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Evolving Landscapes for Advanced Therapy Medicinal Products (ATMPs): Access in the US, UK & EU

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INTRODUCTION

- The advanced therapy medicinal product (ATMP) landscape is evolving rapidly. In 2021, over 2,400 clinical trials for regenerative medicines were ongoing worldwide, with almost 145 being Phase III clinical trials[1,2]
- With the high number of ATMPs gaining marketing authorization in recent years, there is a clear drive to improve patient access to these ground-breaking products.[2] ATMPs are distinct from traditional pharmaceutical products as they may: provide potentially transformative or curative benefits; be subject to more complex pharmaco-vigilance requirements; pose challenges associated with clinical trial design; require manufacturing and storage considerations; be associated with uniquely high administration and upfront costs
- Regulatory bodies must assess the efficacy and safety of ATMPs based on highly limited data to judge whether the risks and benefits are acceptable and favourable for patients. Given the level of innovation and potential for clinical benefit, accelerated regulatory pathways are often applicable
- Increased likelihood of accelerated regulatory approval means that health technology assessment (HTA) agencies are also tasked with assessing clinical and cost-effectiveness evidence that is substantially more uncertain than for traditional pharmaceuticals. Additionally, unlike for regulatory agencies, there are no specialized or centralized HTA bodies with dedicated expertise on ATMPs

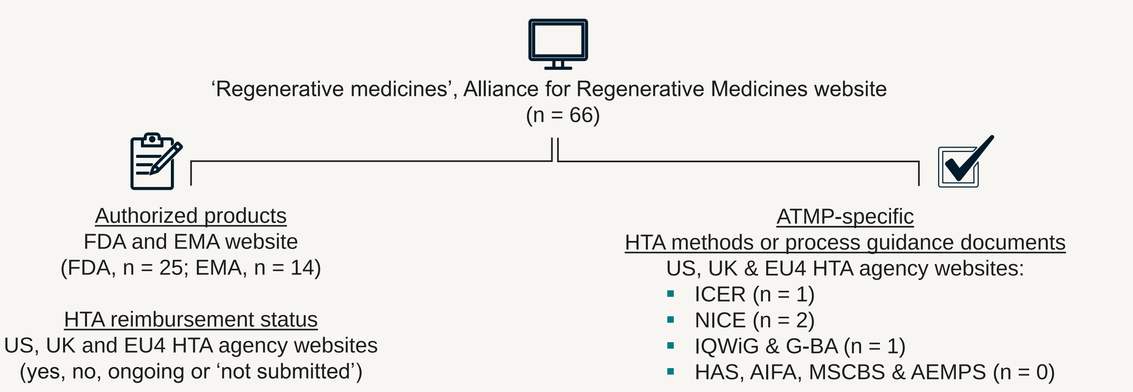
OBJECTIVES

- This research aims to identify developments in the regulatory and reimbursement landscape to improve access for patients when assessing this unique group of therapies

METHODS

- In February 2022, we reviewed online guidance for accelerated pathways for regulatory assessment by the US Food and Drug Administration (FDA) and the European Medicines Agency (EMA), and published ATMP guidance (Figure 1). We identified 66 products classed as regenerative medicines by the Alliance for Regenerative Medicines, which includes cord blood therapies and tissue-engineered products. We searched the FDA and EMA websites for regulatory approval status. We reviewed HTA bodies in the US, UK and EU4 (Germany, France, Italy and Spain) for published ATMP-specific guidance and reimbursement status

Figure 1: Schematic of approach and top-level results



Key: AEMPS, Agencia Española de Medicamentos y Productos Sanitarios (Spanish Drug and Healthcare Products Agency); AIFA, L'Agenzia Italiana del Farmaco (Italian Medicines Agency); EMA, European Medicines Agency; EU4, Germany, France, Italy and Spain; FDA, US Food and Drug Administration; G-BA, Gemeinsamer Bundesausschuss (Federal Joint Committee); HAS, Haute Autorité de Santé (French National Authority for Health); HTA, health technology assessment; ICER, Institute for Clinical and Economic Research; IQWiG, Institut für Qualität und Wirtschaftlichkeit Im Gesundheitswesen (Independent Institute for Quality and Efficiency in Health Care); MSCBS, Ministerio de Sanidad, Consumo y Bienestar Social (Ministry of Health in Spain); NICE, National Institute for Health and Care Excellence.

Box 1: EU HTA collaboration and harmonization[3]

- **In recognition of varying value assessment frameworks across the EU member states, adopting the Regulation on Health Technology Assessment in December 2021 is a positive and collaborative step towards harmonization**
- **However, challenges for ATMPs remain (e.g. stringent evidence requirements that will be difficult to address where RCTs are not possible)**
- **The regulation will apply to oncology and ATMPs from January 2025 and to orphan medicinal products from 2028**

Key aspect in the regulation		Impact for ATMPs
Member states can pool their resources and expertise; HTA bodies will conduct joint clinical assessments and engage in joint scientific consultations.	→	Early engagement is highly recommended for ATMPs; this is likely to streamline regulatory assessments and align HTA bodies ahead of launch across multiple countries.
The regulation focuses on clinical effectiveness and safety aspects, although member states may voluntarily engage further, e.g. on economic HTA aspects.	→	Similar to above, potentially challenging issues could be brought forward to advance resolution and improve access to ATMPs. However, the specific process is yet to be detailed, which is a concern particularly where RCTs are not viable.
Horizon scanning exercises will identify promising health technologies earlier to help health systems prepare for them.	→	Useful because practical preparedness from a treatment, care pathway and funding perspective are critical for ATMPs (as per recent approvals); however, country-specific nuances will remain due to differences in healthcare systems.
The new framework will help address unmet medical needs and facilitate access to innovative medicines and certain high-risk medical devices.	→	ATMPs are highly innovative and would likely be included in innovation initiatives without directly specifying product types further.

Key: ATMP, advanced therapy medicinal product; HTA, health technology assessment; RCT, randomized controlled trial.

RESULTS

1. **The potential benefit, unique characteristics and challenges associated with transformative medicines are recognized by regulatory bodies, although differences exist across ATMPs' classification and assessment processes**
   - The FDA and EMA have accelerated pathways for regulatory assessment that offer flexibility for the approval of products where the risk–benefit ratio is likely to be favourable based on less-than-optimal clinical trial evidence, such as open-label and single-arm studies, studies based on a small number of patients, broader consideration of the relevant clinical endpoints or short duration of follow-up (Table 1)
   - As of February 2022, over 25 products are FDA-approved, including cord blood therapies and tissue-engineered products; 11 of these are only available in the US but not in the EU. Conversely, seven out of 14 EMA-approved products are only available in the EU

Table 1: FDA and EMA options supporting accelerated regulatory approval

FDA pathways	EMA pathways
▪ Priority review ▪ Fast track designation ▪ Breakthrough therapy designation ▪ Accelerated approval ▪ RMAT designation	▪ PRIME designation scheme ▪ Conditional approval ▪ Exceptional circumstances ▪ Accelerated pathway ▪ Compassionate use program

Key: EMA, European Medicines Agency; FDA, US Food and Drug Administration; PRIME, Priority Medicines; RMAT, regenerative medicine advanced therapy.

2. **There are limited ATMP-specific methodological or process guidance documents published by HTA bodies, and each of these has a different aim, focus and conclusion**
   - Only four HTA methodological or process guidance documents specific to ATMPs were identified in the US[4], Germany[5] and the UK.[6,7] Given the differences in the assessment framework across HTA bodies, the purpose and conclusions of each guidance varied. ICER guidance focused on incorporating the perspectives of multiple stakeholders engaged in the healthcare system; NICE assessed the applicability of current HTA methods guidance for ATMPs; and the G-BA legislation was specific to quality control measures in Germany
3. **There are differences in the reimbursement status of products across countries, possibly as a result of differences in HTA processes and methodological preferences**
   - There did not seem to be consistent trends across countries by products or by ATMP classification. The UK and Germany had the greatest number of reimbursed ATMPs. Re-assessment in England, France and Germany is particularly important for ATMPs, especially where post-authorization data are planned
4. **Countries consider a range of pricing and funding models for ATMPs. The level of publicly available detail was generally sparse. Outside the HTA process, many countries continue to support access for highly innovative products more broadly**

   Some examples include:
   - Funding models such as payment at result, outcome-based agreements, gradual discounts or instalment plans were mentioned in published documents for most countries[8]
   - Cost-coverage or cost-containment systems in Germany, France and Spain specifically target hospital-based management. Products' development and production stages are supported in the Netherlands
   - Several countries have provided dedicated pools of funding for innovative treatments, such as England's Cancer Drugs Fund (CDF)[9] or Italy's specialist fund[10]

CONCLUSIONS

- This research reveals differences between EU and US access from a regulatory and HTA perspective. Various pathways for accelerated regulatory assessment are available. The application process for reimbursement differ substantially at country-level
- Across countries, payer and societal priorities may play a different role in supporting patient access. Although many countries are supporting access for highly innovative products outside the HTA process, affordability thresholds and risk management remain a challenge[1,4,9,10]
- Finally, the recently adopted EU Regulation on HTA includes ATMPs within the first group of products it will apply to in 2025 (Box 1).[3] Procedural harmonization and cohesive data collection planning could help close the reimbursement gap within the EU. However, it will be a while until any impact might be seen

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