snapshot-december-2023/.

[6] **European Commission**, "*The Future of European Competitiveness* (Draghi Report), overview page." https://commission.europa.eu/topics/eu-competitiveness/draghi-report_en#paragraph_47059.

[7] **EUCOPE**, *The Economic Lens: Investor Insights on European Life Sciences and the EU Pharma Package* (November 2024). https://www.eucope.org/wp-content/uploads/2024/11/the-economic-lens-investor-insights-into-the-pharma-package-nov2024-final-1.pdf.

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the therapies remains high, so does the failure rate, stressing the need for a policy environment that ensures developers remain committed to the technology.

In this paper, EUCOPE identifies five ATMP manufacturing challenges, and share what we believe is needed to ensure that the manufacturing and delivery systems are prepared to make the promise of ATMPs a reality. We explore the changes and investments developers must make in order to deliver on the promise of this technology and to increase our manufacturing and delivery capacity. Many of these actions cannot be undertaken alone and require an appropriate industrial policy.

Five overarching challenges that serve as barriers to facilitating ATMP manufacturing in the EU include:

1. Access to Raw Materials
2. Limited manufacturing and testing capacity and lack of an appropriate framework for a global manufacturing network
3. Lack of or inappropriate regulatory standards for centralised and decentralised ATMP manufacturing, including the Point of Care framework
4. Inconsistent implementation and limitations imposed by the GMO legislation
5. Lack of sufficient manufacturing expertise and knowledge; immaturity of systems and equipment development to support ATMP manufacturing

Pricing & reimbursement (P&R) models and Health Technology Assessment (HTA) systems need to be updated, healthcare professionals need to be upskilled to identify good candidates for therapies and deliver the treatments, and hospital infrastructure needs to be made fit for purpose. Although these themes will not be addressed in this paper, they are also important in ensuring that the healthcare system absorbs ATMPs and is well prepared. Failing this, it will reduce the interest in investing in ATMP development and by extension, in manufacturing as well. For example, without deep expertise in optimal patient cell collections, manufacturing outcomes will always be compromised, leading to higher manufacturing costs and a longer patient journey. ATMP manufacturing is full of risk, including patient variability, risks associated with manufacturing outcomes, and questions regarding moving from early access programmes to full reimbursement.

Rather than waiting for the number of available ATMPs to increase, and trying to adapt systems after the therapies have been developed, potentially resulting in access bottlenecks, **developers and healthcare systems should already be preparing**. Several developers are already investing in the establishment of manufacturing facilities in the EU. However, both greenfield and brownfield investments will take years to be up and running. The investment case for these expenditures becomes increasingly difficult if there is no appropriate value proposition or viable return on investment. Inconsistency and unpredictability in the policy landscape will also impact investment decisions. To ensure that an appropriate ecosystem is promoted, both EU and national policy is needed.

In the EU, ATMPs rely on two complementary, yet distinct, manufacturing models: the centralised model and the decentralised or Point of Care models. Centralised biomanufacturing, conducted in specialised facilities operating under harmonised EU regulatory frameworks, provides the scale, quality assurance, and cross-border consistency needed to safeguard patient safety and to secure Europe’s competitiveness in the global ATMP landscape. By concentrating expertise and infrastructure in dedicated biomanufacturing facilities, centralised sites enable efficient use of resources, facilitate regulatory oversight, and support the scaling-up on an industrial scale of innovative therapies. In parallel, decentralised manufacturing at the point of care can allow rapid treatment of patients and can improve access for therapies requiring immediate or highly individualised preparation. Both approaches are therefore important within the EU biomanufacturing ecosystem: decentralised models can enhance local responsiveness and access, particularly where there are specific unmet needs and hospital capabilities to address these, as well as scale through scale-out, while centralised facilities play a key role towards Europe’s capacity to ensure quality, scalability, and regulatory alignment across Member States.

A discussion on ATMP development and manufacturing is further complicated as the term "ATMP" covers a range of different technologies and manufacturing practices. The different technologies, be they gene therapies or cell therapies, allogeneic or autologous, have distinct differences. While an underlying basis must be established that covers all technologies, at times different technologies may benefit from more bespoke solutions. In this context, EUCOPE aims to present some of the topline and cross-modality themes. A fundamental theme that must guide policy development is that the EU should not create a multi-tiered regulatory framework leading to different standards. Regulatory standards should account, where possible, for differences between technologies and remove unnecessary barriers, but not compromise the quality, safety, or efficacy of the therapies being developed.

The EU must set itself up for success, expand its manufacturing and testing capability and capacity, and ensure it establishes itself as a leader, not a follower, in this space. In 2002, the Commission's biotechnology strategy summarised that, "Europe is currently at a crossroads: we need to actively develop responsible policies in a forward-looking and global perspective, or we will be confronted by policies shaped by others, in Europe and globally"[8]. Europe is once again at a similar inflection point.

Why establishing a robust manufacturing ecosystem matters

1. **Establishing a critical mass of expertise and promoting further innovation**

Scaling-up or scaling-out ATMP manufacturing is notoriously challenging[9], partly due to the individual nature of the therapies and inconsistencies between manufacturing lines, which do not necessarily benefit from the same economies of scale as conventional therapies. Additionally, various developers are looking at decentralised manufacturing models where the therapies are manufactured closer to patients. However, by expanding the EU's ATMP manufacturing, the EU can amass a pool of technical expertise that is lacking and serve to create more employment opportunities.

1.1 Multiplying ATMP manufacturing expertise and promoting innovation

Many ATMP developers face a shortage of experts, including bioengineers and analytical scientists. By increasing the number of biomanufacturing employment opportunities, the EU can build more home-grown expertise while also attracting established global experts. Evidence has shown that establishing robust Research and Development and manufacturing facilities can help promote further innovation and spin-offs. Developing key biotech hubs in areas close to universities enables developers and manufacturers to influence curricula and obtain high-calibre entry-level employees. Some examples include:

- Experience from Denmark has shown research and small companies growing around Novo Nordisk.
- In Germany, researchers and smaller initiatives have grown out of Miltenyi Biotec or benefited from their expertise.
- A host of small biotechs are clustered around KU Leuven in Belgium.

Thus, by establishing an environment that attracts and fosters the development of ATMP manufacturers, the EU can spur further innovation and ensure continued manufacturing of ATMPs within the region. This will enable the development of ATMPs in the EU, facilitating timely patient access without the

[8] **European Commission**, *Life Sciences and Biotechnology—A Strategy for Europe*, COM(2002) 27 final (23 January 2002). https://eur-lex.europa.eu/legal-content/EN/TXT/?uri=CELEX:52002DC0027.

[9] **BioSpace**, "*Advanced Therapy Medicinal Products CDMO Industry Is Rising Rapidly*" (2024). https://www.biospace.com/advanced-therapy-medicinal-products-cdmo-industry-is-rising-rapidly.

logistics complications of export/import to an ex-EU manufacturer. Such expertise is especially important for therapies that must be delivered to patients within a short timeframe or where speed is of critical importance, particularly those ATMP manufactured with 'fresh' cells and no freezing during the manufacturing process that would enable global logistics/transport. Fundamentally, ATMP manufacturing is an excellence itself and very innovative manufacturing techniques and skills are needed.

1.2 Increasing EU's capacity for ATMP clinical trials

Increased clinical trial capacity can also spur innovation and investment in other parts of the ATMP supply chain and development process. With a robust manufacturing base, it becomes easier to conduct novel research, develop new treatments and also conduct clinical trials as the expertise and knowledge does not need to travel as far. Especially at a time where the EU is falling behind in the number of clinical trials being conducted, it is essential to ensure that multiple different levers are pulled to address this challenge. The experience of the United Kingdom's support for ATMP development, through initiatives such as Cell and Gene Therapy (CGT) Catapult, shows the importance of integrating the full ATMP ecosystem into the healthcare system from the start, as well as the importance of fostering strong connections across various components of the ecosystem to drive success[10].

1.3 Promoting economic growth

Beyond the important access discussions, ensuring that the EU remains a competitive ATMP manufacturing region can serve as an engine for economic growth for the EU and the Member States that host manufacturing sites, universities and research centres[11].

2. Political signal

The Draghi report explicitly refers to ATMPs as an essential area for investment which would improve the EU's global competitiveness. The report lamented the fact that few novel OMPs come from EU-based companies; investing in a robust ATMP environment could play a role in reversing this trend[12].

Developers and investors respond to the intentions and signals sent by policy-makers, especially when legislation is either lacking or still under development. Genuine EU intent to become more globally competitive in biopharmaceuticals requires fostering a robust policy ecosystem for ATMP manufacturing. This will send a clear political signal that the region is a serious player in the ATMP space. This can in turn spur increased investment in both manufacturing and research. Manufacturers also need to have a clear pathway to reimbursement for their ATMPs – recent examples of approved ATMP therapies that failed in EU commercially owing to a variety of factors, including market access challenges and barriers to value recognition[13], weigh on manufacturers when considering investments.

3. Coordinate Member State initiatives

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[10] Rehma **Chandaria**, Philippa Rice, Daniel Baston, Finn Willingham, and Jacqueline Barry, "*ATMP Clinical Trials in the UK*," *Regenerative Medicine* (2024), https://doi.org/10.1080/17460751.2024.2427505.

[11] **OECD**, *New Health Technologies: Managing Access, Value and Sustainability* (Paris: OECD Publishing, 2017). https://www.oecd.org/content/dam/oecd/en/publications/reports/2017/01/new-health-technologies_g1g72f2b/9789264266438-en.pdf.

[12] **European Commission**, *The Future of European Competitiveness: In-DepthAnalysis and Recommendations (2024)* https://commission.europa.eu/document/download/ec1409c1-d4b4-4882-8bdd-3519f86bbb92_en?filename=The%20future%20of%20European%20competitiveness_%20In-depth%20analysis%20and%20recommendations_0.pdf.

[13] Kevin Dunleavy, "*With the Pricing Situation 'Untenable' in Europe, bluebird Will Wind Down Its Operations in the 'Broken' Market*," *FiercePharma*, August 9, 2021. https://www.fiercepharma.com/pharma/situation-untenable-bluebird-will-wind-down-its-operations-broken-europe.

Some Member States have begun taking action on an individual basis in order to attract investment and boost innovation. Several Member States, including Italy[14], Germany[15], and France have either adopted or historically implemented ATMP action plans. In the case of Italy, it adopted a national plan (Piano nazionale malattie rare 2023-2026) that includes a comprehensive framework to enhance innovation and the development of ATMPs, especially within the rare diseases domain. It focuses on infrastructure, data systems, early trials, strategic funding, and international cooperation to ensure that advanced therapies become more accessible and effectively developed within the country. The German cell and gene therapy strategy adopted a mutually reinforcing approach consisting of 8 pillars across the development lifecycle. The new government is committed in the coalition agreement to address the problems mentioned in the strategy. Additionally, Belgium has recently announced its ATMP spearhead initiative that aims to strengthen its ATMP ecosystem across multiple verticals, including regulatory knowledge and improve the attractiveness for investment.

A coordinated horizontal approach is needed across the EU due to the interconnected nature and complexity of ATMP manufacturing. For a number of these Member State initiatives to be truly effective, they must be complemented by EU level action in order to ensure efficiencies in resource sharing, whether these are manufacturing, testing, equipment, digital or knowledge-based resources necessary to further ATMP development.

ATMP Manufacturing Challenges

Manufacturing ATMPs is fundamentally complex and challenging. In addition to being biopharmaceuticals, ATMPs are often individualised therapies (there is a growing body of research investigating allogeneic gene therapies which would allow donor cells to be used for multiple patients). Due to their nature, the manufacturing process of ATMPs cannot not always be fully automated and requires the involvement of specialized knowledge and expertise. It is important to acknowledge that increasing manufacturing and scaling up/out capacity is not the same as for small molecules and biologics, where developers can ‘simply’ increase the number of bio- or chemical reactors. Unlike traditional biologics, ATMPs scale cannot be achieved only by scaling up volumes in a fermenter or bioreactor and requires further specialised knowledge. This in part stems from the fact that genetic tools and manufacturing sequences involved in the manufacturing process.

The discussion is further complicated by the fact that, although often clustered together, cell and gene therapies have distinct differences that impact their manufacturing processes, even within their respective categories.

EUCOPE and its members have identified five overarching themes that serve as barriers to facilitating ATMP manufacturing in the EU;

1. Access to Raw Materials
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4. Inconsistent implementation and limitations imposed by the GMO legislation
5. Lack of sufficient manufacturing expertise and knowledge; immaturity of systems and equipment development to support ATMP manufacturing

[14] **Ministero della Salute (Italy)**, *Piano Nazionale Malattie Rare 2023–2026* (official plan PDF). https://www.malattierare.gov.it/normativa/download/792/PIANONAZIONALEMALATTIERARE2023%281%29.pdf.

[15] **Bundesministerium für Bildung und Forschung (BMBF)**, (policy page, Germany). https://www.bmbf.de/DE/Forschung/Zukunftstechnologien/Biotechnologie/GenUndZelltherapien/genundzelltherapien_node.html

1. Access to raw materials

Access to raw materials and validation of analytical methods and processes for starting materials such as viral vectors, plasmids and gene editing tools used in the production of ATMPs is a major challenge to manufacturing. In addition, the fact that ATMPs are still a relatively 'new' therapy class when compared to other technologies means that some raw materials have not yet been truly commercialized;. Often, these products are also single use or maybe need to be manufactured in a bespoke manner due to both the sensitivity of the process and relatively small scale.

Currently, the EU lacks standards and guidelines for comparing similar raw and starting materials (e.g. cell media, cytokines, growth factors, gene-editing components, reagents, plasmids, viral vectors etc.) used in the manufacturing of ATMPs. Beyond the existing guidelines that address the quality, clinical, and non-clinical requirements for ATMP clinical trials[16], a careful review is needed of the standards for raw and starting materials before they fall under the scope of the ATMP GMP framework. The complexity associated with the existing framework and evolving manufacturing requirements can introduce, additional regulatory complexity, costs, and time for developers when they are manufacturing, testing, and ultimately releasing a product.

The EU is exploring one solution, namely the Additional Quality Master File (AQMF), as presented in the European Commission's proposal in the General Pharmaceutical Legislation (GPL) (Directive Art. 26). An AQMF system would allow for raw material manufacturers to protect confidential and detailed information while substantially reducing the administrative burden currently required for each individual application. When a developer or hospital uses raw materials either for a clinical trial or a marketing authorisation, the manufactures of these materials must submit full documentation related to their quality and efficacy to each national competent authority in the EU and respond to their questions individually. Many of these questions are often similar, resulting in redundant administrative work, thus an AQMF would help expedite the process. Since communication and legal relationships exist between the sponsor and the authority in these constellations, there is an additional risk of disclosure of commercially confidential information belonging to the manufacturer of the starting material. Any AQMF mechanism must also account for a sponsor's and marketing authorization holder (MAH)'s accountability for all process inputs as well as ICH M4Q updates which will allow a cloud based approach to leverage platform and established conditions across products and programs. Mechanisms which enable both adequate demonstration of oversight and leveraging of data for sponsors and MAH need to build into any AQMF mechanism as well. A model for an AQMF already exists with the EU's and US master file system.

Lack of consistency and variations in requirements between Member States is a major challenge for developers[17]. Additionally, when updates are needed in the manufacturing process, the hurdles for proof of comparability cause additional delays. As a result, developers can face complex testing requirements for assays, which are procedures used to assess the efficacy of the therapy on its intended target. In many cases, the manufacturers need to develop their own bespoke, cell-based assays and complex data-processing systems to meet these requirements. A harmonised system would substantially streamline the work of national agencies, and avoid duplication of assessments between authorities. It would also facilitate faster and more efficient manufacturing and testing procedures, reducing some of the associated manufacturing costs. In order to respond to these challenges, and prepare the EU

[16] **EMA**, *Guideline on Quality, Non-Clinical and Clinical Requirements for Investigational Advanced Therapy Medicinal Products in Clinical Trials* (latest PDF). https://www.ema.europa.eu/en/documents/scientific-guideline/guideline-quality-non-clinical-clinical-requirements-investigational-advanced-therapy-medicinal-products-clinical-trials_en.pdf.

[17] Renske M. T. ten Ham, Jarno Hoekman, Anke M. Hövels, Andre W. Broekmans, Hubert G. M. Leufkens, and Olaf H. Klungel, "*Challenges in Advanced Therapy Medicinal Product Development: A Survey among Companies in Europe*," (2018): 121–130. Challenges in Advanced Therapy Medicinal Product Development: A Survey among Companies in Europe

landscape as the ATMP environment evolves, it will be important to allow for more rapid and regular communication between developers and regulators. Systems such as PRIME and early scientific advice are especially important to developers of novel therapies that do not fit in standard models, such as ATMPs. Similarly, the use of the regulatory sandboxes as outlined in the General Pharmaceutical Legislation could have a significant positive impact.

One final overarching challenge is the limited capacity for manufacturing of critical input materials for gene-editing (e.g. media, growth factors, cytokines, vectors, mRNA, enzymes, sgRNAs) at both EU and global level. While this issue cannot be easily overcome in the short term, addressing the various challenges illustrated in this section and throughout the paper could naturally lead to increased manufacturing, thereby boosting production of these starting materials as demand grows. Manufacturing costs, which can be prohibitive with ATMPs, would decrease with increased throughput to match increased demand.

Recommendations

- The EU should introduce **additional guidelines and standards** pertaining to the **use and comparability of critical raw and staring materials** to reduce variations between Members States and the need for complex testing requirements for assays. This can be achieved through the **introduction of the Additional Quality Master File (AQMF)** proposed in the GPL.
- Increase engagement and interaction between regulators and developers of ATMPs in order to allow for early guidance on both clinical development and manufacturing processes. This should exist in tandem to frameworks such as PRIME and accelerated assessments, ensuring that there was a dedicated ATMP contact point that would accompany the development process.
- Ensure that the EMA is sufficiently resourced to **allow for the regulatory network to be upskilled in the assessment and understanding of ATMPs**, ensuring that a baseline understanding of the technology exists throughout the network.

2. Limited manufacturing capacity and lack of an appropriate framework for global manufacturing network

Traditional production processes are not applicable to ATMPs which are often uniquely produced for an individual patient or in small batches. Due to the complexity of manufacturing ATMPs, manufacturing facilities cannot simply be repurposed or reassigned to manufacture a new product[18]. The majority of ATMPs are manufactured by smaller developers[19]. While some large pharmaceutical companies may have their own manufacturing capacity, smaller developers typically rely on Contract Manufacturing Organisations (CMOs). This presents the first barrier in terms of scaling up and ensuring capacity.

A linked challenge relates to the fact that developers must reserve capacity at a CMO. However, due to the nature of autologous ATMPs and the need for these products to be manufactured when a need arises, autologous ATMPs cannot be stockpiled or produced in advance. Thus, developers must anticipate their needs and reserve capacity at a CMO, which may result in financial loss if the reserved capacity is not needed. This stems from the challenge mentioned above that a manufacturing line cannot simply be 'switched' to a new product, which means that the capacity is idle. Moreover, depending on the technology, when manufacturing lines are 'reactivated' or repurposed, it may require operators to be retrained, further introducing delays, costs, and administrative procedures. Other conventional supply planning practices, such as establishing redundant capacity, is also prohibitively

[18] Point of Care manufacturing and other technologies could be exceptions to this challenges, however they are not a replacement or alternative for all ATMP manufacturing and address a specific niche
[19] (Renske M. T. ten Ham, Jarno Hoekman, Anke M. Hövels, Andre W. Broekmans, Hubert G. M. Leufkens, and Olaf H. Klungel, "*Challenges in Advanced Therapy Medicinal Product Development: A Survey among Companies in Europe*," (2018): 121–130. Challenges in Advanced Therapy Medicinal Product Development: A Survey among Companies in Europe

expensive or simply impossible when developing personalised therapies. Fundamentally, these challenges relate to the lack of capacity overall and no quick fixes exist.

For those developers that do establish their own manufacturing capacity, due to the limited volume of ATMPs that are manufactured, it is not realistic to establish manufacturing sites in all regions, let alone in all Member States. Many developers work on the basis of Global Manufacturing Networks. This allows for demand levelling across a wider region, be that an entire geographic region, or globally. As a result, manufacturing often takes place outside of the EU, requiring these products to comply with EU guidelines for the physical sites of importation. ATMPs which are intended for use within the Union but manufactured outside of the EU are subject to analytical release testing both at point of development and after importation. While in some cases Memorandums of Understanding have been signed between countries, these remain rare for ATMPs. These duplicative tests represent additional burdens on both developers and assessors. These discussions are further complicated when discussing the raw and starting materials where different frameworks may apply, be they SoHO materials or ATMP GMP rules.

Recommendations

- Approved ATMPs manufactured in pre-approved facilities should be exempt from the physical site of importation guidelines (Annex 21 of the EU's GMP Guide) to avoid a duplication of inspections and cause delays in product release.
- ATMPs which are manufactured outside of the EU and have been subject to CMC and analytical testing in approved facilities or countries with which the EU has equivalent standards, should be exempt from re-testing when being imported. Often, ATMPs are excluded from mutual recognition agreements which leads to the need for additional inspections before issuing import licenses.

3. Lack of regulatory standards for centralised and decentralised ATMP manufacturing, including the Point of Care framework

In addition to the above recommendations, if the EU wants to meet its biomanufacturing capacity needs, it needs to not only upscale central manufacturing but also facilitate the deployment of Decentralised- and Point of Care-manufacturing as a complementary solution. Indeed, increased investment and expansion of ATMP manufacturing in the EU is impacted by a lack of suitable regulatory standards and harmonisation. Through the revision of the GPL and the proposals in the Life Sciences Strategy, the EU has indicated a number of improvements which could move the EU in a positive direction – it is crucial that these changes deliver the needed reforms. Building on the proposed reforms and looking more broadly at what reforms are needed, EUCOPE sees three specific areas that merit attention, some of which can be addressed in the context of the Biotech Act. Addressing these barriers would send an important political signal to developers and investors when they are considering if and where to establish a manufacturing presence.

Lack of appropriate guidelines for Decentralised- and Point of Care-manufacturing

A technology approach that has been under development over the past decade which allows manufacturing close to the patient is Point of Care (PoC) manufacturing (PoCM). Captured under the broader heading of decentralised manufacturing (DM), PoCM refers to the manufacturing of the therapy as close as possible to the patient, often within the hospital where the patient is treated[20]. PoCM and decentralised manufacturing, in general, should be seen as complementary to existing manufacturing models; for instance where reducing vein-to-vein times is essential or where the use of frozen cells as

[20] Eduardo Bicudo and Irina Brass, "*Institutional and Infrastructure Challenges for Hospitals Producing Advanced Therapies in the UK: The Concept of 'Point-of-Care Manufacturing Readiness'*," *Regenerative Medicine* 17 (2022): 719–737. https://doi.org/10.2217/rme-2022-0064.

part of the manufacturing process is not possible (it is important to note that many centralised manufacturing processes also work on the basis of fresh cells). PoCM and DM could address some of the challenges associated with the complex logistic processes. In this context, it is also important to note that PoCM and DM are not synonymous with Hospital Exemption. PoCM and DM represent a manufacturing technology which relies on a manufacturing authorisation and entails specific regulatory criteria, Hospital Exemption on the other hand is an exemption to the standard marketing authorisation processes whereby an ATMP can be approved for use in a specific Member State on a non-routine basis, to comply with an individual prescription for an individual patient (article 3.7 Directive 2001/83/EC). The exact definition of a Hospital Exempt ATMP is under review as part of the GPL.

The revision of the GPL is unlocking a crucial barrier to these manufacturing models by allowing for a regulatory pathway for decentralised manufacturing. This includes capturing them in the context of the legislation and introducing frameworks to allow for assessment of decentralised sites and the necessary Quality Manufacturing and Compliance (QMC) approvals.

However, the GPL is not expected to go into effect until the late 2020s, and new guidelines and standards will be needed to ensure that they can be rolled out.

For DM, the GPL provides some provisions. In the case of PoCM, which could allow for substantially more flexibility and where potentially the entire product could be manufactured off-site, crucial questions remain. In particular, PoC manufacturing will require updates to and a rethink of GxP (Good Practice (ie GMP, GLP, GDP)), accreditation/inspection and pharmacovigilance frameworks and responsibilities, including how to allow for batch release and accountability for undertaking a host of different quality checks for the final product. These changes should not lead to a lowering of standards or creation of a two-tiered regulatory system. Proposed changes to the GxP should ensure that the regulatory system reflects the realities and differences of PoC while upholding high quality, efficacy, and safety standards.

Regardless of the manufacturing model, PoCM, DM and centrally manufactured ATMPs , technological advancements are enabling increasingly automated and closed systems. This transition offers numerous benefits, most notably:

- Reducing the number of specialised technicians required for ATMP manufacturing, which is currently a bottleneck (challenge 5);
- Reducing the cost of manufacturing, with closed systems needing a lower-grade cleanroom environment
- Reducing the risk of human error, which often leads to tissue collection and manufacturing failures, requiring additional Quality Management System workload, pharmacovigilance measures and repeat collection/manufacturing cycles;

Unlike other therapies, the full automation of all kinds of ATMP manufacturing processes cannot always be achieved due to the complexity of the manufacturing steps. Despite this, various developers are making use of increasingly more automated manufacturing processes, complemented by the involvement of highly-trained technicians. A related element is integrated digitization of systems, enabling near real-time data gathering for advanced manufacturing analytics and enabling rapid disposition. As an evolving field, various experiences exist regarding automation of ATMP manufacturing. Some developers are establishing closed manufacturing systems resulting in potential reductions in the manufacturing costs of each individual product lot, although the high upfront development costs would remain. The automation could result in lower labour costs, fewer handling and intermediate steps, and consistency in manufacturing. While the experience is not universal, efforts should also be made to facilitate and spur increased automation where appropriate, guidelines and regulatory provisions must be updated or adaptable to account for innovative and automated manufacturing processes. For instance, by enabling automation, ATMPs could be manufactured in closed systems, thereby reducing the risk of contamination. To ensure appropriate standards are upheld, automated closed lines should continue to be subject to inspections, however, existing automation guidelines should be further updated and nuanced to account for this reduced risk. Ensuring that guidelines account for this, by clarifying aseptic handling and clean room requirements, would facilitate their roll-out and provide a clear framework for compliance. Greater harmonisation between Member States would also be essential to ensure the uniform rollout of the new technologies and avoid a fragmented regulatory landscape as seen in other areas of ATMP policy, including GMO legislation.

Recommendations

- Audit and harmonise GMP and GPL standards as they pertain to Point of Care ATMP manufacturing and develop, where appropriate, regulatory and technical guidelines specific to Point of Care manufacturing.
- Build on the changes proposed by the European Commission in the GPL that facilitate decentralised manufacturing as complementary to centralised manufacturing, by providing harmonised guidelines that allow for Point of Care manufacturing in a system that is equally safe and efficacious.
- Provide guidelines for automated and highly digitized ATMP manufacturing.

Unpredictable clinical trial standards and data requirements

As our understanding of ATMPs continues to evolve, a degree of regulatory flexibility is essential to allow such therapies to be developed and authorised. While a number of ATMPs have been authorised, these authorizations have been accompanied by extensive discussions with regulatory authorities and required exemptions, changes or adjustments to standard procedures that were developed and intended for the assessment of more traditional therapeutics.

In particular, this refers to data requirements, where suitably powered and comparative (‘head-to-head’) clinical trials remain the preferred standard but are not always possible for ATMPs. This is driven by a number of factors, including the small patient populations, lengthy timelines to manufacture suitable doses, inability to conduct double-blind studies, and ethical questions, such as using placebos as comparators where no other treatments exist, especially where ATMP delivery may be invasive[21]. The inherent lack of predictability when conducting any clinical trial is compounded by the uncertainty about whether data packages will be accepted. The cost and risk is a significant barrier to early considerations for investing in manufacturing footprint. This highlights the need for a regulatory system that allows for the appropriate flexibility and agility to allow for updates to guidance to ensure novel ATMPs can be assessed and safety standards upheld. Faster, more direct access to regulators for ongoing collaboration during clinical trial and manufacturing process development will enable faster and more certain pathways to ATMP approvals.

Establishing a manufacturing site is expensive, both in terms of financial investment and time. Therefore, if a developer is uncertain as to whether their clinical packages and data will be accepted, it is a significant risk to invest in the creation of a new manufacturing facility. Instead, manufacturers may prefer to invest first in a country where there is more regulatory predictability for ATMPs or rely on CMO rather than establishing their own facility.

Recommendations

- Update clinical trial guidelines and data standards to ensure specific rules exist for ATMPs that reflect the particularities of the technology group. This means not treating ATMPs simply as a ‘biologic’ and build in flexibility by design.

[21] **EUCOPE**, “*Position Paper on Real-World Evidence (RWE) across the Lifecycle of ATMPs*,” March 17, 2023. https://www.eucope.org/position-paper-on-real-world-evidence-rwe-across-lifecycle-of-atmps/.

Application of technical standards that are not fully relevant or updated to account for changes relevant to new ATMP manufacturing standards

Beyond the challenges linked to clinical trial data, there are a number of additional regulatory standards that are either out of date or introduce additional bureaucracy which could be simplified to facilitate the manufacture of ATMPs in the Union.

Currently, ATMPs are subject to the regulatory requirements of ICHQ1 and ICHQ5, though these guidelines have limited technical relevance, especially in the context of ATMP manufacturing processes.

In a similar vein, GMP and Good Laboratory Practice (GLP) standards are paramount to ensure that ATMPs are manufactured and developed under appropriate scrutiny to meet safety standards. However, there have been cases where GMP and GLP have been slow to update to novel manufacturing practices, leading to unnecessary delays, additional reviews, or the need to follow protocols which are not aligned with current realities[22]. Additionally, in some Member States, academics and developers have experienced long waiting times and limited capacity by the relevant accreditation bodies to issue GLP certifications. Inspection of manufacturing facilities and processes needs to be conducted by inspectorate well-versed in ATMPs with a deeper legal knowledge in pharmaceutical and regulatory frameworks for gene therapies, since there are notable differences between these modalities and typical biologic/small molecule drugs. Most notably, these stem from the fact that ATMPs are often patient specific and utilise their biological material as a starting material, leading to individual differences.

ATMP manufacturers can benefit from increased digitalisation. Allowing for electronic batch records would substantially reduce the administrative burden placed on technicians, quality units and reduce workloads. Additionally, it would streamline product tracking and shorten feedback loops. This approach would enable continuous process verification and improve supply chain management, ensuring a more accurate real-time picture of the manufacturing process control. Currently, much of this work is still, by requirement, done by hand, which can cause delays of several weeks before trends are noticed and changes can be made to the manufacturing activities. An electronic system would also allow for products to be closely tracked and quick data recall where and if that is needed. Digitization also becomes imperative for manufacturing throughput increases, where chain-of-identity control can become the limiter.

To expand the EU's ATMP manufacturing basis, there should be an increase in the number of contract testing laboratories (CTLs), which are especially important to smaller developers. CTLs provide an essential service, acting as an independent third party providing analytical services for those developers who do not have that expertise in house.

Similarly, the new Substances of Human Origins (SoHO) Regulation (Regulation 2024/1938), which introduces a number of important clarifications and harmonisation, also adds additional hurdles for ATMP developers. The new Regulation increases the obligations on developers through increased harmonisation when they act as SoHO importing and exporting entities. This requirement will have an impact on all cell therapy manufacturers with manufacturing sites outside the EU, such as those in the US. But also in cases where the starting material which usually is defined as SoHO comes for manufacturing from non-EU-countries. The objective of the SoHO Regulation is to protect donors, as ATMPs naturally substantially manipulate donor materials. If GMP requirements are extended far ahead and long before the start of actual manufacturing (which usually starts with the quality control of the

[22] For example since the release of the revised GMP Annex 1, the incorporation of relevant ICH concepts (such as Quality Risk Management (QRM) and Pharmaceutical Quality System (PQS)), the introduction of Contamination Control Strategy (CCS), and recent technological advancements are not yet reflected in the current ATMP GMP guideline (Annex 4).

European Commission, *EudraLex, Volume 4, Annex 1—Manufacture of Sterile Medicinal Products* (revised 25 August 2022; fully applicable since 25 August 2024). https://health.ec.europa.eu/system/files/2022-08/20220825_gmp-an1_en_0.pdf starting/raw materials), SoHO and GMP requirements overlap and gain unnecessary complexity. Thus, these additional guidelines introduce additional and cumbersome procedures where none is needed. By designing, the SoHOs will be processed and subsequently, the ATMP will be subject to more stringent quality and safety inspections.

Recommendations

- Ensure that there is a continuous review of scientific and tissue guidelines, to ensure that they are appropriate to ATMPs and where appropriate provide exemptions. To ensure that this is done, the EMA must ensure dedicated ATMP expertise within the network.
- EU to provide financial support to establish more GMP and GLP accreditation centres.
- EU to invest in developing inspectorate and upskill the regulatory network to be familiar with ATMP development, clinical trials and manufacturing.
- Establish guidelines and standardised processes to allow for digital systems (including electronic batch records and integrated digital systems); EU to provide financial support for manufacturers to incentivize moving towards digitization
- SoHO Coordination Board (SCB) should provide guidelines that ensure that SoHOs that are imported or exported for the explicit and exclusive use for ATMP manufacturing should be exempt from the SoHO Regulation's import and export requirements
- It needs to be clarified that GMP starts with the start of the manufacturing so there are no GMP requirements impacting SoHO

4. Inconsistent implementation and limitations imposed by the GMO legislation

A longstanding issue and regulatory hurdle for ATMP developers has been the application of the GMO legislation when it pertains to therapeutic ATMPs. EUCOPE has strongly welcomed the changes proposed in the GPL which would reduce the burden the GMO framework applies on ATMP developers. It is crucial that these changes are upheld.

The impact of an overly restrictive GMO framework was alluded to in the EU's 2002 Biotechnology Strategy. The current deliberate release[23] and contained use[24] directives introduce restrictions on both the manufacturing and conduct of clinical trials in the EU. This is driven in large part by the lack of harmonisation between Member States and the need for duplicative administration with national competent authorities. The challenge is especially pronounced in the case of multi-country clinical trials, where developers must engage many different regulatory and ethics bodies. It also applies in the context of decentralized and PoC manufacturing as different interpretations of GMO requirements leads to different requirements for one and the same manufacturing system (fully automated closed manufacturing system). A survey was conducted in 2020 to determine if a common application form for GMO submissions would improve facilitate and accelerate clinical trial approvals. While the survey demonstrated a streamlined application did have improvements, the GMO approval process for ATMP clinical trials remains an important hurdle[25]. The GMO legislation was initially designed to address risks associated with GMOs in the agricultural sector but has since had an impact on the pharmaceutical

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[23] **European Union**, *Directive 2001/18/EC of the European Parliament and of the Council of 12 March 2001 on the Deliberate Release into the Environment of Genetically Modified Organisms* (repealing Council Directive 90/220/EEC), OJ L 106, 1–39. https://eur-lex.europa.eu/eli/dir/2001/18/oj/eng.

[24] **European Union**, *Directive 2009/41/EC of the European Parliament and of the Council of 6 May 2009 on the Contained Use of Genetically Modified Micro-Organisms (Recast)*, OJ L 125, 75–97. https://eur-lex.europa.eu/eli/dir/2009/41/oj/eng.

[25] **ARM, EuropaBio, and EFPIA**, "*Call for More Effective EU Regulation of Clinical Trials with ATMPs Consisting of or Containing GMOs*," joint position paper (2020). https://alliancerm.org/wp-content/uploads/2020/11/ARM_EuropaBio-EFPIA-Call-for-action-on-ATMP-GMO-final-combined.pdf.

ecosystem, which is already subject to numerous other safeguards. ATMPs must comply with the standards and precautions laid out in the pharmaceutical legislation, which includes an Environmental Risk Assessment as well as the Clinical Trial Regulation. These provide standards to ensure the quality and safety of the manufacturing process as well. Therefore, any environmental benefit-risk after the clinical trial phase when manufacturing is scaled up is already accounted for. In effect, the GMO framework introduces substantial duplication.

An additional consideration which must be acknowledged is that most ATMPs do not survive long once and if they are excreted by the patient, further minimizing the risk associated with the release of GMOs[26]. ATMPs pose negligible risks to the environment[27].

The EU has recognised that the framework is outdated, referencing GMOs in the 2017 Action Plan, providing a derogation for COVID vaccines, and providing exemptions in the Commission's proposal in the revision of the GPL. The Biotech Act presents an opportunity to introduce a rational policy that reflects the realities associated with the development of ATMPs. A risk-based approach should be considered, which ensures that reasonable derogations are provided for, based on a risk-benefit assessment. This includes considerations such as, can the vectors survive outside of the patient's body.

Recommendations

- In the context of the Biotech Act, the European Commission, with the support of the EMA and wider ATMP community, should create a process allowing for therapeutic ATMPs to be made fully exempt from the GMO framework based on an ex-ante benefit-risk assessment on a product-by-product basis. This would build on the existing discussions in the GPL and derogations provided therein.

5. Lack of sufficient manufacturing expertise and knowledge

The final challenge EUCOPE wants to stress in this context is the lack of knowledge and experienced personnel. This has an impact on both developers as well as regulatory bodies.

ATMP manufacturing is complex and as such requires specialised knowledge. This is further complicated by the fact that between products, specific expertise and equipment is needed, meaning that ATMP manufacturing is not directly interchangeable between products. Developers active in the EU already face challenges in finding sufficient qualified hires due to the growing demand for this expertise and global competition. When qualified technicians are found, they must still undergo additional training to be familiar with the products, processes, equipment, aseptic controls and systems for the specific developer and product. Additionally, due to the fact that colleagues must also be retrained when new processes and products are developed, it can lead to delays in upscaling.

The lack of expertise also impacts the regulatory agencies, which creates hurdles when it comes to assessing products and inspecting manufacturing facilities, resulting in unnecessary complexity and delays. Engagement between regulators and developers should take place throughout the development and authorisation process in order to avoid unnecessary access delays. In addition to access delays, if developers are required to make changes to the manufacturing or commercialisation process at the end of the regulatory process, they incur significant financial burdens as well. Therefore, to support all developers, but especially in the case of ATMPs which are subject to highly complex manufacturing

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[26] "Call for More Effective Regulation of Clinical Trials with Advanced Therapy Medicinal Products Consisting of or Containing Genetically Modified Organisms in the European Union" (October 2021): 997–1003. https://pubmed.ncbi.nlm.nih.gov/33843251/.)

[27] **K. Kaltenborn** et al., "*Assessment of Cell-Binding Capacity of Shed rAAV Particles after Patient Treatment*," *Expert Opinion on Biological Therapy* (2024). https://pubmed.ncbi.nlm.nih.gov/39422109/.)

systems and often based on new and evolving technology, regular engagement with regulators is needed to submit high-quality applications and prevent avoidable questions or concerns from being raised late in the authorization process. This has the added benefit of upskilling the EU's regulatory network as they are exposed to new and evolving technology.

These challenges are compounded by the movement of global talent and possible brain drain. Thus, the EU must also implement policies that support and attract global leaders in ATMPs as well as help retain experts in the EU, avoiding that expertise developed in the EU move abroad. Industry can play a role in this conversation by ensuring competitive and exciting employment opportunities. Governments and policies must ensure that developers are in a position to provide these conditions by establishing an innovation ecosystem. Similarly, the EU should facilitate and remove barriers to allow experts and expertise from other world regions to travel and establish themselves in the EU.

Recommendations

- Ensure that the MFF allocates sufficient funding to support STEM education and life-long-learning programmes at Member State level. Allowing individuals to travel between Member States to learn from experts or being exposed to novel technologies is especially important;
- Member States must provide appropriate funding and incentives to provide high quality STEM education and encourage students to pursue such paths. This will support the creation of a strong cohort of experts that can become engineers or regulators;
- Establish recommendations on educational programmes for biomanufacturing and provide financial support for educational institutes that implement them;
- Ensure visa schemes allow and support technical experts to travel to and work in the EU.

Conclusions

Expanding the EU's ATMP manufacturing base can yield substantial benefits, not only in terms of expanding manufacturing, but also contribute to accelerated access, spur innovation, and foster economic growth, if the EU establishes itself as a globally competitive region. The challenges that exist are multi-facetted and require policy solutions across different domains. Fortunately, the EU and its Member States have various opportunities to introduce mutually reinforcing policies, if a coherent approach is taken. The pharmaceutical sector is characterised by a virtuous and mutually reinforcing cycle, thus improving the EU's manufacturing base will have a positive ripple effect and also be achieved through legislative and non-legislative action in other related areas.

The Draghi report highlighted the importance of the ATMP sector to the EU and presented a number of important proposal to upscale the region's capacity. The combination of new proposals and initiatives being discussed and proposed by the EU, including the GPL, Biotech Act and Life Sciences Strategy present the EU with a unique opportunity effect real change. To drive change, it is essential to take a holistic perspective and avoid piecemeal change. Action will be needed at both EU and national level to achieve the full impact.

Improving the EU's ATMP manufacturing is not incumbent on the EU or national governments alone, developers must, and increasingly are, investing in establishing their footprint. With the right policy framework, the EU and Member States can send a political signal to developers about their willingness to adopt these technologies, providing the developers with the confidence to invest in establishing the facilities and manufacturing sites.