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# Reducing the High Cost of Cell and Gene Therapies

## Through Best-in-class Gene Editing component Development and Manufacturing

White Paper

GenScript
Scripting Possibilities

## Introduction

The approvals of Casgevy™ for sickle cell disease and transfusion-dependent β-thalassemia[1] by the US FDA and EMA in 2023, the first CRISPR-based therapeutic approvals globally- have generated significant optimism in the cell and gene therapy (CGT) field. Developers are leveraging a variety CRISPR approaches to address unmet medical needs, but these therapies face numerous challenges, including complex manufacturing processes and regulatory requirements.

In January 2024, the US FDA released final guidance for industry regarding 'Human Gene Therapy Products Incorporating Human Genome Editing.' This guidance clarified some key Chemistry, Manufacturing, and Control (CMC) requirements for the gene editing reagents and gene-modified cellular drug products for editing human somatic cells. The FDA outlined critical control considerations for CRISPR reagents, where the delivery method dictates whether the gene editing (GE) component is classified as a critical manufacturing component or an active substance. This guidance complemented earlier US FDA documentation from January 2020, which established CMC requirements for upstream manufacturing processes to be included in human gene therapy Investigational New Drug Applications (INDs).

Gene-edited CGT products (hereafter referred to simply as "CGTs") are made for very small patient populations- often just one patient- and are therefore inherently costly. The "vein-to-vein" processes required to produce autologous therapies, such as cell collection in hospitals, CRISPR-based editing in facilities, cryopreservation, and reinfusion, span several weeks and use aseptic procedures, sterile components, and significant labor. An expensive manufacturing footprint used for several weeks that might yield hundreds of thousands of doses for mainstream pharmaceuticals may produce just a few doses for autologous CGTs.

While economies of scale remain challenging for patient-specific CGTs, GenScript is dedicated to targeting incremental cost reductions through optimized processes, leveraging industrial manufacturing strategies and continuous improvements.

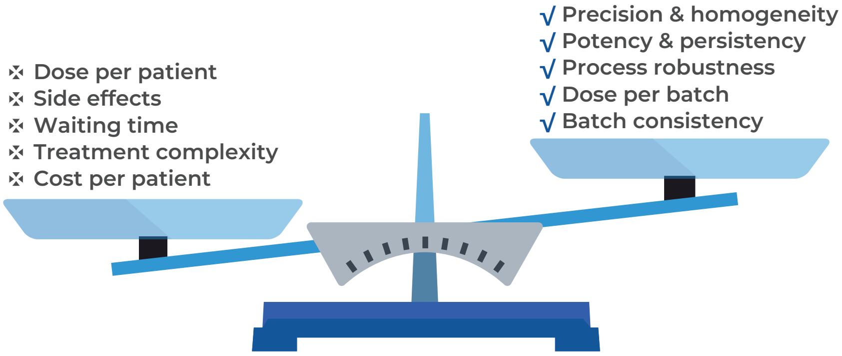


**Figure 1. Balancing Key Factors for Effective CGT Development**

*[1] Parums DV. Editorial: First Regulatory Approvals for CRISPR-Cas9 Therapeutic Gene Editing for Sickle Cell Disease and Transfusion-Dependent β-Thalassemia. Med Sci Monit. 2024 Mar 1;30:e944204. doi: 10.12659/MSM.944204. PMID: 38425279; PMCID: PMC10913280.*

# Technology Improvements Driving More Cost-Effective Processes

## Best-in-class product development and manufacturing

Partnering with the right Contract Development and Manufacturing Organization (CDMO) can streamline development and clinical timelines while aligning manufacturing strategies with affordability goals. GenScript supports CRISPR therapy development across all stages, offering both non-clinical (research-use-only, or RUO) and clinical grade (manufactured under current Good Manufacturing Practices, or cGMP) GE components, including:

- guide RNA (gRNA) manufacturing and regulatory support,
- custom and off-the-shelf Cas proteins and Cas-encoding mRNA, and
- HDR donor templates (e.g., ss/dsDNA and circular DNA).

## GE component manufacturing

CRISPR gene editing relies on two main components: gRNA (usually single guide RNA, or sgRNA,for CRISPR/Cas9-based editing) and a nuclease, such as Cas9. Manufacturing these components involves labor-intensive processes, batch size limitations, and stringent quality control. Strategies such as optimizing gRNA, modifying Cas9, utilizing other Cas variants, and implementing anti-CRISPR proteins mitigate risks like unintended genetic modifications.[2]

### A **cGMP manufacturing facility typically includes:**

- segregated rooms for each manufacturing step to minimize cross-contamination,
- segregated cleanrooms starting from the purification step to maintain low bioburden and reduce contamination risks, and
- small volume, single-use sterile filtration followed by lyophilization and aseptic fill/finish in Grade A isolators.

### Manufacturing cGMP gRNA involves:

1. Solid-phase oligonucleotide synthesis with multiple cycles of deprotection, activation, oxidation, and capping for each nucleotide added,
2. Cleavage and deprotection to isolate crude oligonucleotides,
3. Chromatographic purification to achieve high purity,
4. Desalination to remove residual inorganic materials, and
5. Sterile filtration, lyophilization, and aseptic fill/finish in primary packaging containers.

The typical manufacturing duration for the five steps is at least 14 days, depending on the shift system. Typical output ranges from 100 mg to gram quantities per batch, with a substantial portion consumed by QC testing, which is largely impacted by sterility testing. Key cost drivers include batch size, labor intensity, unit output per square meter of manufacturing footprint, material usage (including consumption for in-process control and QC testing), and non-manufacturing time devoted to maintaining facilities in a clean, qualified, and validated state. For autologous CGTs, one

*[2] Han HA, Kah J, Pang S, Soh B. Mitigating off-target effects in CRISPR/Cas-9 mediated in vivo gene editing. J. Med. 2020;98(5):615-632. doi:10.1007/s00109-020-01893-z*

gRNA batch may only be used for one patient. Increasing gRNA batch size for allogeneic cell editing to treat multiple patients can yield substantial cost improvements.

## Product Design with the End in Mind: A Joint Effort with Innovators

Scientists excel at developing novel approaches during screening and preclinical work, but manufacturability becomes critical as products advance. Collaboration with CGT clients is essential to balance science with affordability. Clear development goals should include cost targets and timelines, focusing on optimizing GE components, which remain less cost-efficient compared to commoditized materials.

Harnessing advancements in gene editing offers a promising pathway to address cost challenges in manufacturing complex therapies like CAR-T treatments by enabling the shift from autologous to allogeneic models. Allogeneic approaches eliminate patient-specific steps, enhancing scalability and reducing failure rates. While early allogeneic immune cell therapies struggled with poor persistence post-infusion, improvements in non-viral CRISPR-HDR technology now allow developers to overcome key barriers while reducing costs and safety risks. For example, Cas-targeting sequence (CTS) modifications have improved HDR efficiency, enabling precise CAR insertion into the desired reading frame with controlled copy numbers. Driven by endogenous promoters, this approach achieves optimal CAR expression and prevents T-cell exhaustion. Additionally, innovative methods like SLEEK (Selection by Essential-gene Exon Knock-in) and SEED (Synthetic Exon/Expression Disruptors) use advanced counter-selection strategies to achieve nearly 90% purity in engineered CAR-T products, meeting critical standards for therapeutic homogeneity. By integrating gene editing advancements such as these, researchers can leverage healthy donor-derived immune cells to efficiently generate potent allogeneic therapies. This enables scalable manufacturing that significantly reduces costs while accelerating patient access.

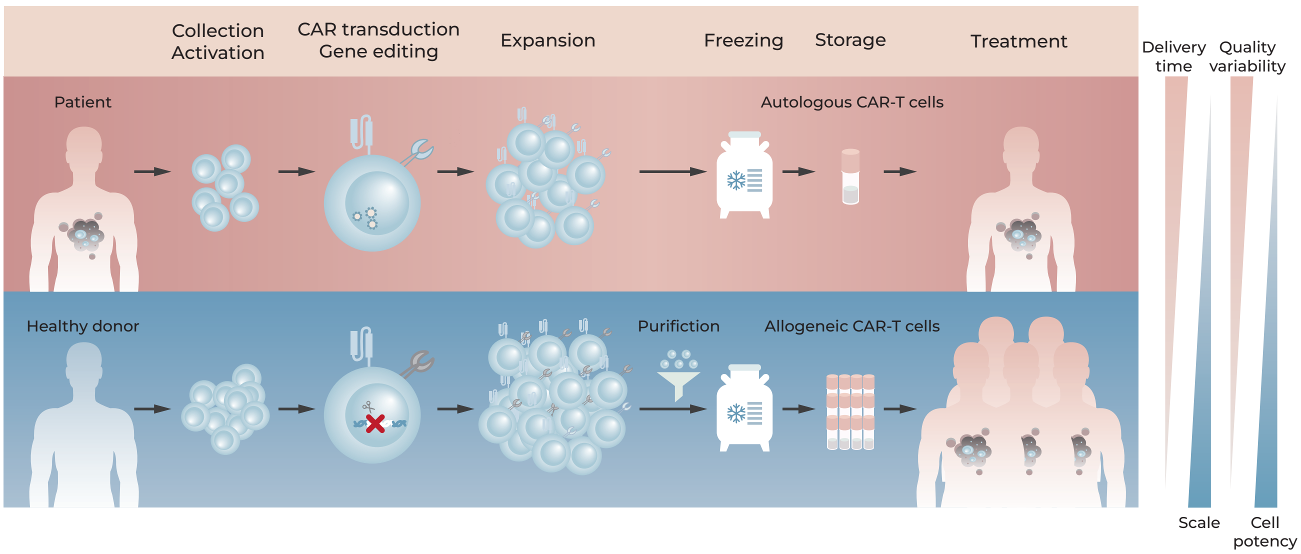


**Figure 2. Processes and advantages of developing an autologous vs. allogenic CAR T-cell therapy**

## Platform Processes Developed for Fit-to-Plant

The starting point for R&D teams is to develop products and manufacturing processes that align with the capabilities and limitations of existing manufacturing assets, such as facilities, equipment, and operating practices. The critical question is determining which parts of the process should be standardized as platform processes versus customized, such as the oligonucleotide sequence and length of gRNA.

Standardized platform processes minimize variability and incorporate: segregated rooms for manufacturing steps, automation, standardized materials, staggered workflows, in-process control testing, and standard batch sizes. Collaboration across manufacturing teams ensures feasibility and adherence to cost-effective best practices.

## Phase-Appropriate GMPs for Clinical Supplies in Preparation for Marketing Authorization

Full process understanding stems not only from product development but also from the insights gained from initial clinical batches. GenScript's cGMP Quality Management System (QMS) differentiates certain elements based on the applicability of cGMP requirements and their level of implementation, as outlined in the diagram below.

cGMP controls are progressively stricter for critical manufacturing steps compared to non-critical steps, aligning with the principle of increasing cGMP expectations for the final drug product administered to patients. Processes can only undergo validation once development is complete as a platform process with established variables and ranges.

Utilizing phase-appropriate materials, such as INDEdit gRNA during the preclinical stage, ensures alignment with FDA and EMA recommendations for IND-enabling studies while employing only essential QC tests required for IND approval. This strategy has the potential to significantly reduce costs leading up to IND filing during CRISPR therapy development.

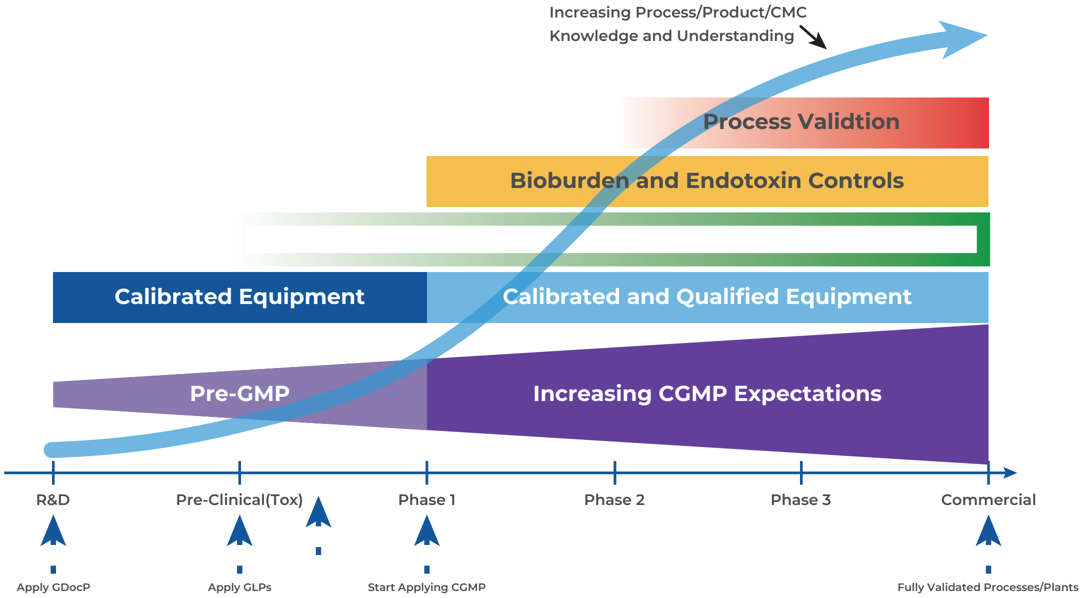


Figure 3. Implementation of cGMP and Quality Systems by Stage of Development

## Relentless Focus on Manufacturing Excellence

At GenScript, we are steadfast in delivering high-quality, cost-effective products on time while maintaining exceptional customer service. cGMP compliance, enabled by a robust QMS, plays a pivotal role in this pursuit. Delivering consistent quality relies on two essential factors: a robust process and a capable manufacturing and QC team to execute batches effectively.

Achieving clinical manufacturing excellence to improve product quality and reduce client cost is a multi-year journey, driven by iterative improvement cycles. Initiatives we have undertaken include:

1. Streamlined documentation: Simplified batch and QC records for clarity and efficiency, reducing data entry.
2. Standardized workflows: Optimized procedures using 5S methodology to increase efficiency and reduce preparation times.
3. Optimizing QMS forms and records: Redesigned Key Quality Management System elements for ease of use and faster issue resolution.
4. Cross-department collaboration: Coordination across R&D, QC, validation, supply chain, and QA for seamless process execution.
5. Incorporation of Lean principles: Performance indicators such as "right the first time," "on time/full delivery," and lead times track efficiency and inform improvement actions.

## Key Takeaway

GenScript supports CGT development across the supply chain, with teams dedicated to early discovery, clinical trials, and product commercialization. Through close collaboration with clients, GenScript aligns processes with therapy goals, affordability, and scalability. This iterative approach reduces GE component costs while addressing emerging needs in gene-edited therapeutic modalities, solidifying GenScript's position as a preferred upstream partner.

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