BioPhorum

ATMP GLOBAL REGULATORY CHALLENGES

Supporting the need for global regulatory harmonization

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About BioPhorum

We enable the global biopharmaceutical industry to connect, collaborate and accelerate progress for the benefit of all.

Since its inception in 2004, BioPhorum has become the open and trusted environment where senior leaders of the biopharmaceutical industry come together to openly share and discuss the emerging trends and challenges facing their industry.

Growing from an end-user group in 2008, BioPhorum's membership now comprises top leaders and subject matter experts from global biopharmaceutical manufacturers and suppliers, working in both long-established and new Phorums. They articulate the industry's technology roadmap, define the supply partner practices of the future, and develop and adopt best practices in drug substance, fill finish, process development and manufacturing IT.

In each of these Phorums, BioPhorum facilitators bring leaders together to create future visions, mobilize teams of experts on the opportunities, create partnerships that enable change and provide the quickest route to implementation, so that the industry shares, learns and builds the best solutions together.

Authors

Merck
Kathryn Martin Remington

Sartorius
Amine Djeffal

BioPhorum
Niamh O'Kane

Contributors

Alexion, a Rare Disease Unit of AstraZeneca
Sarah Fitzgerald
Sagun Shakya

Astellas Pharma Inc.
Melisa Burgos

Bachem
Rüdiger Caesar

Boehringer Ingelheim
Martin Hampel

Charles River Laboratories
Kerstin Brack
Doug Brown
Ulrike Herbrand
Horst Ruppach

Eurofins BioPharma Product Testing
Luca Benedan
Jessica Kilgore
Weihong Wang

Lonza
Tamara Setzer

Merck
Ushma Mehta
Chitra Sudarshan

REGENXBIO
Tammy McCracken

Sanofi
Kalavathi Dasuri
Gillian Payne
Kristin Taylor

Sartorius
Claire Wartel

Ultragenyx
Diana Caroline Sanchez

1.0

Introduction

The recent stabilization of baby KJ Muldoon's condition following CRISPR based treatment for carbamoyl phosphate synthetase 1 (CPS1) deficiency marks a significant milestone in the application of advanced therapy medicinal products (ATMPs). This outcome, which may eliminate the need for a liver transplant, reflects the potential of personalized therapies to address rare, life-threatening conditions.

KJ's case underscores the importance of coordinated efforts among researchers, clinicians, regulators and manufacturers in accelerating the development and delivery of such therapies. The need for streamlined regulatory pathways was a central theme in a recent US Food and Drug Administration (FDA) forum, as reported by BioPharma Dive on 6 June 2025.

In response to these challenges, the BioPhorum ATMP global regulatory challenges workstream has brought together over 30 experts from 20 companies to discuss and align on best practices and propose practical solutions to regulatory barriers. The group supports enhanced collaboration with regulators and is committed to enabling faster, more efficient access to ATMPs for patients worldwide.

For consistency, this article will use the European Union (EU) term ATMPs to refer to these therapies, which are commonly known as cell and gene therapies (CGTs) in the United States (US), refer to Table 1. In addition to CGTs, RNA based therapies and vaccines are also within scope of the workstream and are therefore included under the broader ATMP classification.

Table 1: Terminology for modified gene, cellular and tissue therapies in the US and EU

Region	Terminology	Therapies
United States	Cell and gene therapies	Gene therapies Cell therapies Human cells, tissues and cellular and tissue-based products (HCT/Ps), (if more than minimally manipulated)
European Union	Advanced therapy medicinal products	Gene therapies Cell therapies Tissue-engineered products

2.0

Regulatory challenges in ATMP development

As manufacturers develop promising new therapies, they often encounter regulatory challenges, particularly the lack of globally harmonized regulations and limited access to consistent regulatory advice. Since these advanced therapies are a new modality, some variation is expected, however, misaligned or conflicting feedback from health authorities can impact development. For time-sensitive treatments, like personalized genetic therapy, timely regulatory review is essential to ensure patient access.

Manufacturers need clear guidance to translate regulatory expectations into specific, actionable requirements for their developing therapies. Well-defined expectations will enable manufacturers to generate and provide appropriate data in support of regulatory submissions. Furthermore, insight into how expectations differ across health authorities, and between early- and late-phase development, is essential for effective planning and compliance.

Manufacturers are eager to provide advanced therapies to patients in need, making harmonization of expectations between regulators urgent and essential. Manufacturers of advanced therapies require flexibility to adapt their processes while maintaining safety standards. This flexibility supports innovation without compromising on product quality. Enhancing clarity and reducing unnecessary inquiries during regulatory submissions will help create a swift and harmonized pathway to patient trials.

Many ATMPs target rare or ultra-rare diseases, resulting in limited patient populations. This hinders clinical trial recruitment and complicates the generation of the necessary patient numbers for robust statistical analysis. It also constrains product availability, posing challenges for manufacturers in demonstrating consistency and generating sufficient safety and efficacy data. The absence of appropriate animal models further complicates early development by limiting preclinical evaluations needed to support phase I trials. Robust analytical methods that thoroughly characterize products, produce reference materials, and generate the safety and efficacy data are essential to support regulatory applications. Additionally, the limited batch sizes of ATMPs for these rare diseases impede manufacturers' ability to demonstrate manufacturing consistency. The high cost associated with developing these ATMPs, coupled with the restricted market size, complicates pricing strategies and affects patient access. Addressing these challenges requires close collaboration with regulatory agencies to enable feasible, science-based approaches.

3.0

Market and investment barriers

Despite scientific success, the ATMP sector faces significant market and regulatory challenges that threaten its progress. High development costs and complex regulatory pathways have made investors increasingly cautious, leading to reduced funding and stalled innovation. Over 100 rare disease ATMP programs have been discontinued, not due to clinical failure, but because of market viability concerns[1].

Large pharmaceutical firms are also reluctant to invest heavily in ATMP, citing regulatory and reimbursement challenges as deterrents to investment, while academic labs risk having promising projects abandoned due to a lack of funding and support. These challenges underscore the need for a more supportive regulatory and commercial environment to ensure ATMPs can fulfil their potential.

4.0

Regulatory engagement and expedited pathways

Both the EU and US regulatory frameworks aim to support innovation and patient access while ensuring safety. Opportunities for early and ongoing engagement with regulators exist in both regions, offering a path to more efficient development approval.

Expedited review pathways for advanced therapies are listed in Table 2[2, 3, 4].

Table 2: Expedited review pathways by region

USA	Europe
Formal meeting pathways (Type A, B, C and D)	Innovation Task Force (ITF) briefing meeting
Center for Biologics Evaluation and Research (CBER) Advanced Technology Team (CATT)	ATMP classification
Initial Targeted Engagement for Regulatory Advice on CBER Products (INTERACT)	ATMP certification
Fast track	Parallel Scientific Advice Meetings (European Medicines Agency (EMA) and/or National Competent Authority and/or Health Technology Assessment body)
Regenerative Medicine Advanced Therapy (RMAT) designation	Priority Medicines program (PRIME)
Breakthrough designation	
Accelerated approval	
Priority review	

Non-harmonized regulations across jurisdictions present significant challenges for ATMP developers. Differences in terminology, guidance documents, approval pathways, manufacturing expectations and commercialization requirements necessitate thorough understanding and strategic planning. Early consultation with regulatory experts can help mitigate risks and improve the likelihood of successful market approval.

During these interactions, sponsors should present a comprehensive, up-to-date overview of the product, including information about the disease state, product attributes/characteristics, clinical and nonclinical data, proposed labeling, chemistry, manufacturing and control (CMC) information and safety profile, to proactively address potential regulatory concerns.

5.0

Harmonization and strategic recommendations

To address the challenges faced by the ATMP sector, several regulatory changes are proposed by the BioPhorum workstream. These include the adoption of flexible clinical trial designs and end points tailored to the unique nature of ATMPs and recognizing incremental progress rather than expecting transformative outcomes in a single step.

A two-tier regulatory system, such as China's, could allow faster initiation of first-in-human trials under local ethics review boards, thereby accelerating the development process. Streamlining comparability testing requirements[5, 6] when transitioning production from academic to commercial settings may also reduce delays, though it is important to recognize that this is a challenging proposition. In the US, comparability testing is critical at all stages of product development to ensure safety and efficacy. Emphasizing risk-based assessments can help justify its scope and necessity. Finally, increased sharing of regulatory feedback and case studies would help understanding of FDA and EU expectations and foster a more collaborative development environment.

While reimbursement measures are not in scope of the workstream or BioPhorum activities, members recognized their broader importance in addressing global regulatory challenges that impact the successful development and delivery of ATMPs. Enhanced market support for biotechnology companies is essential to sustain ATMP development and delivery. Incentive mechanisms such as priority review vouchers can help attract investment and encourage innovation[7, 8, 9]. Strengthening collaboration between academia, biotech firms and regulators can also streamline development and accelerate patient access.

ATMPs present unique challenges for healthcare systems due to their novel therapeutic approaches and long-term value propositions. While regulatory approval focuses on safety, efficacy and quality, reimbursement decisions often depend on assessments of clinical and economic value. Health Technology Assessment (HTA) agencies in the EU[10] (e.g. NICE (UK)[11], HAS (France)[12] and IQWiG (Germany)[13]) and organizations like ICER in the US[14] play a key role in evaluating these therapies. Innovative reimbursement models, such as outcome-based agreements and instalment plans, are being explored (outside the BioPhorum collaboration) to address uncertainties and support sustainable access[15, 16, 17, 18]. However, commented on in the external (to BioPhorum) literature, implementation remains complex due to administrative burdens, limited long-term data and variation in national policies. Continued dialog among stakeholders is essential to develop practical, scalable solutions, however, once again this aspect is out of scope of the BioPhorum collaboration.

6.0

Long-term safety and lifecycle regulatory complexities

There are also unique long-term safety risks with ATMPs, especially when integrating vectors that may cause insertional mutagenesis or unpredictable immune responses. Regulators like the FDA and the EMA require risk-based pharmacovigilance plans, often with 15 years of patient follow-up[19]. Real-world evidence (RWE) and patient registries are critical for confirming long-term safety and effectiveness, while good manufacturing practice (GMP) compliance ensures robust tracking through robust chain-of-identity and chain-of-custody systems.

However, challenges persist:

- Long-term follow-up is operationally and financially demanding
- RWE depends on consistent patient registry participation
- Decentralized, patient-specific manufacturing complicates supply chain compliance
- In rare diseases, small patient populations hinder trend analysis and comprehensive safety data collection.

While pharmacovigilance processes may not be inherently difficult, limited patient numbers make meaningful surveillance difficult.

The regulatory environment for investigational medicinal product dossier (IMPD) submissions in the EU is more complex than in the US. For example, in the EU, only drug developers, not raw material manufacturers, can submit drug master files (DMFs), which complicates the process and limits direct interactions between regulators and raw material manufacturers. Drug developers must act as intermediaries, which often leads to delays, especially when proprietary information is involved. Unlike in the US, IMPDs in the EU must include full details rather than cross-referencing DMFs, raising confidentiality concerns. Raw material manufacturers are often unwilling to share sensitive and/or proprietary data with clients, further delaying submissions and risking business losses due to miscommunications and inefficiencies.

In contrast, the US FDA allows both drug developers and raw material manufacturers to submit DMFs[20]. During investigational new drug (IND) applications, the FDA can directly access DMFs describing the CMC of raw materials used in ATMP production, enabling direct engagement with manufacturers. This avoids confidentiality issues and streamlines the process. However, DMFs for drug substance/drug product (DS/DP) cannot be cross-referenced in biologics license applications (BLAs), although facility master files are allowed. While the US approach is more harmonized at the clinical stage, challenges remain at the marketing authorization approval (MAA) and BLA stages, highlighting the need for greater regulatory alignment.

Unlike traditional biologics, ATMPs often undergo significant process changes during development and commercialization, making comparability assessments complex. Even minor alterations such as vector design, cell culture conditions or manufacturing sites, can alter potency and clinical outcomes, sometimes requiring bridging studies or new clinical trials. For autologous therapies, scaling out manufacturing sites is often more practical than scaling up, which complicates technology transfer and regulatory oversight. These lifecycle realities pose challenges: ATMPs are highly sensitive to process changes, current analytical tools cannot fully characterize them and maintaining consistent quality across multiple sites is difficult. Regulatory divergence between agencies like the FDA and EMA further slows lifecycle agility.

7.0

Small and medium enterprise-specific challenges

ATMP development poses disproportionate challenges for small and medium enterprises (SMEs), who are often the most innovative players. High costs for manufacturing and clinical trials, limited financing and lack of in-house regulatory expertise restrict their participation. While support exists, such as the EMA SME Office (fee reductions and regulatory advice), and early access pathways like PRIME, and Horizon Europe[21] that supports translational research, barriers remain. Failure to engage early with health authorities and HTA bodies can lead to regulatory non-compliance or extended development timelines, ultimately delaying patient access and increasing costs.

8.0

Future outlook and conclusion

The ATMP field is at a critical juncture, scientific breakthroughs are advancing rapidly, but progress is constrained by regulatory complexity, financial risk and market access barriers. To unlock its full potential, both the US and the EU regulators must continue to evolve their frameworks to recognize and address the unique challenges of ATMPs. Greater regulatory convergence, particularly around comparability, master file submissions and flexible trial designs, is essential to streamline development and reduce duplication of effort.

Market mechanisms must encourage sustained investment and SME participation, ensuring that innovation is not limited to large pharmaceutical firms. Regulators play a key role here by enabling early engagement, harmonizing global expectations and fostering collaboration across academia, biotech companies and investors.

The BioPhorum ATMP global regulatory challenges workstream will contribute to this effort by acting as a collective industry voice advocating for regulatory streamlining and harmonization by publishing position papers on this critical topic. It will conduct comprehensive reviews and gap analyses of industry literature and guidance for ATMPs, with a primary focus on FDA and EMA regulatory frameworks. By summarizing major regional requirements and expectations, and highlighting areas of common practice and divergence, the workstream members aim to reduce the risk of regulatory delays, accelerate speed to market, and lower manufacturing and development costs. Given the breadth of the regulatory landscape, the team will initially concentrate on impurities guidance. Once this topic area is concluded, members will expand their focus to additional priority areas, ensuring a systematic approach to addressing global regulatory challenges.

Ultimately, the goal is to create a system where patients gain timely and equitable access to transformative therapies. If scientific innovation, regulatory evolution and financial sustainability can be aligned, ATMPs will indeed herald a new era of medicine, bringing lasting hope to patients with rare and previously untreatable conditions worldwide.

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