Successfully Launching Advanced Therapy Medicinal Products in Europe

INDUSTRY PERSPECTIVES

APCO worldwide®

FOREWORD

Advanced Therapy Medicinal Products (ATMPs), including cell and gene therapies, have transformative potential to change lives. For patients with few or no treatment options, ATMPs open up a world of possibility in what would otherwise be a bleak future.

As science evolves, the rare disease patient community will not be the only beneficiary. Today, there are numerous therapies in development designed to target debilitating chronic conditions that affect an increasingly ageing population. Parkinson's, Alzheimer's, diabetes and cardiovascular disease could all be afflictions of the past if these treatments come to fruition.

As new technologies emerge, a myriad of social, ethical and economic questions remain around how they can reach patients. Are societies ready to embrace the potential of ATMPs? Are our health systems, designed for conventional medicines, sufficiently adaptable to support access to such treatments? How can we reconcile disparate national regulatory and value frameworks across Europe to facilitate greater acceptance of ATMP evidence and expedite access? Do clinicians and patients understand these new forms of treatment and their key benefits? Assuming they do, how can health systems and society afford them?

APCO Worldwide advises clients on navigating the rapidly evolving and complex global health care environment. We spoke to 12 industry experts to get their perspectives on these questions as discussions on the reforms of the EU pharmaceutical framework and joint Health Technology Assessments (HTAs) are underway. For companies looking to Europe as a future commercial market for ATMPs, we hope these perspectives serve to inform strategic planning on how to navigate the evolving policy environment.

All experts highlighted that preparation for ATMP launches needs to begin as early as possible during the development stages. Early engagement with ecosystem stakeholders (patient organizations, health care professionals, policymakers and implementation bodies) enhances alignment with stakeholders' expectations and policy agendas. Importantly, the existing perception of ATMPs as 'high cost and high risk' needs to be reframed to 'high opportunity and high value' for patients, health systems and society as a whole.

Sara Cruz
Senior Director
ATMP Lead

Alexandre Marie Saint Germain
Director
European Health Practice Lead

INTRODUCTION

In 2009, Europe achieved a global first by approving the first ATMP—ChondroCelect, a tissue-engineered therapy for treating defective knee cartilage. This pivotal moment signalled hopes that Europe could become a global leader for ATMP launches.

Despite early optimism of Europe as a ripe launch market for ATMPs, the real experiences of many therapeutic developers in recent years have been less than positive. Bluebird bio, for instance, decided to exit the market in 2021 following unsuccessful reimbursement negotiations in Germany for their first gene therapy, Zynteglo. Other companies have faced similar challenges in the past year as benefit assessments and requirements have made the commercial environment untenable.

Despite Europe's best intentions to improve patient access to innovation, recent EU reforms to its pharmaceutical legislation and the future EU Joint Clinical Assessment for HTA could further degrade the environment for commercialization. In April 2023 the Alliance of Regenerative Medicine (ARM), stated: "The European Commission's proposed revision of the pharmaceuticals legislation remains focused on the conventional medicines of the past rather than the Advanced Therapy Medicinal Products (ATMPs) of the future. It fails to build upon the Commission's statement in its 2020 Pharmaceutical Strategy for Europe that cell and gene therapies represented 'milestones of major progress' in healthcare."[1]

A major obstacle to the adoption of ATMPs is the perception of risk associated with this new category and the risk appetite of regulators, payers, physicians and patients, who still operate within the classical drug paradigm. One of the primary challenges for ATMP manufacturers is the need to demonstrate economic and clinical evidence, modelled on frameworks that were developed for conventional therapies (e.g., small molecules or drugs for highly prevalent chronic diseases).

Addressing this perception of 'high-cost, high-risk' is crucial to a launch strategy for ATMPs. For those ATMPs developed for rare diseases, the lack of a large patient population makes standard randomized clinical trials difficult to execute. Existing regulatory and pricing assessments are designed for conventional therapies and industry is challenged to provide generalisable evidence that does not typically exist for ATMPs. Existing clinical trial regulations and HTA requirements are not fit for purpose.

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Such challenges to ATMP development stymie innovation, R&D investments, as well as patient access to treatments, ultimately leaving those without life-changing or potentially curative treatment options behind. It is incumbent on innovators and the industry to align with regulators, patients, physicians and payers to bring them along the journey of evolution in pharmaceutical innovation—with a focus on creating value for all stakeholders, and patients at the very core.

The following sections will explore further the key roadblocks and optimal strategies to shape the policy environment for successful commercial launches, especially at a time when there are greater constraints in health care expenditure and increased calls for efficiencies.

[1] https://alliancerm.org/press-release/arm-releases-statement-on-recent-draft-eu-pharmaceuticals-legislation/

KEY ROADBLOCKS TO COMMERCIALIZATION SUCCESS

1. PERCEPTION OF RISK AND UNCERTAINTY OF ATMPS' CLINICAL AND COST EFFECTIVENESS

A fundamental challenge to commercial success is risk. In a world where resources are not limitless, decision-makers need to justify the trade-offs of paying for one drug over another. However, the evidence base at the point of marketing authorization for ATMPs tends to be insufficient to accurately estimate either clinical and cost-effectiveness of a drug in clinical practice or its budget impact. The uncertainty, due to the lack of data, results in delays to reimbursement decisions and patient access.

One respondent said: "ATMPs are built around a system that has expectation of evidence even though this is hard to come by since they are one-time treatments." Another respondent suggested that due to the potentially curative effect of ATMPs, many patients do not return for subsequent treatment and payers are denied the follow-up data they have come to expect from chronic therapies.

Regulators and payers are not yet receptive to a risk-based approach to evaluating ATMPs. Risk sharing or managed entry agreements such as outcome-based payments are still not widely practised given the complexity of implementing such agreements. Nonetheless, they offer pathways to access—particularly for rare disease treatments that are unlikely to be supported by robust data. Regulators and payers' openness to adaptive assessments will greatly support patient access and address unmet needs.

Getting over the regulatory hurdle is one part of the problem in spreading innovation. Diffusion of ATMP technology is not only affected by clinical approvals and reimbursement decisions, but also prescribers' and patients' knowledge, attitudes and behaviour. Most respondents have suggested that more needs to be done to create awareness and educate prescribers as well as patients to allay fears of adverse side effects and risks.

> "Physicians play a vital role in prescribing and administering ATMPs. Their confidence and belief in the medicine's efficacy and safety are essential for successful adoption and patient acceptance."

> "Patients need to be convinced of the benefits and be willing to pursue the treatment options."

2. ONE SINGLE MARKET, 27 DIFFERENT MARKET ACCESS STRATEGIES

Despite the EU being a single trading bloc, pharmaceutical companies have to develop strategies that comply with Member States' respective regulatory and HTA requirements that are shaped by national needs. Such fragmentation means that one pan-European strategy cannot be deployed in all markets.

Diverse policies in Europe create a postcode lottery of access to ATMP treatment. Even though ATMPs may be centrally approved by the European Medicines Authority, it does not mean that every patient will have access to the new drug.

> "There needs to be more collaboration between countries within Europe to ensure a unified approach to the commercialization of ATMPs as well as more streamlined regulations and pricing models to make it easier for companies to launch therapies in Europe."

The EU has attempted to reduce fragmentation by creating a new Joint Clinical Assessment (JCA) for HTA that will require evidence to be submitted only once at the EU level from 2025. It is hoped that by avoiding multiple country-specific assessments, the EU will improve the functioning and transparency of a single market. Respondents have expressed apprehension about whether these changes would ultimately reduce duplication inherent in pursuing HTA assessment across multiple markets.

> "To restore confidence in Europe as a launch market for ATMPs, several actions can be taken. Firstly, the European regulatory framework, such as the new EMA regulations, needs to be fit for purpose and provide a clear pathway for ATMP approvals. Additionally, robust outcomes and successful uptake of ATMPs in the European market, similar to the case of Zolgensma and other products, can help build trust and convince companies to invest in launching their therapies in Europe. Finally, ensuring a favourable reimbursement environment and willingness to pay for these therapies in larger European markets would further support the confidence of companies considering Europe as a launch market for ATMPs."

Several recommendations proposed by Alliance for Regenerative Medicine would modernise the JCA process to reduce sources of uncertainty. These include the provision of EU-wide guidelines on real world evidence and single arm trials, and continued collaboration between ATMP developers and the European Medicines Agency via Joint Scientific Consultations through to the end of the JCA process.[2]

3. FAILURE TO TAILOR APPROACHES ACCORDING TO LOCAL ENVIRONMENT AND MARKET NEEDS

One of the reasons that commercialization has not been as successful as anticipated is the failure to adequately anticipate market demand. This may include accurate data on population type, unmet need, population size, pricing corridor and stakeholders' receptiveness towards ATMPs and risk-sharing or alternative payment models. These are important considerations for future ATMP launches.

Novartis' launch of Zolgensma was broadly seen as an example of a successful commercialization. One respondent believed the company had understood the local market environment and customised solutions to the individual health system. Specifically, their offer of an innovative financing mechanism supported market access. Other positive examples include the launch of Imlygic for the treatment of inoperable melanoma and Blincyto for acute lymphoblastic leukaemia. Their success was attributed to the companies' understanding of how to target stakeholders and address their needs in each individual market. Providing a 'white glove' personalised approach post approval assisted the delivery of the product.

[2] https://alliancerm.org/press-release/joint-clinical-assessment-methodology/

BEST PRACTICES IN NAVIGATING AN INCREASINGLY CHALLENGING ENVIRONMENT

Pharmaceutical companies **need to start planning their access strategy as early as phase 1 and 2 in the development phase** to condition the environment for potential launch. In all interviews, **early engagement with stakeholders** was highlighted as a critical success factor in navigating the challenges of market access and supporting commercial launch planning.

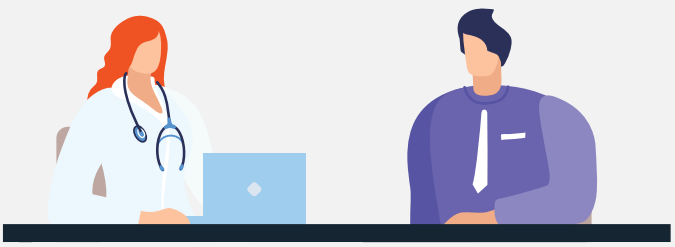
A successful access strategy should include the following steps:

CONNECT WITH ECOSYSTEM STAKEHOLDERS EARLY

Engagement strategy should be informed by an understanding of players and decision-makers critical to market access.

> "Creating a stakeholder engagement plan is really important. Engaging stakeholders at an early stage is a big part of your story. Helping them understand what you are trying to do early will help take out fear and make the process easier."

Aligning with stakeholders in early phases can help support the design of the trials and smooth the path to regulatory approval and reimbursement. Determining—together with stakeholders—the priority for different patient populations and how they measure value can speed access.



EMPOWER PATIENTS AND PHYSICIANS

Including patients in conversation with payers, regulators and reimbursement decision-makers is important to pave the way for access. This means involving patients in clinical trial designs and HTA evaluation. The movement towards the inclusion of real-world evidence can support the delivery of patient-centered solutions.

Educating physicians and patients on the benefits of ATMPs can help companies build support for the therapy at the grassroots level. As aptly explained by a respondent:

> "Physicians, Key Opinion Leaders and patients are the most important people to reach when launching an ATMP as they are the people who will need, administer or advocate for treatment. It is important to start planning and creating connections as early as possible, consulting with advocates who can assist with conversations with policymakers and regulatory authorities. Always keep patients and physicians top of mind as you need their support to stay functional, as well as being able to adapt to different markets and not use the same strategy for each."

BUILD MARKET LANDSCAPE ANALYSIS INTO ACCESS STRATEGIES

The success of a therapy in one region compared to another can be influenced by various factors beyond the regulatory and reimbursement processes. "Factors such as market dynamics, pricing strategies, availability of alternative treatments and patient populations can also play a role," said one respondent. An understanding of the economic, political and social factors that drive technological uptake and the market landscape informs decisions on market access and commercial strategies including launch sequencing between the United States and Europe.

> "Right from clinical development, you need to be clear on your ambition as to which market you want to target and how you want to target it, understanding if the system in that market will be suitable in terms of pricing, timelines and so on, in order to know if your therapy will be attractive in that market or not."

TELL A VALUE STORY

Develop a narrative that is backed by strong socioeconomic data and aligns with stakeholders' perception of value.

> "It's always more difficult to say, 'please pay me €50,000 for this car right now' than 'please pay €500 per month.' You have the feeling that it's less expensive, but in the end, it's probably even more expensive."

Essential to tackling the issue of 'risk versus cost' is telling a story that addresses the value drivers from a patient, physician and payer/health system perspective. The value story must clearly articulate the therapy's proposition and the role it plays in the existing health care system or clinical pathway. Both political, economic, social and technology (PEST) and stakeholder analyses can help to identify outcomes that matter most to stakeholders and, from there, what is defined as value, coinciding with the hard data that is required from a regulatory and HTA perspective.

BUILD TRUST

'Building trust' was repeatedly mentioned in the interviews. An astute public and government affairs strategy helps to build and manage a company's reputation, credibility and trust with policy decision-makers ahead of the launch process. One respondent said: "The reputation of the company is crucial in convincing payers. A positive reputation instils confidence and trust in the product's quality, efficacy and safety. Unknown or negatively perceived companies may struggle to gain payer support."

Another respondent said: "Involve stakeholders from the start, build trust and understanding with the patient community and clinicians, and understand the reimbursement model to ensure successful launch of the ATMP."

An education drive to improve awareness of the unmet need and how a therapy will benefit patients and wider society was mentioned as a success factor. "Generating awareness of the severity of the disease is important. While payers have their regulatory framework, they don't act in a vacuum. The media and public opinion matters."

> "Continued advocacy and dialogue are essential to address these challenges and create a supportive environment that fosters the development and accessibility of ATMPs within the EU."

CONCLUSION

There is cautious optimism for Europe as a thriving market for cell and gene therapies. Despite a few isolated setbacks, Europe still has the potential to blaze the trail for cell and gene therapies if it can develop a quicker and more flexible regulatory regime.

Moreover, the market is accustomed to using ATMPs in the screening, diagnosis and treatment of genetic and rare disorders, which suggests a fertile ground for long-term growth. ATMP manufacturers can take advantage of recent EU pharmaceutical policy changes by uniting with stakeholders behind the common goal of increasing patient access.

We recommend incorporating these key steps when developing a commercial strategy for ATMP launch:

1. **Conduct a thorough assessment of the landscape** to understand the market and stakeholders.

2. **Connect with policymakers and local payers as early as phase 1** to inform clinical trial design and identify market needs for the therapy. Involve physicians and patients in the entire process to help advocate for the therapy.

3. **Advocate at the national, rather than European, level and tailor strategy to the countries in which companies plan to launch.** At the same time, work with policymakers at a pan-European level to catalyze the evolution of regulation and assessment.

4. **Build a narrative that demonstrates an understanding of stakeholders' expectations and what they perceive as value to patients and the system.** The value story should explain where the therapy fits in the health system and be accompanied by compelling evidence and real-life patient testimonies.

5. **Raise patients' and physicians' awareness of the benefits of ATMPs.** Patient support and advocacy are crucial for the acceptance and adoption of ATMPS.

6. **Proactively build a position as a trusted partner.** Positioning the company as an industry and health ecosystem partner in driving innovation, access and value supports stakeholder relations and lends credibility to the company and its products.

ABOUT THIS REPORT

This report is based on a series of interviews undertaken by APCO Worldwide with 12 senior leaders in the ATMP space during Autumn 2022 and Spring 2023.

We would like to thank the following experts for their contributions:

Alexander Natz
Secretary General of EUCOPE

Doug Danison
Head of Commercial, Cell & Gene Therapy Unit, Bayer

Etienne Régulier
Global Head of Patient Access, Cell and Gene Therapy, Santen

Gerry Downey
Statistical Scientist – Gene Therapy, Rare Diseases, RWD/RWE, previously Senior Director, Bluebird Bio

Jŭrgen Wasem
Professor of Health Services Research, University of Duisburg-Essen, Germany

Lucia Faccio
Partner, Sofinnova Partners

Matthias Wilken
Managing Director, Market Access, Markets and Supply, German Pharmaceutical Industry Association (BPI)

Nadia Bahmad
Market Access & Public Affairs Director, France, CSL Behring

Seren Phillips
Former Senior Director EMEA Health Economics, Market Access, Policy, Novartis Gene Therapies

Susanne Digel
German General Manager, Amylyx

Ulrike Sager
Head of Market Access, Germany and Austria, Oncopeptides AB

Ugo Capolino Perlingieri
General Manager of Europe and Middle East Operations, AlloVir, an ElevateBio Company

For more information please contact:

Sara Cruz
scruz@apcoworldwide.com

APCO worldwide®