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GENE THERAPY'S NEW ERA: FDA LEADERSHIP, INNOVATION, AND ACCESS IN RARE DISEASE TREATMENT

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ABSTRACT

Gene therapy, defined as the introduction of genetic material into a patient's cells to treat or cure disease, has entered a transformative phase, particularly for rare genetic disorders. Thousands of rare diseases affect millions of individuals worldwide, most of which still lack effective treatment options. Gene- and cell-based therapies offer the potential for long-term or curative outcomes by addressing underlying genetic defects. As of recent years, multiple gene therapies have received regulatory approval, with many more under development. This review explores the scientific principles of gene therapy, including viral vectors, gene editing technologies, and both ex vivo and in vivo approaches. It also outlines the clinical development pathway from early research to clinical application. Special emphasis is placed on regulatory advancements, including expedited approval pathways, innovative designations, and evolving frameworks that support the development of therapies for rare diseases. Additionally, the review discusses key challenges such as patient access, cost, long-term safety, and the need for collaborative healthcare models. Overall, gene therapy represents a rapidly advancing field with significant potential to transform the treatment landscape for rare diseases, while also presenting important scientific and regulatory challenges.

KEYWORDS: Gene therapy; Rare disease; Regulation; Drug development; Accelerated approval.

INTRODUCTION

Rewriting the Genetic Code of Medicine

Gene therapy – broadly, the use of genetic material to treat or prevent disease – has transitioned from experimental concept to clinical reality.[12] By manipulating DNA or RNA, gene therapies can directly address the root cause of monogenic disorders, offering curative potential often with a single administration. This approach is particularly suited to rare genetic diseases, ~80% of which arise from a single gene mutation.[2] The collective impact of rare diseases is large: in the U.S. alone, an estimated 30 million people (≈1 in 10) live with a rare disease, and for the majority no approved treatment exists.[1] The unmet need and scientific advances have converged to spur unprecedented growth in CGT development. As of 2025, over 30 cell and gene therapies have FDA approval[3], and CAR T-cell therapies **Kymriah/Yescarta** for blood cancers[14], the 2019 approval of **Zolgensma** (AAV for spinal muscular atrophy)[15], and in late 2023 the first CRISPR-based therapies for hemoglobinopathies (Casgevy, Lyfgenia).[4]

At the same time, regulatory frameworks have evolved to keep pace. The FDA and EMA have created specialized pathways (e.g. RMAT, PRIME) to expedite these treatments. In 2023–26 the FDA in particular reorganized and innovated: FDA's CBER established a new *Office of Therapeutic Products (OTP)* as a "super office" to consolidate cell and gene therapy expertise[9], and the agency launched a forthcoming *Rare Disease Innovation Hub* to coordinate cross-center efforts.[10] In 2026, FDA introduced a draft "Plausible Mechanism Framework" to support individualized N-of-1 gene therapies for ultra-rare diseases, acknowledging that randomized trials may be infeasible.[16] At the same time, FDA's emphasis on accelerated pathways has grown:

former CBER director Marks predicted that accelerated approval would become the norm for gene therapies[17], and indeed several recent approvals (e.g. Sarepta's *Elevidys* for Duchenne MD) have used surrogate endpoints when other options were lacking.[18] These regulatory changes underscore a new era in which scientific innovation and regulatory leadership converge to bring hope to patients with devastating rare diseases.

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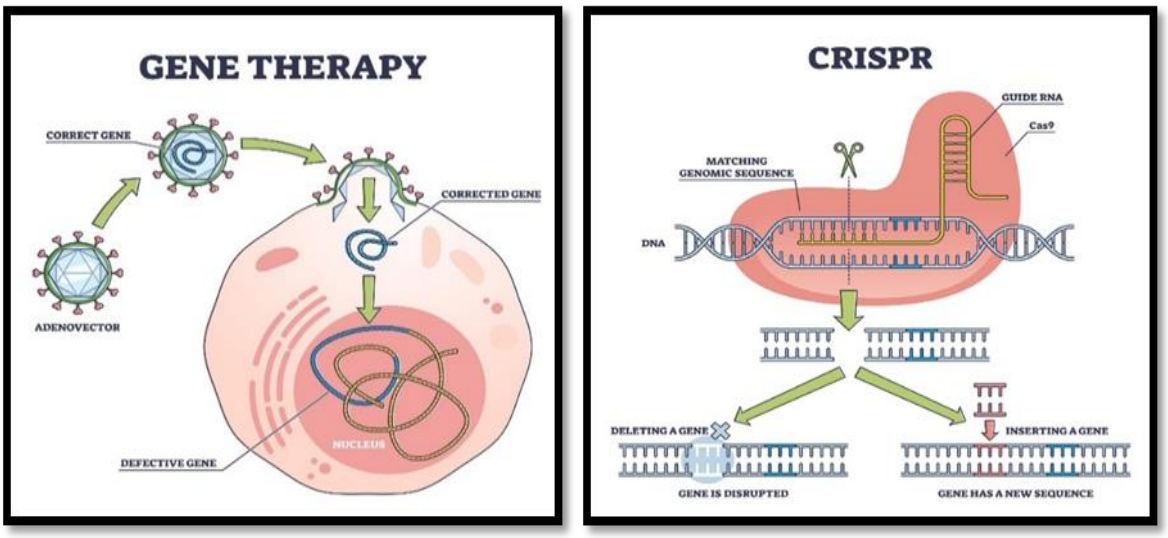

Figure 1: Gene Therapy.

From Molecule to Mission: The FDA's Role in Gene Therapy

The U.S. Food and Drug Administration (FDA) plays a central role in overseeing the development, evaluation, and approval of gene therapy products. Within the FDA, the Center for Biologics Evaluation and Research (CBER) is charged with ensuring the safety and efficacy of biological products, including cell and gene therapies. Recognizing the increasing complexity and volume of gene therapy submissions, the FDA launched the Super Office of Therapeutic Products (OTP) in 2023. This reorganization aligns review disciplines more closely and increases regulatory capacity by expanding expertise in areas such as pharmacology, toxicology, clinical development, and manufacturing quality.[22] OTP is structured into specialized divisions focused on Gene Therapy Chemistry, Manufacturing, and Controls (CMC); Cellular Therapy and Human Tissue; Plasma Protein Therapeutics; and Clinical Evaluation and Review Management. By creating this integrated framework, the FDA aims to streamline its review processes while adapting to the evolving scientific landscape of gene therapy.

A Universe of Possibilities: Types of Gene Therapy Products

Gene therapy encompasses a broad array of platforms and biological mechanisms. Product types are differentiated based on delivery method, vector type, and therapeutic goal. Ex vivo gene- modified cell therapies, such as Chimeric Antigen Receptor T-cell (CAR-T) treatments, involve the extraction, genetic modification, and reinfusion of patient cells. In contrast, in vivo therapies— like those using adeno-associated virus (AAV) vectors—deliver genes directly to targeted tissues inside the body. Non-viral platforms, including mRNA or plasmid DNA, are gaining attention their reduced immunogenicity and flexible manufacturing profiles. Viral vectors remain widely used due to their high efficiency, with lentivirus and retrovirus suitable for stable integration and AAV preferred for non-integrative delivery. Emerging modalities such as microbial vectors and induced pluripotent stem cells (iPSCs) are broadening the therapeutic toolbox, offering new ways to treat cancers, metabolic disorders, and immunological conditions.

Designing the Delivery: Ex Vivo vs. In Vivo Strategies

A core consideration in gene therapy is the mode of gene delivery. Ex vivo delivery allows cells to be genetically engineered in a controlled laboratory setting before reintroducing them into the patient. This method is advantageous for hematologic malignancies and immune disorders due to the ability to monitor and select modified cells. In vivo gene delivery, by contrast, introduces therapeutic DNA or RNA directly into the patient's body, often using viral vectors like AAVs or lipid nanoparticles. This strategy is particularly effective for neurological and muscular diseases where targeted delivery is critical. Each approach presents unique risks and benefits. Ex vivo therapies offer precision and control but require sophisticated infrastructure and patient conditioning. In vivo therapies are less invasive but may provoke immune responses or off-target effects. Choosing the appropriate delivery mechanism is a pivotal decision that shapes the therapy's success, scalability, and safety profile.

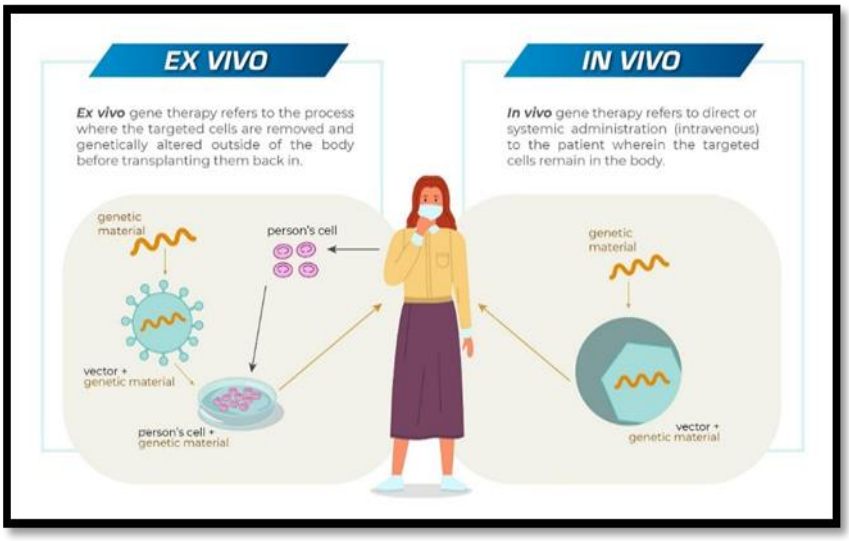

Fig. 2: Design Delivery.

From Bench to Bedside: The Regulatory Pathway

The development of a gene therapy product follows a well-structured regulatory path aimed at ensuring patient safety and therapeutic efficacy. This begins with an INTERACT meeting, where sponsors can seek early feedback on preclinical data and product development strategies. Subsequently, a Pre-Investigational New Drug (Pre-IND) meeting facilitates a deeper dive into planned studies and submission requirements. Once an IND is submitted, the clinical development progresses through Phases 1 to 3, punctuated by end- of-phase meetings that review safety data, dosage adjustments, and study designs. Upon successful trials, a Biologics License Application (BLA) is submitted for final FDA approval. Even post-approval, manufacturers are required to conduct long-term surveillance to monitor safety signals like insertional mutagenesis, immune responses, and therapy durability. The entire regulatory lifecycle reflects a balance between innovation and public safety, especially given the irreversible nature of gene therapies.

Experimental to Essential: Clinical and Preclinical Considerations

Gene therapies require rigorous preclinical testing using animal models to determine biodistribution, persistence, and potential toxicities. Such studies help establish a safe starting dose and guide design for first-in-human trials. Clinical development then proceeds through phases designed to assess safety, immunogenicity, and therapeutic effectiveness. Given the novelty of these interventions, clinical trials often involve intense monitoring, including assays for vector shedding, immune response markers, and transgene persistence. Regulatory authorities recommend a risk-based approach to trial design, requiring sponsors to justify monitoring frequency, duration, and data endpoints. For rare diseases, adaptive trial designs and Bayesian modeling may be used to overcome limitations in patient availability while preserving statistical power. These considerations ensure that gene therapies meet high scientific standards while also addressing the urgency of life- threatening conditions.

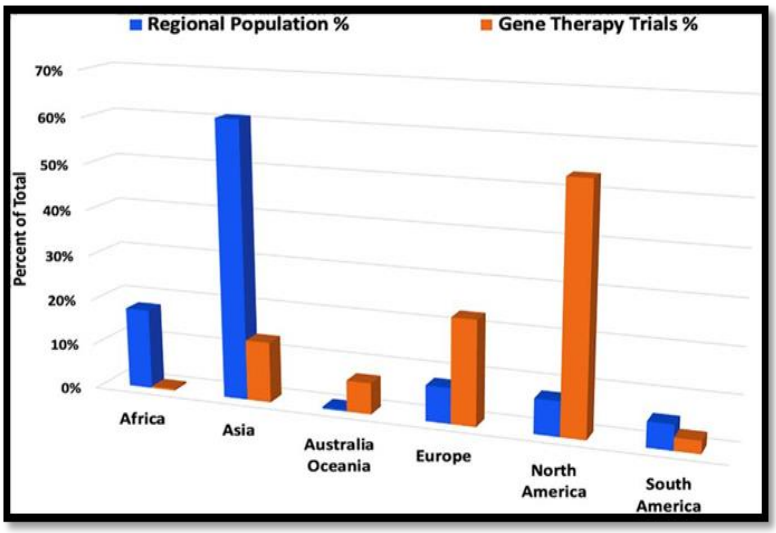

Fig. 3: Gene therapy trials.

Speeding Hope: The FDA's Expedited Approval Toolbox To accelerate access to promising gene therapies, the FDA offers several expedited approval pathways tailored to serious and life-threatening diseases. The Fast Track designation facilitates more frequent communication and rolling reviews for drugs addressing unmet medical needs. Breakthrough Therapy designation offers intensive guidance based on preliminary evidence of substantial clinical benefit. The Regenerative Medicine Advanced Therapy (RMAT) designation is specific to regenerative biologics, offering benefits similar to Breakthrough Therapy. Accelerated Approval allows earlier market entry based on surrogate endpoints reasonably likely to predict clinical benefit. Finally, Priority Review shortens the FDA review time from ten to six months. These programs not only reflect regulatory flexibility but also show responsiveness to patient communities urgently awaiting treatment options.

Challenges and Future Horizons

Despite its promise, gene therapy faces significant hurdles that could limit its accessibility and sustainability. One major challenge is manufacturing scalability—producing high- quality viral vectors or genetically modified cells at commercial scale remains complex and costly. Additionally, long-term durability and safety data are still maturing, raising questions about the longevity of therapeutic effects and the risk of delayed adverse events. Immunogenicity, particularly with repeat dosing of viral vectors, continues to be a barrier, necessitating innovation in immune modulation and vector design.

Equity and affordability are also pressing concerns. The cost of gene therapy, often exceeding $1 million per treatment, can strain healthcare systems and limit patient access. Novel payment models—such as outcomes-based contracts and installment plans—are being explored to address this challenge, but widespread adoption is still limited.

Looking forward, advances in genome editing (e.g., CRISPR/Cas systems), synthetic biology, and AI-driven design are expected to open new possibilities. Personalized gene therapies tailored to individual mutations and real-time genomic surveillance may redefine the standard of care. Collaborative global regulatory frameworks, harmonized clinical trial standards, and investment in workforce training will be crucial to sustaining momentum in the field.

Table 1. Exemplars of innovative reimbursement mechanisms used for gene therapies in Germany.

Therapy	Access scheme used	Nature and source of data collected for access scheme	Ref
Luxturna® (voretigene neparvovec)	CED: health technology reassessment based on additional cohort data	• CED based on data from EMA safety study and long-term follow-up data from pivotal trial (to be collected until 31 December 2021)	[40]
Kymriah® (tisagenlecleucel)	CED: health technology reassessment based on additional cohort data Outcomes-based rebates linked to IPD offered to statutory health insurance companies	• CED based on data from final 5- year follow-up data from the ELIANA study (to be submitted by 1 September 2023) Rebates based on survival	[31,2]
Yescarta® (axicabtagene ciloleucel)	CED: health technology reassessment based on additional cohort data Outcomes-based rebates linked to IPD offered to statutory health insurance companies	• CED based on data from final 5- year follow-up data of the ZUMA-1 study (to be submitted by 15 May 2022) Rebates based on survival	[23,24]
Zolgensma® (onasemnogene abeparvovec)	Outcomes-based rebates linked to IPD offered to statutory health insurance companies	• Rebates of up to 100% based on several patient- relevant outcomes (not specified further in publicly available sources) - Potentially using data from RESTORE (a global registry based on existing country registries)	[15–17]
Zynteglo® (betibeglogene autotemcel)	- CED: health technology reassessment based on additional cohort data - Outcomes-based agreement linked to IPD offered to statutory health insurance companies	• CED based on long- term follow-up data from HGB- 207 and HGB-212 studies and 5-year follow-up data from the LTF-303 study (to be submitted by 15 May 2025) Outcomes-based agreement based on transfusion independence	[26-27]

CED: Coverage with evidence development; IPD: Individual patient data.

CONCLUSION

The Genetic Revolution in Reach

Gene therapy represents a paradigm shift in the treatment of rare and genetic diseases, offering the potential for long-lasting and even curative outcomes. While scientific and regulatory advances have accelerated progress, significant challenges remain. Continued innovation in vector design, manufacturing processes, and clinical trial methodologies will be essential. Equally important is the development of sustainable models for access and affordability. By fostering collaboration among scientists, regulators, industry, and patient communities, the future of gene therapy can be both effective and equitable. As this genetic revolution unfolds, it brings not only hope but a real opportunity to transform modern medicine.

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