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Cell and gene therapy on the ascent

Transformative biopharma space primed for investments

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Contents

Executive summary

The cell and gene therapy (CGT) sector has seen unprecedented growth, emerging as a transformative force in disease treatment. With around 2,960 drug candidates in the pipeline and more than 40 products already in the market (see *List of marketed CGT drugs, Page 23*), the industry is at a point of inflection following extensive innovation and clinical progress in recent years.

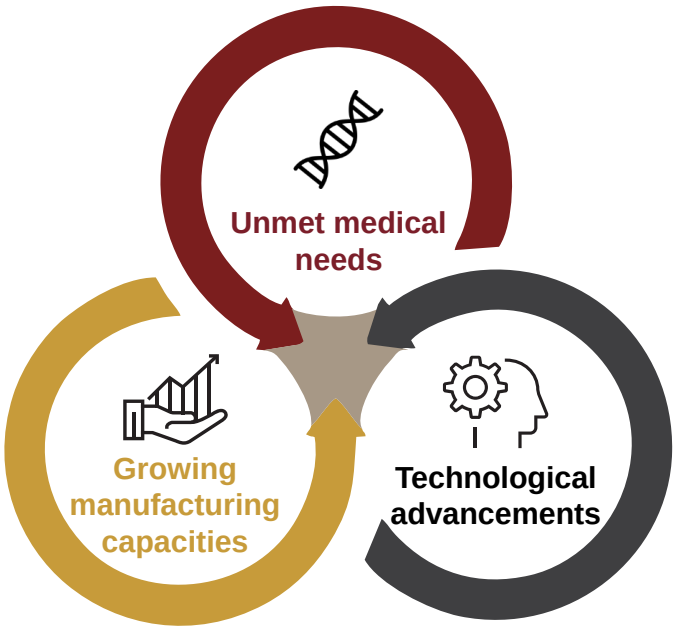
This paper offers institutional investors key considerations and spotlights opportunities and risks in the space.

Huge growth potential backed by unmet medical needs and technological advancements

The global CGT market size was valued at $18 billion in 2023 and is projected to reach ~$97 billion by 2033, translating to a compound annual growth rate (CAGR) of 18%[1].

That's significantly higher than the CAGR of 8.2% the biopharma market is expected to log between 2023 and 2032[2]. CGT drug approvals in 2024 are expected to rise to double digits from six in 2023.

- **Unmet medical needs**: Rare diseases currently afflict 300 million people worldwide and 30 million people in the US alone, but 95% of these diseases lack Food and Drug Administration (FDA)-approved treatment. With eight of 10 rare diseases having a genetic origin, it becomes evident that effective treatments are vital for the well-being of patients. Notably, 21% of CGT sales between 2021 and 2028 were from the treatment of rare genetic disorders[3]
- **Technological advancements**:
  - Gene editing advancements, such as CRISPR-Cas9, hold immense potential for developing better CGT. Biopharma companies are actively leveraging these technologies and applications that offer promising avenues for safer and more effective treatments in the future
  - Emerging advancements in the field include novel nucleic acid formats, innovative techniques for viral biosynthesis, non-viral gene therapy delivery methods, specialised equipment, such as cell therapy manufacturing units (good manufacturing practice boxes or GMP boxes), microfluidics-based or encapsulation-enhanced cell culture systems, *in vivo* cell therapy approaches, non-chromatographic separation technologies, advanced GMP-compliant cell sorting methods and state-of-the-art optical tools for nanoscale analytics



- **Surging manufacturing capacities**: The manufacturing landscape for CGT is diverse and poses challenges, such as complexity, scalability and cost. But contract development and manufacturing organisations (CDMOs) are sharpening focussing on these and expanding capabilities, which should drive growth. CDMOs also offer process and assay development, cell therapy production and testing services, which help the market evolve. Collaborative strategies between CDMOs, biopharma companies and life sciences supply-chain are vital to optimise CGT manufacturing and delivery. On their part, regulators, are streamlining processes around manufacturing to improve accessibility and affordability of treatments. The US FDA and the UK Medicines and

Healthcare products Regulatory Agency (MHRA) are leading the push for distributed manufacturing for efficient delivery. The FDA's 'Advanced Manufacturing Technologies (AMT) Designation Program' guidance issued in 2023 aims to streamline regulatory pathways for innovative manufacturing technologies

- **Momentum in the pipeline**: There are 2,960 CGT clinical trials in progress across various stages, with gene therapies constituting 32% of the pipeline and cell therapies accounting for the rest[4]. Despite a lower success rate, the high number of active CGT trials indicates continued research activity and industry support. The regulatory environment is also becoming more supportive, with the FDA exploring ways to accelerate the development of gene therapies for rare diseases and streamlining the approval process for CGT drugs. The Bespoke Gene Therapy Consortium has been established to develop standards and protocols for gene therapy development and the FDA is supportive of using accelerated approval pathways for gene editing products and expanding this programme to all CGTs. These developments suggest a potential future with diverse treatment options for various diseases

Market promising for investors, buzzes with deal activities

The rise in the number of new CGT companies creates opportunities for private investors to deploy capital. The appetite from large biopharma companies to acquire or partner with CGT companies in the research and development (R&D) phase and the good reception for primary offerings of CGT companies provide an exit for private investors. As for public investors, new listings allow them to invest capital as the CGT market is still in its nascence and investors stand to gain over the long term as productisation accelerates.

The CGT sector has seen consistent deal activity in recent years, with a growing proportion of all life sciences deals. While deal activity across other segments in the past two years has eased, CGT deals haven't as much, indicating increasing confidence and interest in these modalities (see *CGT attracts increasing proportion of all life sciences deals, Page 16*). Private investments in CGT companies have risen over the past decade, including first-round investments that indicate a surge in the launch of new companies, and larger companies are partnering with or acquiring early-stage CGT leaders. These emerging companies are poised to drive growth in clinical trials, FDA approvals and public offerings, solidifying their role in shaping the future of the CGT industry.

Long-term outlook buoyant despite near-term challenges

The development of CGT market is hindered by stringent regulatory oversight, insufficient infrastructure support, high business complexity, lack of awareness and affordability and access challenges. But regulators' willingness to streamline the process, investments channelled towards manufacturing capacities and novel patient access models are some of the measures that can help overcome these near-term challenges.

Over the long term, the CGT market holds potential for multiple stakeholders to grow. For investors, it provides a great investment opportunity with an estimated market size of ~$97 billion by 2033, growing at a CAGR of 18% — significantly faster than the biopharma sector.

The biopharma industry can tap large unmet medical needs with the help of evolving regulator support for streamlining development process and by collaborating with downstream supply chain for efficient delivery. For the larger economy, CGT therapies can save long-term healthcare costs by improving patient outcomes and boosting economic activity with innovations and investments in the field and downstream supply chain.

Background

The first wave of innovation of small molecule drugs dates to the 19th century when chemical, synthetic pharmaceutical drugs were discovered.

Aspirin, known as the 'wonder drug' for its myriad uses till date, is one of the earliest small molecule drugs discovered by Bayer AG in 1899, which gave an impetus to the development of modern medicine.

Though biological drugs were discovered in the early 1920s marked by animal-based insulin, it was only in the 1980s that the second wave of innovation took place with the approval and usage of human insulin. This was followed by the discovery of antibodies to treat cancer and other rare diseases. Biological drugs are derived from living sources, such as humans, animals, plants or microorganisms, placing it higher in the complexity chain, compared with small molecule drugs.

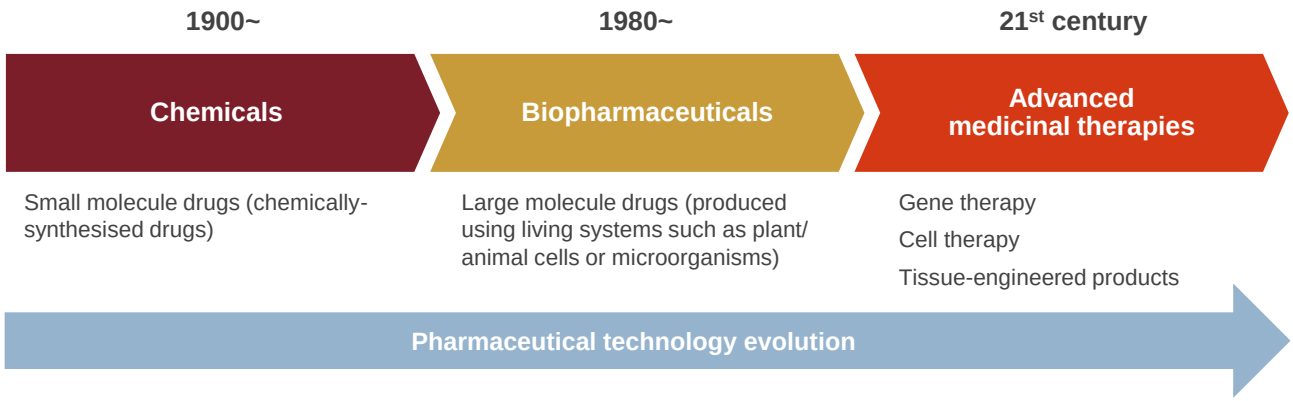
As of 2023, seven of the top 10 global best-selling drugs were biologics, highlighting the advancements and benefits of such drugs.

Elevating to the complexity of treatment, we are now in the nascent stages of the third wave of innovation with the approval and usage of CGTs, which is the next generation of biological medicine that can offer patients a transformational clinical benefit and significantly improve their quality of life by targeting the underlying cause of a genetic disease rather than simply managing symptoms.

- **Gene therapy:** Introduces or modifies genetic material to treat diseases caused by genetic mutations or deficiencies. Examples include gene therapy for cystic fibrosis and haemophilia
- **Non-genetically modified cell therapy:** Involves the manipulation or transfer of living cells for therapeutic purposes. Examples include stem cell therapy for blood disorders
- **Genetically modified cell therapy:** Cells are genetically manipulated to fix the faulty elements of DNA within the gene. Examples include chimeric antigen receptor (CAR)-T cell therapy for cancer

CGT can be further categorised into *ex vivo* (cells or genes manipulated outside the body) and *in vivo* (cells or genes manipulated within the body) approaches.

The concept of CGT dates to the early 20th century with bone marrow transplantation considered as the first form of cell therapy. Since then, significant strides have been made in CGT, especially with the approval of treatment for leukaemia in 2017, marking a new era to treat cancer, resulting in its establishment as a standard therapy. Similarly, the first successful gene therapy trial was conducted in 1990 for severe combined immunodeficiency (SCID). Technologies have progressed extensively in vectors, targeting strategies and manufacturing processes and gene editing. For example, clustered regularly interspaced short palindromic repeats and CRISPR-associated protein 9 (CRISPR)-Cas9 have fuelled the growth of CGT research and development (R&D) in recent years.

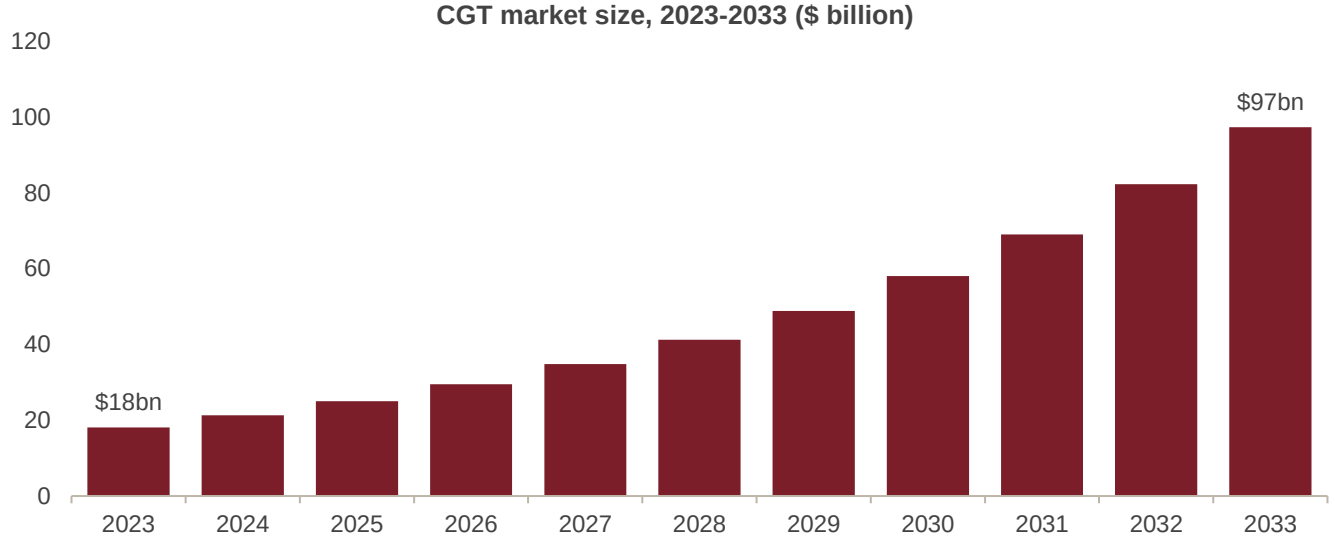



The CGT market is set on a growth trajectory, driven by extensive technological advancements, huge unmet need for cancer and other genetic diseases and partnerships between biopharma companies and CDMOs

Huge growth potential backed by unmet medical needs

Huge unmet needs and growing prevalence of cancer and other genetic disorders are augmenting the demand for CGT worldwide and has driven significant growth in the CGT market over the past five years. Although there are varying and wide-ranging estimates for the market size, we believe the market to be valued at ~$97 billion by 2033, registering a CAGR of 18% from 2023. There have been extensive innovations and clinical progress in the CGT market in the recent years and we are at an inflexion point with total CGT drug approvals in 2024 expected to rise to double digits from six in 2023.

CGT market size, 2023-2033 ($ billion)



Source: Nova One Advisor estimates

- **Delivery chain catches up to drive wider adoption of CGT:** Beyond clinical innovation in developing and manufacturing drugs, the delivery of these drugs to the patients also plays a key role in the adoption of CGT drugs as these are highly specialised and need proper handling in every step of delivery. However, the delivery chain is slowly catching up with the pace of clinical innovation and collaborations and innovations in the supply chain, increasing the adoption of CGT drugs by physicians. Payers experimenting for an optimised reimbursement model are making the environment conducive for the wider adoption of CGT driving the growth of the market.

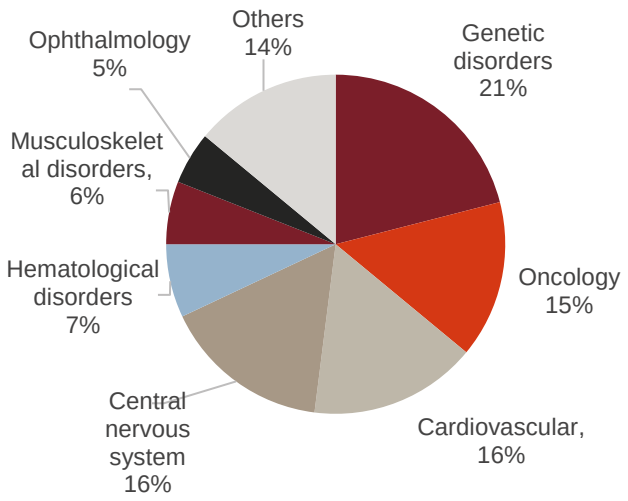
Rare genetic disorders seen key driver of CGT drug sales

Currently, rare diseases afflict 300 million people globally and 30 million people in the US alone. However, 95% of these diseases lacked FDA-approved treatment as of January 2023. For example, in Europe, a rare disease is defined as one affecting fewer than five in 10,000 people, while in the US, such a disease impacts lesser than 200,000 people. With eight of 10 rare diseases having a genetic origin, it becomes evident that effective treatments, rather than preventive measures, are of vital importance for the well-being of patients. Notably, 21% of CGT sales between 2021 and 2028 were from the treatment of rare genetic disorders.

Few prominent examples of treating rare genetic disorders are:

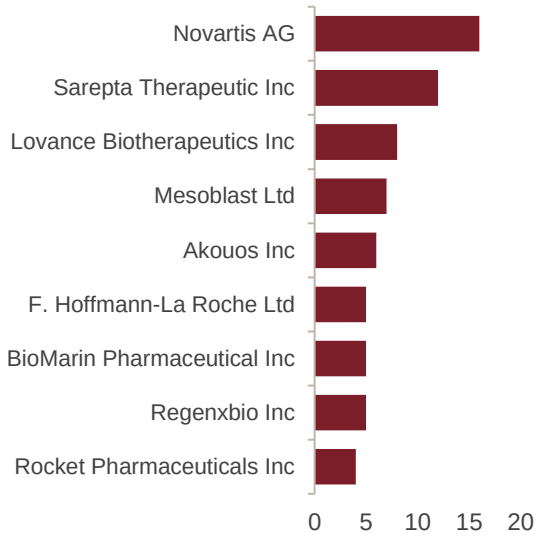
- Novartis has a leading gene therapy portfolio with approved treatments for spinal muscular atrophy and blindness. They are also developing gene therapies for other conditions such as neurofibromatosis and sickle cell disease
- Sarepta Therapeutics is currently marketing Elevidys, the first gene therapy to treat Duchenne Muscular Dystrophy, with more in the pipeline

Therapeutic share of projected CGT drug sales, 2021-2028



Source: GlobalData estimates

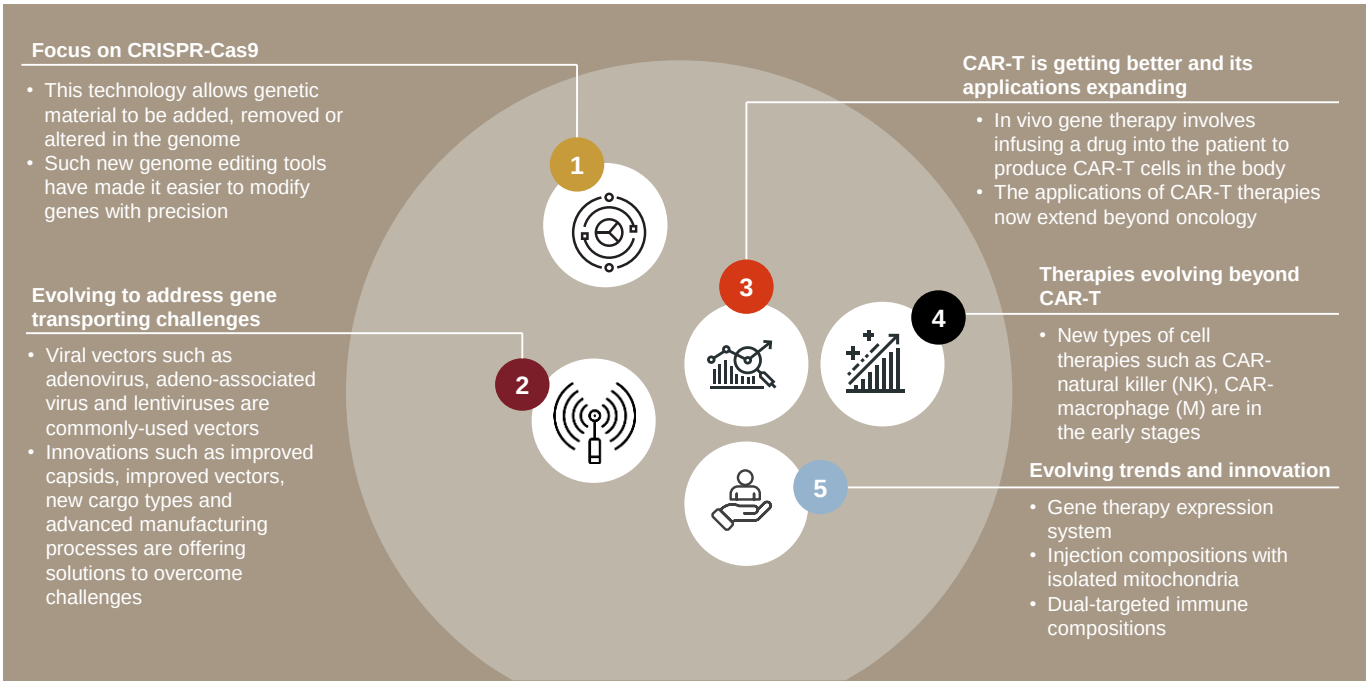
Companies by projected CGT drug sales 2021-2028 ($ billion)



Source: GlobalData estimates

Technological advancements underscore future growth potential

The next five years mark a pivotal period for CGT as it is set to integrate technological innovations, strategic collaborations and significant transformations in drug discovery, manufacturing and distribution.



A. Advancement of gene editing and transport technologies

CRISPR-Cas9, a breakthrough innovation in gene editing: Genome editing (also called gene editing) is a group of technologies that enable scientists to change an organism's DNA. These technologies allow genetic material to be added, removed or altered at specific locations in the genome. Several approaches to genome editing have been developed, among which CRISPR-Cas9 is a well-known one. The CRISPR-Cas9 system has generated a lot of excitement in the scientific community because it is faster, cheaper, more accurate and efficient than other \methods. The development of such new gene editing tools has made it easier to modify genes with precision that could lead to the development of more effective CGT.

CRISPR-Cas9 has transformed genome editing, but has drawbacks such as off-target effects (DNA double-strand breaks at target genomic loci, the requirement to include a donor DNA molecule and activation of DNA repair mechanisms), leading to the development of alternative technologies such as:

- **Base editing:** Enables precise DNA base pair conversions without double-strand breaks, reducing off-target effects
- **Prime editing:** Combines CRISPR-Cas9 with reverse transcriptase for direct genetic modifications with minimal off-target effects
- **RNA editing:** Allows direct modification of RNA molecules, offering temporary changes in gene expression without altering DNA

Innovative solutions evolve to address gene transporting challenges: Vectors have the ability to deliver the modified or healthy gene into target cells in the human body. Adenovirus, adeno-associated virus and lentiviruses are commonly used vectors but pose challenges, such as immunogenicity, large dosage requirement and optimal transgene expression. Innovations such as improved capsids and vectors, new cargo types, advanced manufacturing processes and enhanced pretreatment and conditioning regimens are offering solutions to overcome these challenges. Beyond these, non-viral vector delivery systems, including lipid

nanoparticle delivery, have emerged as a viable alternative to viral vectors and offer the benefits of low immunogenicity and easy production. They promise delivery of gene therapies, particularly for diseases where sustained expression is not necessary or immune responses to viral vectors are a concern.

B. Advancements in cell therapies — CAR-T and beyond

CAR-T is getting better, with its applications extending beyond oncology: Existing CAR-T cell therapies are *ex vivo* where white blood cells from patients are taken to the laboratory where the T cells are altered by adding a gene for CAR and are multiplied before infused back to the patient. Scientists are now working to make this process *in vivo* where the drug is infused to the patient for CAR-T cells to be produced within the body. This method can potentially solve challenges, such as logistics, waiting time, need for chemotherapy and complex manufacturing process involved in *ex vivo* therapies. Among the large biopharma players, Astellas has recently inked a research collaboration deal worth $800 million with Kelonia to develop off-the-shelf *in vivo* CAR-T cell therapies. With technological advancements, applications of CAR-T therapies are also extending beyond oncology and being studied as a potential treatment for cardiovascular and neurological disorders.

Cell therapies evolve beyond CAR-T: Owing to the success of CAR-T therapies, researchers are studying the CAR engineering method to modify other types of immune cells and experimenting with new types of cell therapies, such as CAR-natural killer (NK), CAR-macrophage (M), CAR-γδT, and CAR-natural killer T (NKT). Though these studies are at their early stages, increasing number of clinical trials involving these methods indicates the potential in this mechanism of actions. Additionally, tumour-infiltrating lymphocyte (TIL) therapy, engineered T-cell receptor engineered T-cell therapy (TCR-T) are two other prominent cell therapy mechanisms that are promising.

C. Other technological advancements

- **Gene therapy expression system:** Alleviates cardiac toxicity while expressing proteins in skeletal muscles, making heart-safe gene therapy possible
- **Injection compositions with isolated mitochondria:** Enhance stability and prevent blood clots, potentially treating mitochondria-related diseases
- **Dual targeted immune regulating compositions:** Modulate cell activity to treat autoimmune disorders and cancers
- **Compositions and methods for enhancing donor oligonucleotide-based gene editing**: Modify genomes at higher frequencies, enabling safer and more effective treatments

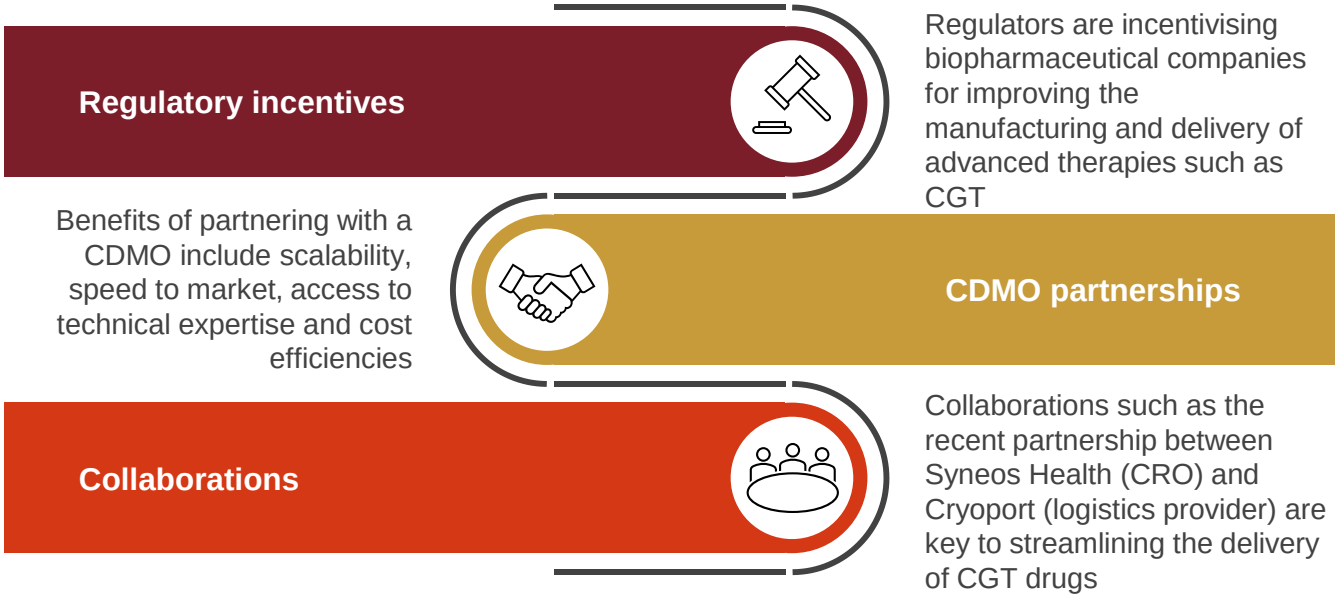
We note several groundbreaking treatments and therapeutic advancements that are driving CGT segment through a transformative journey. Novel developments, including nucleic acid formats and viral biosynthesis techniques, non-viral gene therapy ‘printers,’ cell therapy ‘GMP boxes,’ microfluidics or encapsulation-based cell culture, *in vivo* cell therapy, non-chromatographic separations, advanced GMP cell sorting and cutting-edge optical methods for nanoscale analytics are among the advancements on the horizon.

In the coming years, the industry is poised to produce a multitude of drug candidates for clinical trials, with the aspiration of introducing numerous drugs on a significantly amplified scale. Achieving this ambitious goal demands crucial enhancements in both the quality and productivity of the processes involved.

Surging manufacturing capacities complement clinical innovation

CGT manufacturing has a diverse landscape and has its own set of challenges, be it complexity, scalability or cost. Gene therapy dominates majority of CDMO's focus, closely followed by expanding cell therapy and viral vector-based technologies, owing to the rise of CDMOs and strategic collaborations among biopharma companies, CDMOs and life science supply chain players.

Notable growth in cell therapy and viral vector technologies are driven by advancements in CAR-T cell therapies and gene editing methods. The CDMOs' participation in the evolution of CGT market is expected to soar in the coming years, in the form of R&D support and manufacturing capabilities to the biopharma companies, making it a win-win proposition for CDMOs and biopharma companies and ultimately driving the growth of the market.



Regulators incentivise for better and efficient manufacture and delivery of advanced therapies

We note that decentralised manufacturing (or *distributed manufacturing* or *point of care manufacturing*) models are emerging to improve accessibility and affordability of treatment. However, strategic collaborations remain key to navigating this complex landscape. The US FDA and UK MHRA are leading a regulatory push for distributed manufacturing in the biopharmaceutical industry, recognising its potential to improve accessibility and affordability to advanced therapies, such as CGT. This concerted effort reflects a vital shift in approach, aimed at fostering innovation and efficiency while ensuring the highest standards of safety and efficacy.

Concurrently, the FDA's release of the AMT designation programme guidance in 2023 further signifies the regulator's commitment to streamlining regulatory pathways for innovative manufacturing technologies that vastly improves the quality and efficiency of manufacturing process. This guidance outlines the framework for manufacturers to obtain the AMT designation, offering details on eligibility criteria, the application process and associated benefits. Upon securing the AMT designation, drug sponsors get the benefit of enhanced interaction with the FDA through drug development to application submission phase and prioritised review of the submitted application. Together, these initiatives underscore the regulator's dedication to adapt regulatory frameworks to accommodate emerging manufacturing models, ultimately advancing a more agile and patient-centric approach to drug development and delivery in the biopharmaceutical sector.

CDMOs play a key role in the evolution of CGT market

- CDMOs offer a range of services, including process development, assay development, cell therapy production and testing. The pressure for innovation and optimisation in manufacturing incentivises CGT biopharma companies to seek third-party partners with technical, manufacturing and regulatory expertise
- Benefits of partnering CDMOs include scalability, speed to market, access to technical expertise without overhead costs, and cost efficiencies
- Geographically, the distribution of CDMOs varies, with concentration in North America, Europe and Asia. Their presence in emerging regions such as China and India is rising, offering cost-competitive alternatives to manufacturers

With large CGT biopharma companies increasingly engaging with CDMOs, investor enthusiasm toward the latter has increased with new investments in the sector. This has helped CDMOs build capacities, which is a win-win proposition for the biopharma and CDMO industry.

Collaborative strategies for optimising CGT manufacturing and delivery are vital

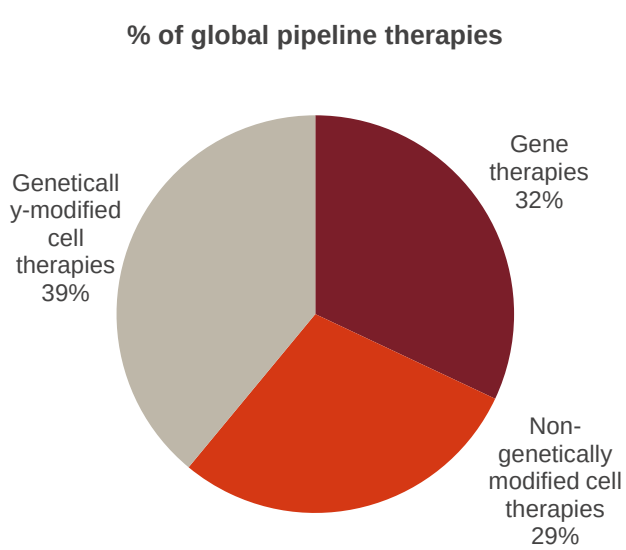
The rising demand for CGT puts pressure on biopharma companies and CDMOs to streamline their manufacturing and delivery processes.

- Galapagos, a biopharma company developing CAR-T therapies, has tied up with Blood Centres of America, one of the largest blood supply networks in the US; the latter will provide decentralised manufacturing services for Galapagos' CAR-T candidates. Such a tie-up helps take manufacturing closer to the treatment centres and helps efficient and quicker delivery. This is an example of how autologous therapies manufacturing are going to evolve, optimising the manufacturing and delivery process and thus reducing cost
- Collaboration between Syneos Health, a CRO, and Cryoport, a life science-focused logistics solution provider, is another example of partnership in streamlining the drug delivery process, bringing together specialised skills and resources to overcome challenges. This integrated approach combines supply chain management with biopharmaceutical solutions, enabling faster development and delivery of treatments. Such partnerships support CGT advancement, offering a fully integrated solution for the industry

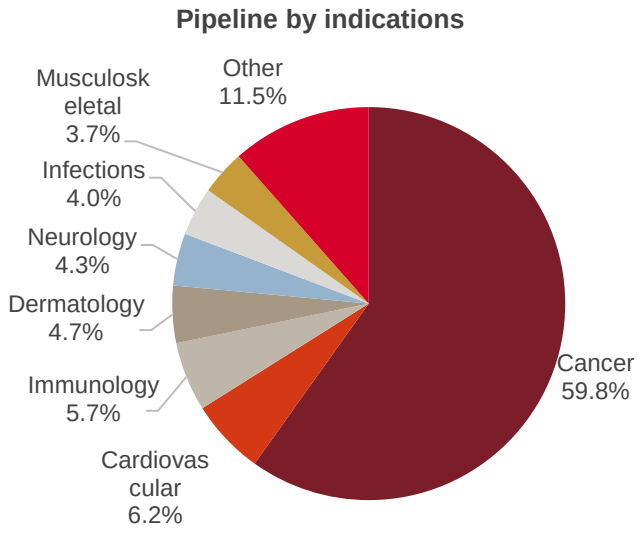
Healthy pipeline propelled by regulatory support

With ~ 2,960 CGT trials under way, the pipeline is thriving

A whopping 2,960-plus (as of December 2023) CGT clinical trials are in progress across the preclinical, clinical and pre-registration stages. Genetically modified cell therapies lead the pack with a 39% share of the pipeline (from the preclinical to preregistration phase), followed by gene therapies (32%) and non-genetically modified cell therapies (29%). Though CGT candidates in trials make up only a fraction of all clinical trials, the extensive CGT pipeline and the growing proportion of CGT drugs among marketing approvals indicate a vibrant and growing CGT field, suggesting a future with diverse treatment options for various diseases.

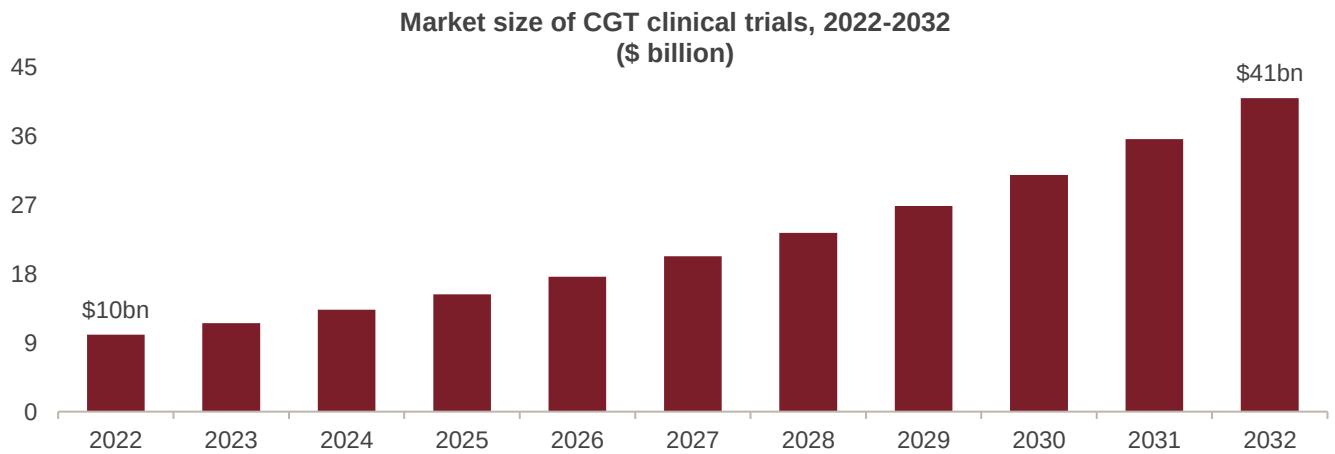


Source: Pharmaprojects | Citeline, December 2023



Source: Evaluate Pharma, RSM US

To understand the future growth trajectory of the CGT pipeline, we looked at the CGT clinical trials market as a proxy. The CGT clinical trials market, which was estimated to be $12 billion in 2023, is projected to grow at 15% till 2032, reaching a potential market size of $41 billion[5]. This indicates healthy growth in the CGT pipeline, ultimately leading to potential growth in the number of CGT drug approvals.



Source: Precedence Research estimates

R&D investments continue despite low success rate, underscore high risk-reward proposition

According to data compiled by Evaluate Pharma, the median duration from Phase 1 trials to regulatory approval for drugs stands at nine years. This extends notably for all CGT trials. Presently, CGT drugs exhibit a relatively low clinical success rate, with only 14% of Phase 2 candidates progressing to marketing approval. Despite this lower rate, the significant volume of ongoing CGT trials underscores sustained research efforts and industry backing. Advancements in technology offer the potential for companies to forecast the success rates of clinical candidates during early development stages, fostering heightened research and development efficiency and improved success rates.

Regulatory support will only make CGT space attractive for investment

FDA is exploring the regulatory support in its ambit that can propel the development of CGTs and bring newer treatments to the market that can address unmet medical needs.

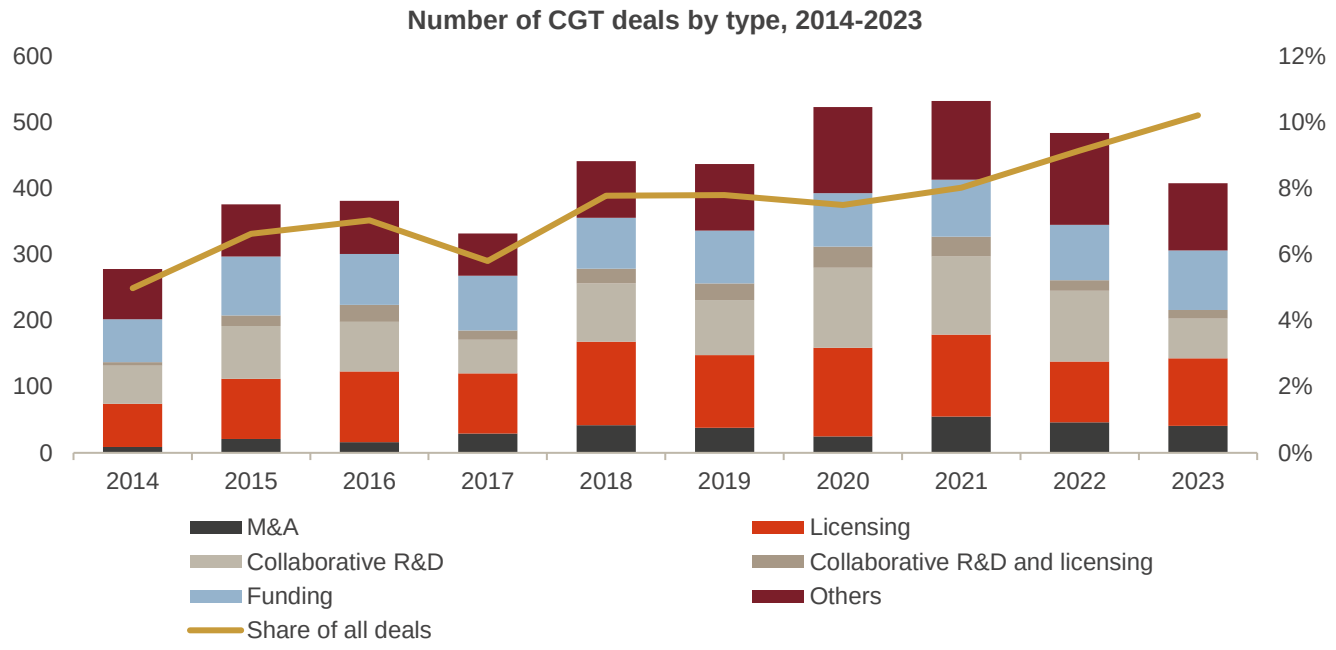
- Bespoke Gene Therapy Consortium is an initiative that is set up to develop standards and protocols that the research community can use to accelerate the development of gene therapies for rare diseases
- FDA, in its final guidance issued in January 2024, is supportive of the use of accelerated approval pathway for gene editing products using surrogate endpoints. FDA is also inclined to expand this programme to all CGTs, especially for treating rare diseases
- FDA is planning to issue guidance to streamline the New Drug Application or Biologics License Application submission process, allowing the applicant to reference data from a previous application that uses the same technology or platform that will vastly help the CGT drugs vying for approval

Market promising for investors, buzzes with deal activities

The CGT market holds promise for both private and public investors. The rise in the number of new CGT companies creates opportunities for private investors to deploy capital. The appetite from large biopharma companies to acquire or partner with CGT companies in R&D phase and the good reception for primary offerings of CGT companies provide an exit pathway for the already invested private investors. As for public investors, the new listings allow capital investment as the CGT market is still in its nascent stage and the investors stand to gain in the long term as the pipeline progresses to the market.

CGT attracts increasing proportion of all life sciences deals

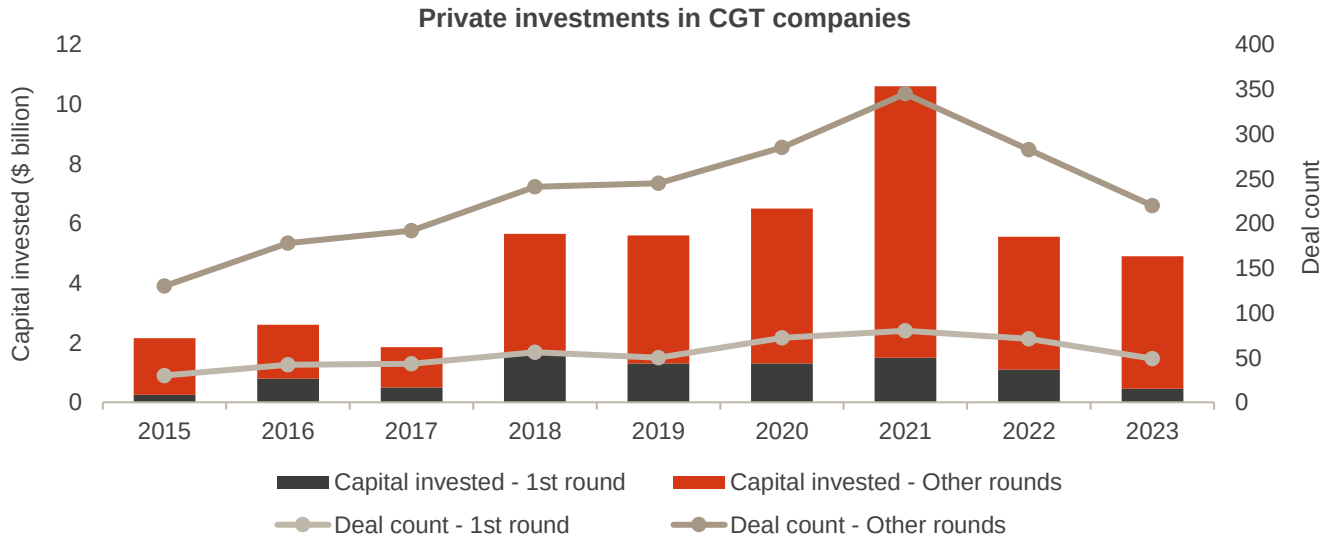
The CGT space has experienced consistent deal activity in recent years. While the number of CGT deals decreased 14% in 2023, compared with 2022, it has surged 46% over the past decade. The declining trend in deal activity over the past two years mirrors that of the broader life sciences industry. However, despite this decrease, CGT deals constitute a growing proportion of all life sciences deals, comprising 10% in 2023, up from 8% in 2021 and 5% in 2014. This uptick underscores the increasing confidence and interest in these modalities, as CGT deal activity has not decelerated as much as in other segments within the biopharma industry. Notably, the value of venture capital and private equity investments in the life sciences industry has clocked a CAGR of 18% from 2010 to 2021 while the growth rate in CGT companies was 61%.



Source: IQVIA Pharma Deals, IQVIA Institute, Jan 2024

Remarkable growth in private investments

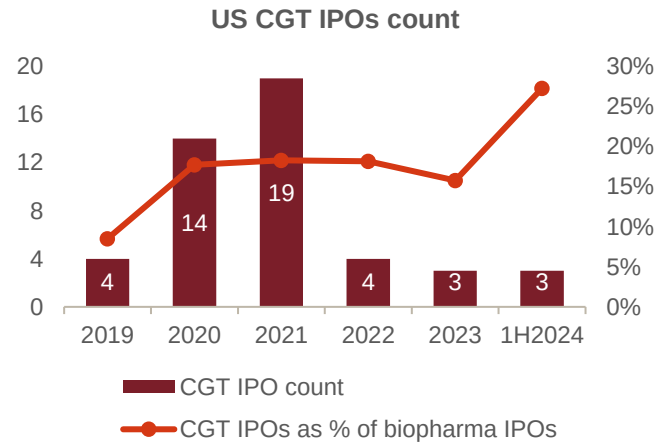
Over the past decade, private investments in CGT enterprises have consistently risen, including first round investments that act as a barometer for the establishment of new companies. However, private funding of CGT companies did slow down post 2021, consistent with the larger biopharma funding, due to the cautious approach of investors driven by macro headwinds. This scenario may be short-lived as we do not expect macro headwinds to persist, and private investors should use the current low valuation cycle to pick and choose relatively lower risk CGT companies with proven data in early stages of trials for their investments.

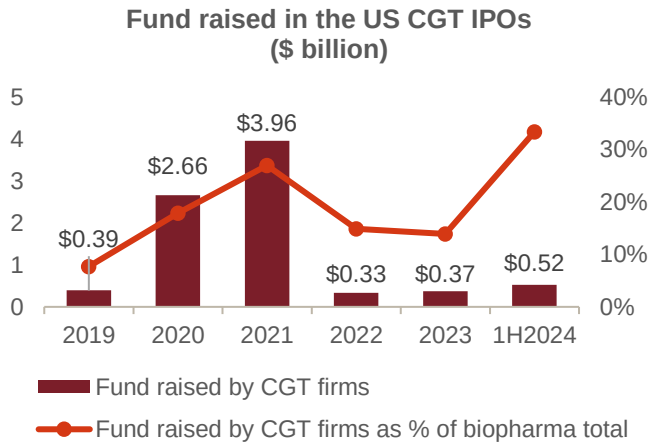


Source: cellandgene.com, PitchBook, RSM US

CGT firms accessible to public markets as well

Since 2019, there were 47 public listings of CGT companies in the US, raising a total capital of $8.2 billion (see *List of CGT IPOs since 2019*, *Page 26*), highlighting the investment opportunities provided to the public investors. Notably, these companies have raised $8.5 billion of private capital before the listing, enabling these investors to exit their position. Since 2022, the sector-wide slowdown has caused a slump in new listings, pushing companies to rely more on private capital and collaboration deals for funding. Given most of the CGT companies are in the early stages of development, public market access is currently tough due to the slowdown and risk averseness in the overall biopharma new listings. We expect the sentiment to improve soon with recovery in valuation on the back of expected decrease in federal funds rates, paving the way for the rise of biotech as well as CGT initial public offerings (IPOs).





Source: BioPharma Dive, CRISIL analysis

Investors rewarded by appetite of large biopharma players

Larger and more established companies recognise the transformative power of gene therapy and are eager to partner with or acquire the early-stage leaders in the CGT space, even without a robust track record of approvals. This trend signals that the future of CGT space holds exciting possibilities for collaboration and shared success. By diversifying their income streams through strategic partnerships and licensing deals, CGT companies can navigate the challenges of complex development phase and secure their place at the forefront of this ground-breaking field. Large biopharma companies have paid good premium over the current valuation while acquiring CGT companies, handsomely rewarding the investors.

Notable deal activities by large biopharma players in the past five years

Year	Acquirer (large-cap company)	Target company	Deal value	Key asset/ area
2018	Novartis	AveXis	$8.7 billion	Gene therapy for SMA
2019	Vertex Pharmaceuticals	Exonics Therapeutics	$420 million	Gene therapy for neuromuscular diseases
2019	Roche	Spark Therapeutics	$4.3 billion	Gene therapy for haemophilia
2019	Bayer	BlueRock Therapeutics	$240 million	Cell therapy for inflammatory diseases
2020	Astellas Pharma	Audentes Therapeutics	$3 billion	AAV gene therapy platform
2020	Ionis Pharmaceuticals	Akcea Therapeutics	$500 million	Gene therapy for lipid disorders

Year	Acquirer (large-cap company)	Target company	Deal value	Key asset/ area
2020	Bayer	AskBio	$4 billion	AAV gene therapy platform
2022	AstraZeneca	LogicBio Therapeutics	$68 million	Genomics and rare diseases
2022	Eli Lilly	Akouos	$600 million	Gene therapy for inner ear conditions
2023	Regeneron Pharmaceuticals	Decibel Therapeutics	$109 million	Gene therapy programmes for hearing loss
2023	AstraZeneca	Gracell Biotechnologies	$1.2 billion	Cell therapies for cancer and autoimmune diseases

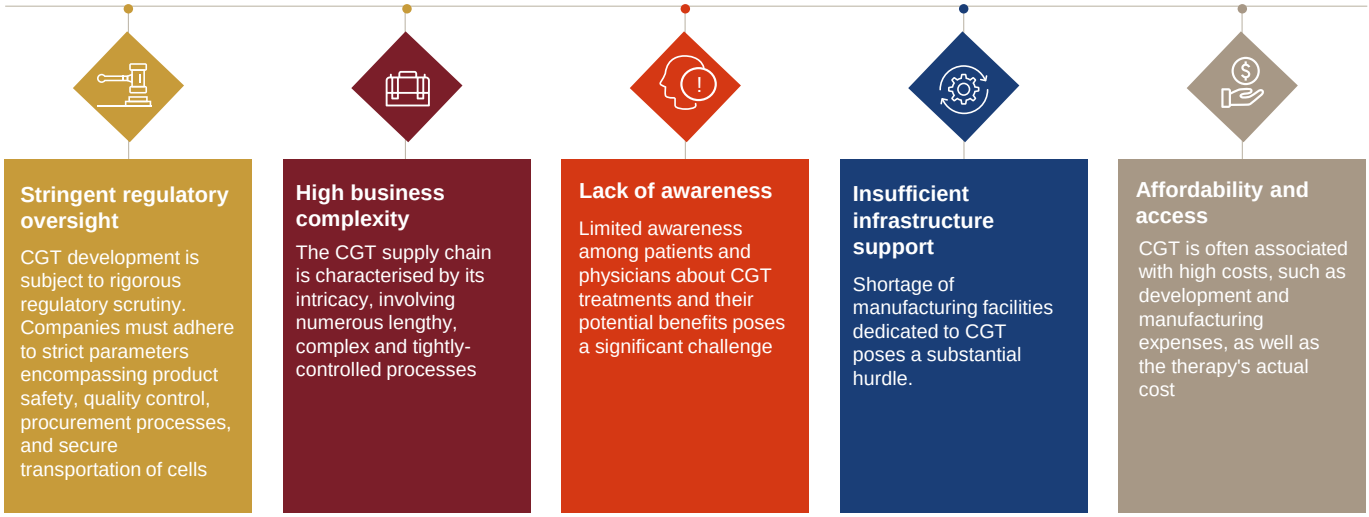
Source: Phacilitate 2023, Pharmaceutical Technology, Jan 2024, company press releases

Other players benefit from CGT evolution as well

- **CDMOs:** According to Nova One Advisor, the CGT CDMO market accounted for $6 billion in 2023. It is estimated to increase to $69 billion by 2033, growing at 28% CAGR[6]. Given the highly specialised and complex nature of development and manufacturing of CGT drugs, biopharma companies are increasingly resorting to outsourcing the development and manufacturing activities for efficient and cost-effective solutions. Evolving regulatory support, a growing pipeline, increasing pace of approval and rising demand for development and manufacturing of CGT drugs bode well for the growth of CDMO industry
- **Manufacturing companies for T-cells:** These companies focus on producing T-cells, which are a type of white blood cell important for the immunity function. They may develop processes for isolating, expanding and modifying T-cells for therapeutic purposes, such as cancer immunotherapy. With the growing adoption of T-cell therapies in CGT, there is an increased need for manufacturing capacity and capability to produce these T-cells on large scale
- **Bioprocessing companies:** These companies focus on optimising biomanufacturing processes to increase production yields and reduce manufacturing costs. They develop technologies and solutions for efficient cell culture, purification and downstream processing in the production of biopharmaceuticals and other biologics. Demand for bioprocessing technologies and solutions are growing to support the manufacturing of CGT therapies
- **Logistics companies:** This market comprises specialised logistics firms equipped to transport sensitive medical samples, particularly those requiring specific temperature controls, to processing facilities. They typically utilise temperature-controlled packaging and vehicles to maintain the integrity of the samples during transit. As the demand for CGT increases, there is a greater need for transporting patient samples to processing facilities
- **Compliance companies:** These firms ensure biomanufacturing processes comply with regulatory standards for safety and quality. They provide oversight, auditing and consulting services to biotech companies to ensure adherence to regulations set by agencies such as the FDA or European Medicines Agency

Principal challenges

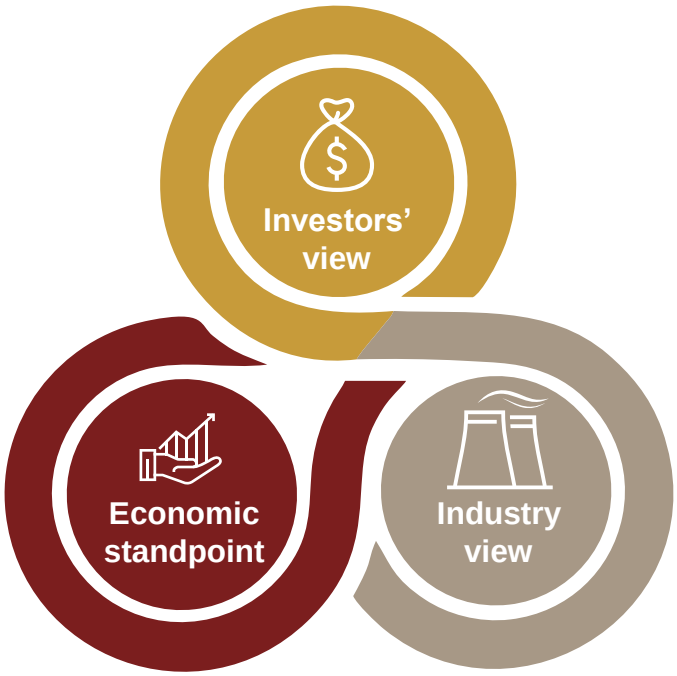
While the market has good growth potential, challenges lie ahead. The sub-industry is still at a nascent phase. Limited awareness among patients and physicians regarding CGT treatments, high costs of development, access challenges due to high pricing and shortage of manufacturing facilities are hurdles limiting its adoption.



1. **Stringent regulatory oversight:** CGT development is subject to rigorous regulatory scrutiny. Companies must adhere to strict parameters encompassing product safety, quality control, procurement processes and secure transportation of cells. At the same time, regulators are starting to support the development of CGT drugs, given the great potential this modality of treatment holds.
2. **High business complexity:** The CGT supply chain is characterised by its intricacy, involving numerous lengthy, complex and tightly controlled processes. This complexity was especially evident during the pandemic, revealing vulnerabilities in the supply chain that require strategic planning to enhance resilience. High-level collaboration is required among the different players, from CGT development through till delivery of drugs to patients to streamline the process and maintain quality.
3. **Lack of awareness:** A significant challenge stems from limited awareness among patients and physicians regarding CGT treatments and their potential benefits. The relative novelty of these therapies, combined with their relatively low adoption rates, contributes to this lack of awareness, limiting the uptake of CGT drugs. As more CGT drugs are getting approved, the awareness level should increase among patients and physicians, leading to increased adoption of these therapies.
4. **Insufficient infrastructure support:** A shortage of manufacturing facilities dedicated to CGT poses a substantial hurdle. In the United States, for instance, the limited number of CGT manufacturing facilities (~100) constrains capacity to deliver these therapies to a broader patient population each year. Increased investment by CGT-focused CDMOs to build manufacturing capabilities should help overcome this hurdle.
5. **Affordability and access challenges:** CGT treatments are often associated with a substantial price tag due to the high costs involved for development and manufacturing. Though there are economic justifications that CGT treatment can help save millions in long-term downstream treatments, the higher upfront cost presents a barrier to patient accessibility and can limit the acceptance of these innovative therapies by healthcare providers. Recent initiatives such as Centers for Medicare & Medicaid Services' CGT Access Model to experiment with outcomes-based agreements holds the key in addressing the access barrier and improving the health outcome for patients.

Outlook buoyant, opportunities for multiple stakeholders

The global CGT market, forecast to be worth $97 billion by 2033, offers a lucrative opportunity for investors with a long-term play. For the biopharma industry, collaboration with regulatory agencies and academic institutions are key to make progress. Economically, evolution of the CGT market has the potential to reduce long-term healthcare costs, create jobs and boost economic activity.



- **Investors:** The global CGT market is forecast to be worth $97 billion by 2033, growing at 18% CAGR. This presents a lucrative opportunity for early-stage investment in promising companies and technologies. Investors can diversify risk by allocating funds across the CGT value chain, including cell manufacturing, delivery vectors, gene editing tools and therapeutic applications, which also allows for exposure to various growth drivers within this space. Given the longer development timelines in CGT as opposed to traditional drugs, investors should consider a long-term investment strategy to capture the full potential of this innovative field.
- **Industry:** CGT biopharma companies should work with regulatory agencies to establish clear guidelines and standards for safety, efficacy, manufacturing and pathways to accelerate the approval process. Developing therapies focusing on unmet needs can offer faster regulatory pathways and significant market opportunities. Companies should collaborate with academic institutions to tap cutting-edge expertise and invest in R&D to stay ahead of the curve.
- **Economy:** By targeting the root cause of diseases, CGTs have the potential to reduce long-term healthcare costs associated with chronic and debilitating conditions and improve patient outcomes. Supporting startups and fostering innovation across the value chain, from cell collection and engineering to delivery vectors and therapeutic applications, can create jobs, boost economic activity and drive further advancements in the field.

Market unpredictability, global economic instability and the operational complexities inherent in an emerging market are inevitable obstacles that cell and gene companies will confront as they mould the future of healthcare. While business leaders and the scientific community grapple with these challenges, it is crucial to acknowledge the remarkable potential of this sector and the fundamental reasons driving increased investment and research in CGT.

Appendix

1) List of marketed CGT drugs

Drug (trade name)	Year of first approval	International Nonproprietary Name (INN)	Company	Approved region	Indication
Beqvez	2024	Fidanacogene elaparvovec-dzkt	Pfizer, Inc.	US	Treatment of adults with moderate to severe haemophilia B.
Amtagvi	2024	lifileucel	Iovance Biotherapeutics	US	Treatment of adult patients with unresectable or metastatic melanoma.
Casgevy	2023	exagamglogene autotemcel [exa-cel]	Vertex Pharmaceuticals	US/ EU	Sickle cell disease (SCD)
Elevidys	2023	delandistrogene moxeparvovec-rokl	Sarepta Therapeutics, Inc.	US	Treatment of Duchenne muscular dystrophy (DMD).
Lyfgenia	2023	lovotibeglogene autotemcel [lovo-cel]	bluebird bio, Inc.	US	Treatment of vaso-occlusive events (VOEs).
Vyjuvek	2023	beremagene geperpavec	Krystal Biotech, Inc.	US	For the treatment of dystrophic epidermolysis.
Lantidra	2023	donislecel	CellTrans Inc.	US	For treatment of adults with Type 1 diabetes.
Omisirge	2023	omidubicel-onlv	Gamida Cell Ltd.	US	For use in adults and pediatric patients 12 years and older with hematologic malignancies.
Ebvallo	2022	tabelecleucel	Atara Biotherapeutics Inc.	EU	Epstein-Barr virus positive post-transplant lymphoproliferative disease (EBV+ PTLD)
Roctavian	2022	valoctocogene roxaparvovec-rvox	BioMarin Pharmaceutical	US/ EU	Haemophilia A
Upstaza	2022	eladocagene exuparvovec	PTC Therapeutics International Limited	EU	L amino acid decarboxylase (AADC) deficiency
Carvykti	2022	ciltacabtagene autoleucel	Johnson & Johnson.	US/ EU	Multiple myeloma
Adstiladrin	2022	nadofaragene firadenovec-vcng	Ferring Pharmaceuticals A/S	US	For the treatment of adult patients with high-risk Bacillus Calmette-Guérin (BCG)
Hemgenix	2022	etranacogene dezaparvovec-drlb	CSL Behring	US/ EU	Haemophilia B
Skysona	2022	elivaldogene autotemcel	Bluebird Bio	US/EU	Early, active cerebral adrenoleukodystrophy (CALD)

Drug (trade name)	Year of first approval	International Nonproprietary Name (INN)	Company	Approved region	Indication
Zynteglo	2022	betibeglogene autotemcel	bluebird bio Inc.	US	For treatment of adult and pediatric patients with ß-thalassemia.
Breyanzi	2021	lisocabtagene maraleucel	Bristol-Myers	US/ EU	Large B-cell lymphoma (LBCL)
Stratagraft	2021	allogeneic cultured keratinocytes and dermal fibroblasts in murine collagen-dsat	Stratatech Corporation	US	To promote durable wound closure and regenerative healing in the treatment of adult patients.
Rethymic	2021	allogeneic processed thymus tissue – agdc	Enzyvant Therapeutics GmbH	US	For immune reconstitution in pediatric patients with congenital athymia.
Abecma	2021	idecabtagene vicleucel	Bristol-Myers	US/ EU	Multiple myeloma
Tecartus	2020	brexucabtagene autoleucel	Kite Pharma	US/ EU	Mantle cell lymphoma (MCL)
Lenmeldy/ Libmeldy	2020	atidarsagene autotemcel	Orchard Therapeutics	US/ EU	Metachromatic leukodystrophy (MLD)
Zolgensma	2019	onasemnogene abeparvovec	Novartis	US/ EU	Spinal muscular atrophy (SMA)
Zynteglo	2019	betibeglogene autotemcel	bluebird bio Inc.	US/ EU	Transfusion-dependent beta thalassemia
NA[#]	2018	HPC, Cord Blood - MD Anderson Cord Blood Bank	MD Anderson Cord Blood Bank	US	Transplant of HPCs from human cord blood.
Alofisel	2018	darvadstrocel	Takeda & TiGenix	EU	Complex perianal fistulas
Luxturna	2017	voretigene neparvovec	Roche	US/ EU	Retinal dystrophy
Kymriah	2017	tisagenlecleucel	Novartis	US/ EU	Acute lymphoblastic leukaemia and large B-cell lymphoma
Yescarta	2017	Axicabtagene ciloleucel	Kite Pharma	US/ EU	Large B-cell lymphoma
NA[#]	2016	HPC, Cord Blood - Bloodworks	Bloodworks	US	Transplant of HPCs from human cord blood.
NA[#]	2016	HPC, Cord Blood - LifeSouth	LifeSouth Community Blood Centers, Inc.	US	Transplant of HPCs from human cord blood.
MACI	2016	Autologous Cultured Chondrocytes on a Porcine Collagen Membrane	Vericel Corp.	US/EU	Cellularised scaffold to repair cartilage defects of the knee.
Strimvelis	2016	Autologous CD34+ enriched cell fraction	Orchard Therapeutics	EU	Severe combined immunodeficiency due to adenosine deaminase deficiency (ADA-SCID).

Drug (trade name)	Year of first approval	International Nonproprietary Name (INN)	Company	Approved region	Indication
Clevecord	2016	HPC, Cord Blood	Cleveland Cord Blood Center	US	Transplant of HPCs from human cord blood.
Imlygic	2015	Talimogene laherparepvec	Amgen	US/ EU	Unresectable melanoma
Allocord	2013	HPC, Cord Blood	SSM Cardinal Glennon Children's Medical Center	US	Blood cell transplant derived from umbilical cord and placenta.
Ducord	2012	HPC, Cord Blood	Duke University School of Medicine	US	Transplant of HPCs from human cord blood.
Gintuit	2012	Allogeneic Cultured Keratinocytes and Fibroblasts in Bovine Collagen	Organogenesis Inc.	US	Treat certain mucogingival conditions
NA[#]	2012	HPC, Cord Blood	Clinimmune Labs, University of Colorado Cord Blood Bank	US	Transplant of HPCs from human cord blood.
Laviv	2011	Azficel-T	Fibrocell Technologies	US	Fibroblasts to improve the appearance of moderate to severe nasolabial fold wrinkles.
Hemacord	2011	HEMACORD (HPC, Cord Blood)	New York Blood Center	US	Transplant of HPCs (hematopoietic progenitor cells) from human cord blood.
Provenge	2010	Sipuleucel-T	Dendreon Corp.	US	Antigen presenting cells are activated and used to treat certain types of prostate cancers.

Source: FDA, EMA. [#] Does not have trade name

2) List of CGT IPOs since 2019

Year	Company name	Therapeutic focus	Treatment type	Stage of development at IPO	Fund raised in IPO (million)
2024	Fractyl Health	Metabolic diseases	Gene therapy	Preclinical	$110
2024	Kyverna Therapeutics	Immune diseases	Cell therapy	Phase 2	$319
2024	Metagenomi	Rare diseases	Gene editing	Preclinical	$94
2023	CytoMed Therapeutics	Cancer	Cell therapy	Preclinical	$9.6
2023	Turnstone Biologics	Cancer	Cell therapy	Phase 1	$80
2023	Cargo Therapeutics	Cancer	Cell therapy	Phase 2	$281
2022	Arcellx	Cancer	Cell therapy	Phase 1	$124
2022	TC BioPharm	Cancer	Cell therapy	Phase 1	$18
2022	Prime Medicine	Rare diseases	Gene therapy	Preclinical	$175
2022	Coya Therapeutics	Central nervous system (CNS) disorders	Cell therapy	Preclinical	$15
2021	Gracell Biotechnologies	Cancer	Cell therapy	Phase 1	$209
2021	Sana Biotechnology	Cancer	Cell therapy	Preclinical	$588
2021	Vor Biopharma	Cancer	Cell therapy	Phase 1	$177
2021	Immunocore	Cancer	Cell therapy	Phase 3	$258
2021	Decibel Therapeutics	Ear diseases	Gene therapy	Phase 1	$127
2021	NexImmune	Cancer	Cell therapy	Phase 1	$119
2021	Longeveron	Anti-Aging	Cell therapy	Phase 2	$27
2021	Instil Bio	Cancer	Cell therapy	Preclinical	$320
2021	Achilles Therapeutics	Cancer	Cell therapy	Phase 1	$176
2021	Talaris Therapeutics	Immune diseases	Cell therapy	Phase 3	$150
2021	Verve Therapeutics	Heart diseases	Gene therapy	Preclinical	$267
2021	Lyell Immunopharma	Cancer	Cell therapy	Preclinical	$425
2021	Century Therapeutics	Cancer	Cell therapy	Preclinical	$211
2021	Graphite Bio	Rare diseases	Gene therapy	Preclinical	$238
2021	TScan Therapeutics	Cancer	Cell therapy	Preclinical	$100
2021	Caribou Biosciences	Cancer	Gene therapy	Phase 1	$304
2021	Tenaya Therapeutics	Heart diseases	Gene therapy	Preclinical	$180
2021	IN8Bio	Cancer	Cell therapy	Phase 1	$40
2021	MiNK Therapeutics	Cancer	Cell therapy	Phase 1	$40
2020	Beam Therapeutics	Rare diseases, cancer, liver diseases, CNS disorders, eye diseases	Gene therapy	Preclinical	$180
2020	Passage Bio	CNS disorders	Gene therapy	Preclinical	$170
2020	Legend Biotech	Cancer	Cell therapy	Phase 2	$424
2020	Generation Bio	Rare diseases	Gene therapy	Preclinical	$200
2020	Akouos	Ear diseases	Gene therapy	Preclinical	$213

Year	Company name	Therapeutic focus	Treatment type	Stage of development at IPO	Fund raised in IPO (million)
2020	Nkarta	Cancer	Cell therapy	Preclinical	$252
2020	Poseida Therapeutics	Cancer	CGT	Phase 2	$224
2020	AlloVir	Infectious diseases	CGT	Phase 2	$276
2020	Freeline Therapeutics	Rare diseases	Gene therapy	Phase 1	$159
2020	Taysha Gene Therapies	CNS disorders	Gene therapy	Preclinical	$157
2020	Kiromic Biopharma	Cancer	Cell therapy	Preclinical	$15
2020	SQZ Biotech	Cancer	Cell therapy	Phase 1	$71
2020	Sigilon Therapeutics	Rare diseases	Cell therapy	Phase 1	$126
2020	4D Molecular Therapeutics	Eye, heart and lung diseases	Gene therapy	Phase 1	$193
2019	TCR2 Therapeutics	Cancer	Cell therapy	Preclinical	$75
2019	Precision BioSciences	Cancer	Cell therapy	Preclinical	$126
2019	Prevail Therapeutics	CNS disorders	Cell therapy	Preclinical	$125
2019	Cabaletta Bio	Immune disease	Cell therapy	Preclinical	$66

Source: BioPharma Dive

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