

Practical Recommendations for Accelerating Cell and Gene Therapies

INTRODUCTION

Cell and gene therapies (CGTs) have been in development since the 1980s. The first NIH-approved gene therapy procedure was successfully performed on September 14, 1990¹ on a four-year-old girl born with severe combined immunodeficiency (SCID). Today, cell and gene therapies are widely accepted as the next wave of therapeutic innovation in the life sciences industry and account for around 12% of the clinical and at least 16% of the preclinical pipeline². According to a 2022 HI report published by the Alliance for Regenerative Medicine (ARM)³, there are more than 1,300 companies globally focusing on CGTs and over 3,500 therapies in preclinical and clinical development.

The ARM report also mentions that 2,093 cell and gene therapy clinical trials were ongoing globally at the end of June 2022. Of those trials, cell therapies make up the largest category (968, 46%), followed by cell-based immuno-oncology (721, 34%) and gene therapies (372, 18%). Tissue-engineered therapies comprise the remaining 32 (2%). By region, North America leads with 808 active clinical trials, followed by Asia Pacific with 640 trials, Europe with 329, and 88 active trials in all other regions. Oncology and rare diseases are the top two therapeutic areas being targeted by CGTs. There are 22 gene therapies and 59 non-genetically modified cell therapies approved globally for clinical use⁴. The global cell and gene therapy market was estimated at \$2.6 billion in 2020 and is expected to grow at a compound annual growth rate of 33.82% to reach \$14 billion by 2027⁵.

The U.S. Food and Drug Administration (FDA) expects to receive more than 200 investigational new drug applications for CGTs and to approve 10 to 20 new cell and gene therapies per year⁶. In 2024 alone, up to 21 cell therapy launches and as many as 31 gene therapy launches are expected. Because of this anticipated increase in workload, the FDA has elevated and reorganized its Office of Tissues and Advanced Therapies (OTAT) to a “Super Office” within the Center of Biologics Research and Evaluation (CBER). Proposed structural changes will improve functional alignment, increase review capabilities, and enhance expertise on new cell and gene therapies.



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CELL AND GENE THERAPIES

Cell therapy is a type of therapeutic where live cells are delivered into patients to treat a disease. There are generally two approaches:

- 1. Autologous:** Cell product is manufactured using the patient's own cells.
- 2. Allogeneic:** Cell product is manufactured from cells obtained from voluntary donations, often from healthy individuals.

The most common type of cell therapy is blood transfusion, in which red blood cells, white blood cells, or platelets are transfused from a donor to a patient. Another common cell therapy is the transplantation of hematopoietic stem cells to treat a variety of blood cancers and hematologic conditions. CAR-T cell therapy is another popular cell therapy approved for certain types of B-cell malignancies such as acute lymphoblastic leukemia (ALL), chronic lymphocytic

leukemia (CLL), lymphoma, and multiple myeloma. In addition to CAR-T cells, the FDA currently lists chondrocytes, cord blood, dendritic cells (DCs), fibroblasts, keratinocytes, and thymus as approved cellular and tissue-based therapeutics.

Gene therapy involves the treatment of diseases by either replacing a disease-causing gene with a healthy copy, inactivating a disease-causing gene, or introducing a new or modified gene into the body to help treat a disease. There are two types of gene therapies:

- 1. In vivo gene therapy:** The gene is delivered directly into a patient. AAV-based gene therapy is an example of this therapy.
- 2. Ex vivo gene therapy:** Target cells are removed from a healthy donor/patient, genetically modified in vitro, and delivered into the patient (**FIGURE 1**).

FIGURE 1: Cell and Gene Therapy Product Journey

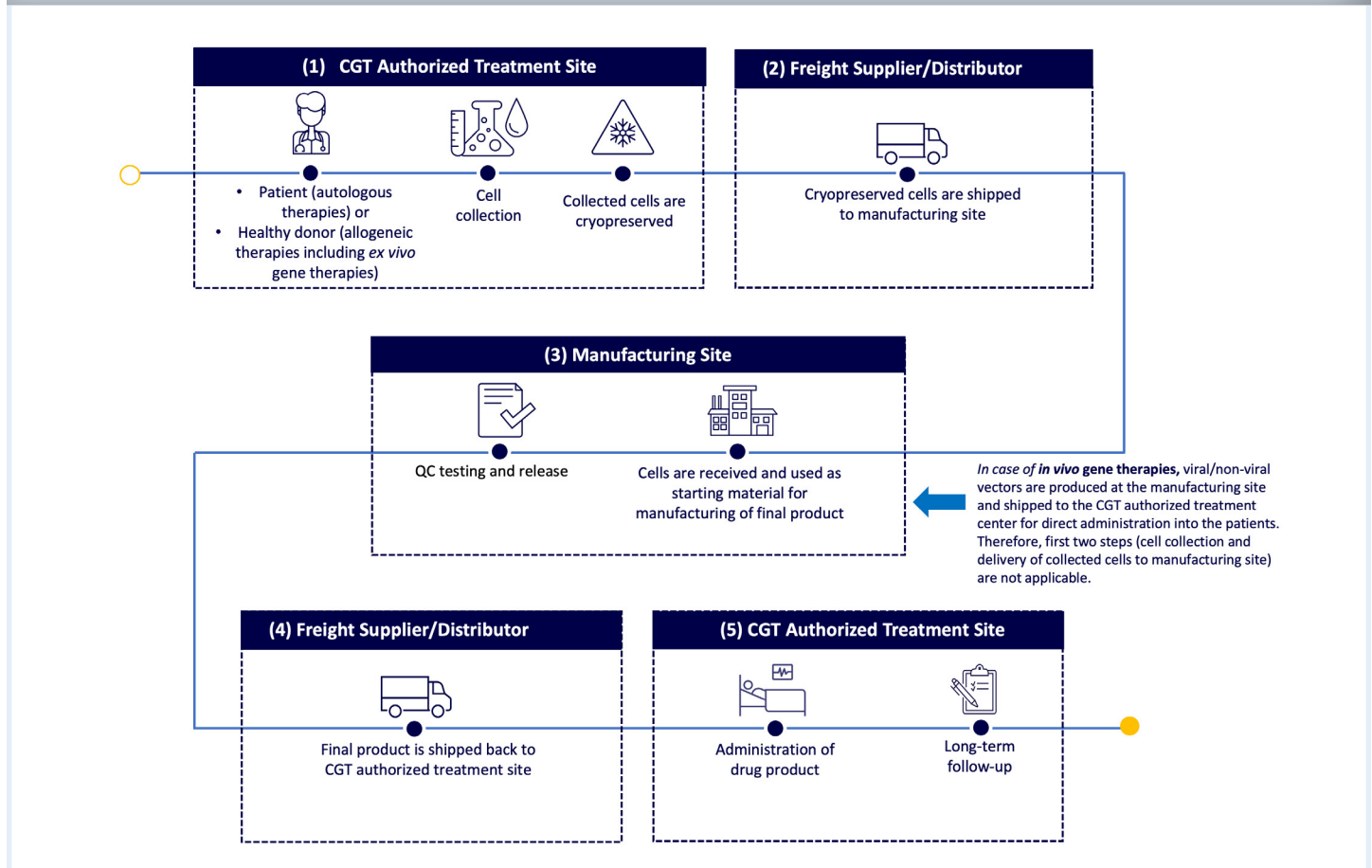








FIGURE 2: Differences between CAR-T Cell Therapy and Traditional Biopharma

	 Lead Time	 Raw Materials	 Scale	 Demand and Supply	 Cost	 Tracking and Tracing
Cell and Gene Therapy	<ul style="list-style-type: none"> • Demand/order-driven manufacturing • No inventory is maintained 	<ul style="list-style-type: none"> • Patient/donor starting material and viral/non-viral vectors • High variability 	<ul style="list-style-type: none"> • Customized • Difficult to scale 	<ul style="list-style-type: none"> • Inconsistent 	<ul style="list-style-type: none"> • Relatively higher cost • Payer reimbursement process is not streamlined 	<ul style="list-style-type: none"> • End-to-end tracking of chain of custody and chain of identity
Traditional Pharma	<ul style="list-style-type: none"> • Forecast-driven manufacturing • Order fulfilment from inventory 	<ul style="list-style-type: none"> • Standardized raw materials • Limited variability 	<ul style="list-style-type: none"> • Systematic • Economies of scale 	<ul style="list-style-type: none"> • Consistent 	<ul style="list-style-type: none"> • Relatively lower cost • Streamlined reimbursement process 	<ul style="list-style-type: none"> • Product serialization

Emergence of cell and gene therapies as a new pillar in medicine is leading the pharmaceutical industry to diversify from its earlier focus on small-molecule drug discovery and recombinant-protein therapeutics. There are however significant differences between cell and gene therapies and traditional biopharma (**FIGURE 2**).

SPEED TO MARKET CHALLENGES

Companies have made significant investments in R&D, preclinical, and clinical development of these exciting products and it's important that they are able to launch them in ways that maximize the number of patients who can benefit. Successful launches of these products would also ensure a sufficient return on companies' investments – thereby encouraging them to expand their CGT pipeline. However, while the industry has many successes to show for its decades of development, significant challenges remain that impede the velocity with which cell and gene therapies can be brought to the global market, including:

- Availability, lot-to-lot variability, and high cost of critical raw materials such as plasmids and viral vectors
- Process development/analytical development
- Supply chain, manufacturing, and distribution

- Complex clinical protocols, global regulatory requirements, patient recruitment, and availability of trained staff
- High cost of CGTs and lack of long-term efficacy and safety data making it necessary to develop innovative payment models

We see these challenges playing across three main areas – manufacturing, clinical trials and regulation, and pricing.

MANUFACTURING

Cell and gene technologies are currently outpacing the underlying enablers – such as supply chain, manufacturing, and distribution – needed to take them to the market. One of the biggest challenges in this area is the availability, lot-to-lot variability, and high cost of critical raw materials such as plasmids and viral vectors. There is not enough viral manufacturing capacity at an appropriate level of quality to satisfy the surging demand of the industry.

This has left viral production companies with complex allocation problems. They struggle to sort through which clients to satisfy, the forms and terms of contracts to accept and honor, and how to factor these industry-wide challenges into their continued investments in

manufacturing capacity. At the same time, these companies must also consider that given the rapid evolution of viral vector needs versus the complexities and approval timelines of commissioning new capacity they may be left with stranded assets.

We have seen in the past that with every new technology, the industry, government regulators, researchers, doctors, providers, payers, and patients are essentially constantly learning and making their processes more robust as they go. Cell and gene manufacturing is still somewhat of a niche industry. It is in its infancy and, as a result, is still very fragmented. Although there has been some consolidation, future strategic mergers, acquisitions, and partnerships across the industry will drive the scale and expertise required to service patients effectively with these lifesaving therapies. The next 5 years are critical for the establishment and growth of major players across the world and ensuring success of these therapies as mainstream and first-in-line treatment options.

There are already some standout companies in final product manufacturing, including Lonza, Catalent, Patheon, Wuxi Advanced Therapies and Charles River Laboratories. Millions of dollars have been invested in acquiring some of these manufacturers, which had small or negligible sales, primarily because these smaller players have platforms that can be leveraged by more established scale players. The private equity financiers welcome the idea of global platforms, which allows a drug-sponsor firm to partner with one group rather than having to negotiate different arrangements, contracting, and quality systems.

There are some solutions that might help solve for the manufacturing bottleneck. First though, it is important to understand the current process to better identify which solution might be the most viable.

For example, in the current configuration of the autologous CAR-T manufacturing process, T cells are isolated from a patient and shipped to a CAR-T manufacturing site where they are genetically engineered to express chimeric antigen receptor (CAR) on their surface. These engineered CAR-T cells are then expanded ex vivo and shipped back to the treatment site and infused into the same patient. This process typically takes 10-17 days.

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However, Novartis has developed a next-generation CAR-T manufacturing platform called T-Charge⁷ and is conducting phase I clinical trials with YTB323 (anti-CD19) and PHE885 (anti-BCMA) to evaluate the feasibility, safety, and preliminary antitumor efficacy of autologous CAR-T cells manufactured using this platform. In T-Charge, CAR-T cell expansion occurs primarily within the patient's body (in-vivo), eliminating the need for an extended culture time outside of the body (ex-vivo).

Expansion of CAR-T cells in vivo preserves T cell stemness (the ability to self-renew and mature), an important T cell characteristic closely tied to its therapeutic potential, which results in a product containing greater proliferative potential and fewer exhausted T cells. The T-Charge platform aims to revolutionize CAR-T cell therapy by reducing manufacturing time and cost while improving clinical outcomes (such as safety and efficacy) compared to traditional CAR-T.

A similar platform known as FasTCAR is being developed by Gracell Biotechnologies⁸. This platform offers several advantages such as shorter manufacturing times, improved production quality, reduced cost, and expanded access and enhanced T cell fitness.

Several companies, including Solaris Biotech and Ori Biotech, are investing in automation to increase efficiency. As part of the current system, expensive, sophisticated equipment is used for just one patient at a time. Cells need to mature or expand before the next

patient's cells can be introduced to the clean room. This idle time contributes to the exorbitant cost of cell and gene therapies.

Another cost contributor is people, as technicians must undergo special training to operate in a highly controlled, regulated environment. Supplanting this model with automated equipment could make a difference. Machines can run longer, and they can be controlled and monitored from outside the clean room. The future should include a combination of increased automation and reduced staff costs. Many investors are interested in automation, because they are attracted to the idea of betting on a piece of equipment that can be applied to various solutions rather than a single therapy.

CLINICAL TRIALS AND REGULATION

Challenges in clinical development should be examined not just from the point of view of the safety and efficacy evidence required to get a drug product approved, but also in the context of an evolving technical landscape that poses challenges to regulators. Global regulatory agencies have recognized that CGTs require new approval processes, as well as scientific and regulatory expertise, housed within the agencies to help guide them.

Recognizing the challenges of developing complex, multi-component biologic drug products, including unanticipated risks associated with on-target and off-target activities, the FDA's CBER updated its guidance agenda in June 2022. These documents describe the FDA's recommendations for preclinical and clinical testing; chemistry, manufacturing, and controls (CMC); and information that should be included in investigational new drug (IND) applications to ensure proper identity, potency/strength, quality, and purity of the investigational drug products.

The FDA recommends early communication between sponsors of such products and OTAT in CBER during early product development prior to IND submission to discuss the product-specific considerations in preparation for transitioning to the clinical phase.

Working towards global convergence on CGT regulatory expectations, and ultimately regulatory harmonization, will benefit patients in all regions of the world by helping to facilitate access to

The Many Angles of CGT Regulation

The FDA and other regulatory bodies will need to reshape their traditional structures and processes to effectively regulate cell and gene therapies. It's a multi-faceted challenge, with key considerations including:

- **CAR-T cell design and development** – This includes vector design (for example, non-integrating or integrating vectors), the risks associated with delayed adverse events of vectors, the impact of other functional elements included in vectors on safety and efficacy, starting cellular materials, and quality controls for fresh or cryopreserved products.
- **Vector manufacturing and testing** – This includes the collection, handling, and testing of cellular starting materials, in-process testing at relevant time points, and CAR-T cell analytical testing.
- **Safety and activity testing of the vector and cellular component(s) of CAR-T cells** – This would also include in vivo testing (which may involve use of animal models in proof-of-concept studies to assess functionality), in vitro and in vivo testing for T cell clonality, karyotypic analysis, specificity for antigens, on target/off target toxicities, and cytotoxicity testing.
- **Myriad plans and approaches** – This includes tissue agnostic approaches, target identification, treatment plans, the impact of variations in transduction efficiency on dose calculation, a staggered treatment approach to limit the number of subjects exposed to unanticipated risks, contingency plans for manufacturing delay or failure, clinical pharmacology considerations, safety evaluation, clinical monitoring, toxicity grading, and long-term follow up, etc.

these potentially transformative products, which are among the most advanced medical products available. Harmonization is the key to support timely product development and access, in part, because it allows product developers to submit regulatory applications more efficiently and cost-effectively across different jurisdictions.

The European Medicines Agency (EMA) and the FDA should have a consensus on standards. For the European market, this would open access to a US market that is double its size. For the US, it would expand its market by another 50%. The good news is that the FDA is investing

significantly more resources into cell and gene therapies, which will help. Harmonization across regulators will facilitate CGT approvals across major markets and reduce instances such as GenSight's eyesight saving Lumevoq being approved in France, but not in the US.

A clear regulatory pathway affects the entire lifecycle: A scientist should be able to generate an idea and then have a reasonably predictable way to develop it. This would also help investors know how to finance it and help operators know how to implement it. If clinical development is thought of as generating a body of evidence to prove or disprove a hypothesis related to the efficacy mechanism with appropriate tests for toxicity and safety, the public – being represented by the regulators – have an interest in understanding the trials and how they meet or do not meet standards, which vary by country. Clinical development and the regulatory environment cannot be separated.

It's also important for companies to be prepared to strategically scale up manufacturing at the time of IND submission. A company can conduct clinical trials with or without the help of a partner CDMO or CMO. Once the product is approved and is in pre-registration, a company must make a key strategic decision: whether to take on in-house manufacturing, a hybrid approach, or to rely on a CDMO/CMO.

PRICING

Next-generation therapies offer the hope of durable and curative one-time treatments. If they can replace a lifetime of expensive maintenance treatments this may lead to cost savings in the long run. Yet, the high upfront costs, uncertainty surrounding long-term durability, and adverse events have led to some concerns among payers and regulators. A health plan, for example, would be apprehensive about paying for a multimillion-dollar therapy if there is no guarantee that the disease won't resurface several years after the treatment. It is therefore crucial to develop and implement innovative, outcomes-based payment models that provide profitability for the developer and therefore encourage them to invest in expanding their operations and pipeline while maintaining affordability for the patient and the system at large.

All stakeholders in the cell and gene therapy ecosystem need to come together to develop industry standards for measuring benefits and outcomes like productivity gains, improved quality of life, and the

avoidance of additional medical expenditure. The industry should collaborate with health economists and payers to help design and conduct real-world evidence (RWE) studies, scrutinize the data, and help define the lifetime value of a therapy. Cell and gene companies also play a vital role in this; they need to identify what types of data will demonstrate the value and effectiveness of a therapy and how that data can be collected.

Setting and negotiating a price for these treatments can be challenging. Conducting a pharmacoeconomic analysis as to the benefit of the treatment versus the cost of ongoing care and a decreased quality of life – maybe a shortened life – can't alone justify the million-dollar price tags. Some regulators have approved this because at this point there is a low level of administration, so the global numbers are not significant. However, this is on a collision course as these therapies become more accepted and run into the billions.

There needs to be an effective way to reduce the cost of treatment, including increased automation and streamlined regulations.

There needs to be an effective way to reduce the cost of treatment, including increased automation and streamlined regulations. The industry also needs to invest more in public relations, because the current message is that these are exorbitantly expensive treatments. Companies need to explain why the prices make sense and are reasonable. The industry could gain support from communicating the lifetime benefits of these therapies, especially once there is a track record.

With clearer regulatory pathways, more straightforward clinical trials, and a production environment that is more cost effective, many anticipate that the costs of development and treatment will eventually reduce. Still, the developers of these therapies will need to look at alternate models for payment.

For example, the high cost could be distributed over the course of the expected life of the patient. However, this model could get complicated in a fragmented private-payer environment like in the US, where significant churn leads to situations in which a private payer may pay for the cost of an expensive therapy today, only for the benefits of future medical treatment avoidance to accrue to another private payer if the patient subsequently changes insurance carriers.

This is less of an issue with countries that have a universal payer, which may explain why CGT therapies are often approved for reimbursement in ex-US jurisdictions. Other options exist in addition to universal payer models. These include an equated monthly installment (EMI) approach and a discount approach, where if there is insufficient response to cell therapy, a discount is provided based on the level of efficacy achieved. Whether it's government intervention for societal good or whether the cost of the patient travels with them from payer to payer, alternate payment models are necessary for the continued market success of CGTs.

Market success also requires investing in data. Alternative payment models and various forms of contracting will require longitudinal tracking to show that the therapies work. As a result, registries – and the ability to combine electronic data capture (EDC) data with electronic medical record (EMR) data – will be needed. Stakeholders in the cell and gene therapy ecosystem need to collaborate with health economists to understand how to gather and share data, as there needs to be enough data to demonstrate the value and effectiveness of the therapies.

Unfortunately, there is a current lack of evidence and transparency in data gathering that needs to be addressed. People are not sharing enough data about the strategies to gather real-world evidence. Convincing data, combined with the power of artificial intelligence, will aid the ability to offer outcomes-based contracting.

CONCLUSION

Cell and gene therapies are positive disruptors of the biopharma industry. We are expecting 10-20 new CGT approvals every year. This means that the industry must be fully prepared to launch them successfully. Successful launches will benefit patients, healthcare providers, and the companies that develop and distribute them. It is imperative that the product, the company, and the market are fully prepared to commercialize these next-generation therapies.

Today, we are on the cusp of solutioning many of the problems that have held back development and adoption of cell and gene therapies. Our considerations above reflect on the many approaches that have been tried over these previous 3 decades and picks on themes that we now know can work, and when incorporated into practice will unleash the promise and the power of durable and curative cell and gene therapies.

REFERENCES

1. Anderson WF. (1990). September 14, 1990: the beginning. *Hum Gene Ther* 1:371-372. <https://www.liebertpub.com/doi/10.1089/hum.1990.1.4-371>
2. Pharmaprojects. Informa. (2022). <https://pharmaintelligence.informa.com/products-and-services/clinical-planning/pharmaprojects>
3. Regenerative Medicine: The Pipeline Momentum Builds. (2022). Alliance for Regenerative Medicine. HI 2022 Report. <https://alliancerm.org/sector-report/hi-2022-report/>
4. American Society of Gene and Cell Therapy, Citeline. (2022). Gene, Cell, & RNA Therapy Landscape Q3 2022 Report. <https://asgct.org/global/documents/asgct-citeline-q3-2022-report.aspx>
5. Global Cell and Gene Therapy Market, Analysis and Forecast, 2021-2027. (2021). BIS Research. <https://bisresearch.com/industry-report/global-cell-gene-therapy-market.html>
6. Hale C. (2019). FDA planning new guidance, hires in cell and gene therapies for 2019. Fierce Pharma, January 2019. <https://www.fiercebitech.com/biotech/fda-planning-new-guidance-hires-cell-and-gene-therapies-for-2019>
7. Charging towards the next-generation of CAR-T. (2022). <https://www.novartis.com/research-development/technology-platforms/cell-therapy/charging-towards-next-generation-car-t>
8. FastTCAR. Our Autologous Platform. (2021). Gracell Bio, <https://www.gracellbio.com/fastcar/>