ORPHAN CELL AND GENE THERAPY APPROVALS IN THE US AND EUROPE: A COMPARATIVE ANALYSIS

HPR119

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INTRODUCTION

- Cell and gene therapies (CGTs) represent a rapidly expanding therapeutic class for the treatment of severe and rare diseases, offering the potential for durable or even curative benefit.[1]
- By directly targeting the underlying genetic or cellular cause of disease, CGTs have the capacity to address high unmet need in conditions where conventional pharmacological approaches have been ineffective or are unavailable.[1]
- However, the development and evaluation of CGTs presents significant challenges for regulators. Clinical evidence is often generated in small or highly selected patient populations and often lack long-term follow-up at the time of regulatory submission.
- These uncertainties place increased emphasis on risk-benefit analysis, post-authorization data generation, and the acceptability of uncertainty at approval.
- Given their high upfront costs, complex manufacturing processes, and dependence on sustained market access to remain commercially viable, regulatory decisions for CGTs have far-reaching implications beyond initial authorization, influencing development strategy, patient access, and long-term product availability.
- Building on our prior 2025 analysis[2], this study compared regulatory decisions for CGTs between the US Food and Drug Administration (FDA) and the European Medicines Agency (EMA), to explore whether regulatory decision-making patterns for CGTs have changed over time.
- The objective of this research was to examine differences in regulatory decision-making between the FDA and EMA for cell and gene therapies, focusing on approval timing, withdrawals, and refusals, and the implications for timely and sustained patient access across the US and Europe.

METHODS

- The FDA website[3] was searched for all CGTs approved by the FDA.
- Medicine name, approved indication, orphan status, and date of approval were recorded.
- The EMA website[4] was searched for the corresponding approval in Europe.
  - Approval could have been provided at any time since the EMA regulations for advanced therapy medicinal products were established in 2007.
- Approval dates, orphan designation status, reasons for withdrawal/refusal of marketing authorization (MA), and indication were noted.

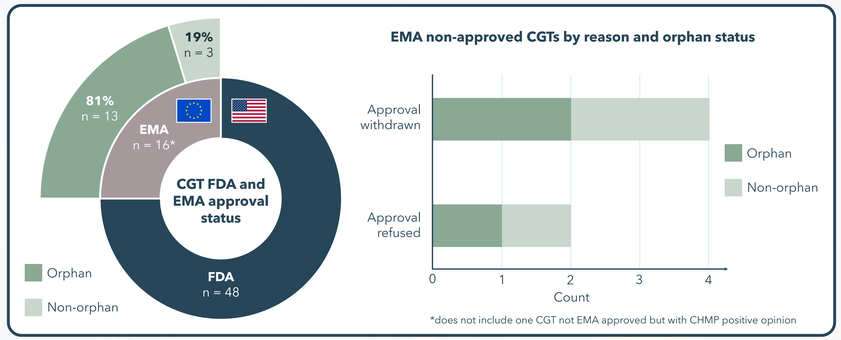
RESULTS

- As of 2nd April 2026, 48 CGTs have been approved by the FDA, 33 with orphan status.
- Nine of these approved therapies are cord blood therapies. An additional four products are cellular scaffold products.
- These 13 cord blood or cellular scaffold therapies have not been approved centrally by the EMA.
  - In some cases, these products may have been approved under European or national mutual recognition or decentralized procedures (MRP/ DCP).
  - Some products may not be defined as a medicine and are regulated by blood/ cell tissue authorities nationally.

RESULTS

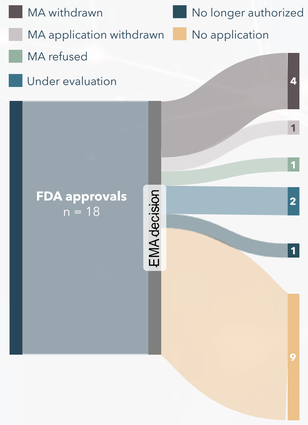
- The EMA have approved 16 (33%) of these CGTs, 13 (81%) with orphan status (Figure 1).
- A further one CGT has recently been given a positive CHMP opinion for a non-orphan indication but is not yet EMA approved.

Figure 1: Number of FDA CGT approvals and corresponding EMA outcomes and orphan status



- EMA MA was withdrawn for four CGTs at sponsor request (Figure 1), all for commercial reasons.
- EMA MA was refused or the MA application was withdrawn for two CGTs, due to inadequate efficacy data (Figure 1) and the MA for one CGT expired.
- The remaining 11 CGTs have not (yet) progressed to European authorization although two therapies are currently under evaluation by the EMA (Figure 2).

Figure 2: CGTs with FDA approval without current EMA authorization



Drug	Indication	FDA approval year
Sipuleucel-T	Metastatic prostate cancer	2010
Elivaldogene autotemcel	Cerebral adrenoleukodystrophy	2022
Betibeglogene autotemcel	Beta-thalassemia	2022
Fidanacogene elaparvovec	Hemophilia B	2024
Lifileucel	Unresectable or metastatic melanoma	2024
Delandistrogene moxeparvovec	Duchenne muscular dystrophy	2024
Onasemnogene abeparvovec	Spinal muscular atrophy	2025
Zopapogene imadenovec	Respiratory papillomatosis	2025
MACI	Cartilage defects of the knee	2024
Azficel-T	Nasolabial fold wrinkles	2011
Lovotibeglogene autotemcel	Sickle cell disease	2023
Omidubicel	Hematologic malignancies	2023
Donislecel	Type 1 diabetes	2023
Remestemcel	Acute graft versus host disease	2024
Afamitresgene autoleucel	Advanced synovial sarcoma	2024
Atidarsagene autotemcel	Metachromatic leukodystrophy	2024
Revakinagene taroretcel	Macular telangiectasia	2025
Prademagene zamikeracel	Epidermolysis bullosa	2025

- The majority of CGTs included in the analysis received their first regulatory approval from the FDA rather than the EMA.
  - 12 CGTs were first approved by the FDA, with EMA approval following on average 262 days later, although individual timelines varied.
  - For the 4 CGTs first approved by the EMA, subsequent FDA approval occurred after an average of 312 days.

CONCLUSION

- This comparative analysis highlights persistent and meaningful differences in regulatory outcomes for CGTs between the FDA and the EMA.
- While the FDA continues to approve a growing number of CGTs, only a minority progress to authorization in Europe, contributing to ongoing disparities in patient access across the US and Europe.
- These findings contrast with our previous analysis of orphan drug approvals, which showed that during 2022-2023, 73% of FDA-approved orphan medicines were also approved by the EMA.
- In the current analysis, 33% of CGTs approved by the FDA were also approved by the EMA suggesting that the access gap observed for CGTs cannot be attributed to orphan designation alone but reflects challenges that are particularly pronounced for advanced therapies.
- Although most EMA-approved CGTs hold orphan designation, orphan status alone does not ensure long-term access.
- Marketing authorization withdrawals occurred across both orphan and non-orphan indications, suggesting that challenges related to commercial sustainability extend beyond rare disease therapies and reflect broader pressures affecting CGTs in Europe.
- However, the impact of MA withdrawals may be greatest for orphan indications, where alternative treatment options are limited and patient populations are small.
- In contrast, marketing authorization refusals were relatively uncommon and primarily driven by unresolved uncertainty regarding efficacy evidence, highlighting the continued importance of robust evidence packages at time of submission.
- Most therapies without EMA approval received FDA authorization between 2023-2025 suggesting that timing delays could be a factor in differences between regulatory outcomes.
- Differences in evidentiary expectations and tolerance for residual uncertainty between the FDA and EMA may also contribute to observed disparities in approvals, withdrawals, and long-term availability of CGTs.
- Together, these findings suggest that the European access gap for CGTs reflects a combination of regulatory, evidentiary, and commercial factors that extend beyond rare disease status alone.
- Addressing these challenges will be critical to ensuring that the orphan drug framework continues to support innovation in advanced therapies, and that regulatory approval translates into durable and meaningful patient access, particularly for patients with rare and severe diseases.

Abbreviations:

CGT, cell and gene therapy; CHMP, Committee for Medicinal Products for Human Use; DCP, decentralized procedure; EMA, European Medicines Agency; FDA, US Food and Drug Administration; MA marketing authorization; MRP, mutual recognition procedure.

References:

1. Cetin et al (2024) Gene and cell therapy of human genetic disease: Recent advances and future directions. J Cell Mol Med. 28 (17), e70056. https://doi.org/10.1111/jcmm.70056
2. Fulthorp et al (2025) Orphan drug approvals in the US and Europe: A 2-year comparison. Value in Health. 28 (S2). ISPOR - Orphan Drug Approvals in the US and Europe: A 2-Year Comparison
3. https://www.fda.gov/vaccines-blood-biologics/cellular-gene-therapy-products/approved-cellular-and-gene-therapy-products
4. www.ema.europa.eu/en/medicines