From hype to reality: How to succeed in the cell and gene therapy market

January 2023

pwc

Introduction

Gene therapies and genetically modified cell therapies have generated enormous interest among scientific researchers, manufacturers, investors and patients alike over the last decade.

For pharma, which has been underperforming other sectors in relative shareholder returns, the breakthrough potential of these novel medicines is attractive for both patients and companies. But the path to success has been challenging. The promise of one-time, revolutionary treatments for patients suggested that a massive disruption to the life science industry was imminent. However, as it turned out, manufacturing and commercial challenges slowed the development of the cell and gene therapy (CGT) market.

Sales of CGT therapies were lagging behind projections, and these products were available in only a handful of US ZIP codes, according to a PwC report on the market in 2019. We have updated our analysis of the market and found a resetting of expectations for these paradigm-shifting brands. Developers are working through the logistical issues, hundreds of treatment sites are open, and some products are performing well.

Manufacturing of cell and gene therapies is still a very customized, complex and expensive process but the clinical promise is very real and the pipeline of new therapies is abundant. In this report, we highlight seven key challenges in the CGT space and provide recommendations on how organizations can overcome these barriers to achieve success.

1. Sales ramped up more slowly than expected

Despite the enthusiasm for innovative cell and gene therapies, the market has taken longer to develop than initially expected. Some gene therapies with blockbuster potential didn't launch as expected — some due to safety or efficacy concerns. Total sales for five CGT products — all autologous cell therapies — had reported earnings in 2021 of $3.1 billion. (See chart below.) Some fell short of projections made at the time of launch, while others have far exceeded forecasts.

Select FDA-approved cell and gene therapies, 2021 actual sales

Product	Initial approval date	Type of therapy	2021 annual sales (% change from 2020)
Kymriah (tisagenlecleucel)	August 2017	Autologous CAR-T	$587 m (+24%)
Yescarta (axicaptagene ciloleucel)	October 2017	Autologous CAR-T	$695 m (+23%)
Zolgensma (osasemnogene aberparvovec-xioi)	May 2019	Adeno-associated virus (AAV) gene therapy	$1.4 bn (+46%)

Tecartus (brexucabtagene autoleucel)	July 2020	Autologous CAR-T	$176 m (+300%)
Abemca (idecaptagene vicleucel)	March 2021	Autologous CAR-T	$164 m (NA)
Breyanzi (lisocaptagene maraleucel)	May 2021	Autologous CAR-T	$87 m (NA)

Source: FDA.gov, company earnings reports

The leukemia therapy Kymriah (tisagenlecleucel) was the first autologous CAR-T product approved by the US Food and Drug Administration (FDA) with the support of a study that involved 63 patients.[1] The manufacturer launched the therapy at the price of $475,000, with payment over time and a pledge to offer outcomes-based options.

Costs for managing toxicities and hospitalization of CAR-T patients have added up, and some health providers have said that it's a challenge to break even.[2]

Gene therapies entered at a higher price point. Novartis' Zolgensma, a one-time gene therapy treatment for spinal muscular atrophy that was approved in 2019, has a list price of $2.1 million. In August 2022, the FDA approved Bluebird bio's one-time beta thalassemia treatment Zynteglo (betibeglogene autotemcel) and the company is planning a commercial launch in 2023.[3] The US list price was set at $2.8 million per patient. Bluebird bio won European approval for Zynteglo in 2019, but it later withdrew the drug from the region citing "challenges of achieving appropriate value recognition and market access."[4] Bluebird's other recently approved gene therapy Skysona (eli-cel) was priced at $3 million per one-time treatment. A $3.5 million gene therapy for hemophilia was approved in the fourth quarter of 2022 in the US.

IQVIA highlighted the substantial hurdles and uncertainties for next-generation biotherapeutics in its Global Use of Medicines 2022 report.[5] Following the first launches in 2010, the current generation CGT therapies were released in or after 2017, and total global spending on cell, gene and RNA products did not reach $1 billion until 2018.

According to the report, excluding messenger RNA (mRNA) vaccines, total global spending has now passed $5 billion and with dozens of new product launches, that figure could rise to $20 billion by 2026. However, the market is somewhat difficult to predict. "Many of these therapies have very high costs. When combined with uncertain numbers of patients, this is generating significant attention and resistance from payers, and is dampening expected spending levels in the lower end of expectations," according to IQVIA authors.

One study on market access, published in the journal Health Policy, concluded that "US plans are substantially more restrictive in their coverage of cell and gene therapies compared with other orphan products, for which coverage is restricted in about 30% of health plan policies.[6]" Coverage in Canada and the five major European markets is even more limited, according to the same study.

Despite these struggles, there have been some positive developments for the field. New payment models involving multiyear and outcomes-based contracts have been in development. The influential US Institute for Clinical and Economic Review (ICER) determined that Zynteglo — approved for patients who require regular red blood cell transfusions — met value thresholds at the price of $2.1 million (approaching the eventual $2.8 million), when it includes an option for 80% payback if benefits are not durable.[7] In its assessment, ICER highlighted the value of eliminating transfusions and concluded that

Zynteglo “met its criteria for high-impact single and short-term therapies and for treatments of serious, ultra-rare conditions.”

Bluebird bio maintains that the lifetime cost of alternative medical care for a potential Zynteglo patient could reach $6.4 million.[8] The company plans to provide access to Zynteglo to US patients through risk-sharing agreements with insurance companies that involve rebates of up to 80% if treatment doesn’t work.

Meanwhile, the US Centers for Medicare and Medicaid (CMS) has been developing policies for value-based purchasing to make innovative therapies more available to beneficiaries.[9]

Expectations for the market have been reset with rising awareness that it takes time to build capacity and demand for innovative, potentially curative new therapies. Long-term data showing the durability of response to CAR-T cells for over a decade are now being published.[10]

Identifying the right patients for treatment will be crucial going forward. Ensuring that treatment is focused on patients likely to have good outcomes is critical for patient care and will also save money for healthcare systems. Appropriate patient selection and real-world evidence of benefits could support higher pricing, on par with orphan drugs. Using real-world evidence, pharma companies can gain a better understanding about which patients will be responders and can communicate that information to health providers.

How companies can help build the CGT market:

- **Partner on patient identification.** Pharma companies must spend more time thinking through and establishing partnerships with health systems, data aggregators and diagnostic testing companies. Through partnerships, they will be better equipped to identify and select patients for treatment and provide supporting evidence to justify high pricing.
- **Educate patients and providers.** More effort needs to go into educating patients and providers in community settings about the clinical value of new cell and gene therapies.
- **Ramp up real-world evidence (RWE) programs.** Collect data over the long term to bolster evidence in registrational programs and reassure medical professionals about safety and efficacy.
- **Continue development of outcomes-based contracts**. These contracts have proven to be complicated, but there are signs that drug developers and large insurers want to make them work for promising new cell and gene therapies.[11]

2. Administration sites are inconvenient

Beyond the price of these drugs, ease of use remains an issue for both patients and healthcare facilities.

Most healthcare facilities are unable to serve cell therapy patients because they lack the capabilities to perform apheresis and infusion on a carefully controlled schedule. Treatment today must be offered at specialized academic centers, limiting access for patients in rural communities. The complexity of administration has relegated the treatment to an inpatient setting, where costs are bundled and less lucrative for providers.

To put this in perspective, consider that the total cost — including hospitalization, treatment with the drug tocilizumab to prevent cytokine storm, and long-term toxicity management — for CAR-T treatment ranges from $500,000 to $1 million per patient, according to some estimates.[12]

However, there are signs that this paradigm could shift in the coming years. It’s possible that CAR-T activities could move to an outpatient setting, which could expand the flexibility of treatment locations and limit bottlenecks that occur at the administration site.[13]

Testimony from doctors and healthcare administrators provides further evidence for the need to move toward outpatient treatment to lower costs and increase capacity, as cell therapy therapeutic areas expand beyond blood to solid cancers and a far larger patient base.[14]

Driving factors for outpatient setting administration include:

- Current reimbursement models limit the financial viability of CAR-T.
- A shift toward providing CAR-T therapies in outpatient centers has the potential to increase competition and availability, which may reduce costs.

There is a growing body of literature focusing on how best to redesign the provider operating and care delivery models for new cellular therapies with more community-based treatment approaches. It is critical that outpatient support systems design the appropriate operating models to ensure patient safety and optimize outcomes.[15] An effective outpatient program will still require the infrastructure of a hospital or hospital partner.

In addition to the expansion of administrative sites, better integration between patients, pharmaceutical companies and key stakeholders like front-line healthcare providers (HCPs) will ensure a more successful experience and better clinical outcomes.

The creation of integrated digital platforms that holistically serve the needs of staff, patients, supply chain providers and pharmaceutical companies is another opportunity in this space. These integrated platforms are able to provide value in numerous ways, and the deployment of such patient-centered CGT integrated platforms can happen in a matter of weeks.[16] These sorts of initiatives can help expand the serviceable patient population and may also help to improve the overall value these therapies can provide to patients and their insurers.

How companies can improve ease of use:

- **Streamline handoffs between pharmaceutical companies and providers.** Some opportunities include improving manual operations like label printing or the processing of incoming shipments from the manufacturing site – activities that are particularly complicated when dealing with CGT products that require specific chain of identity protections. These activities will likely become more challenging as the number of commercial products and companies increase.

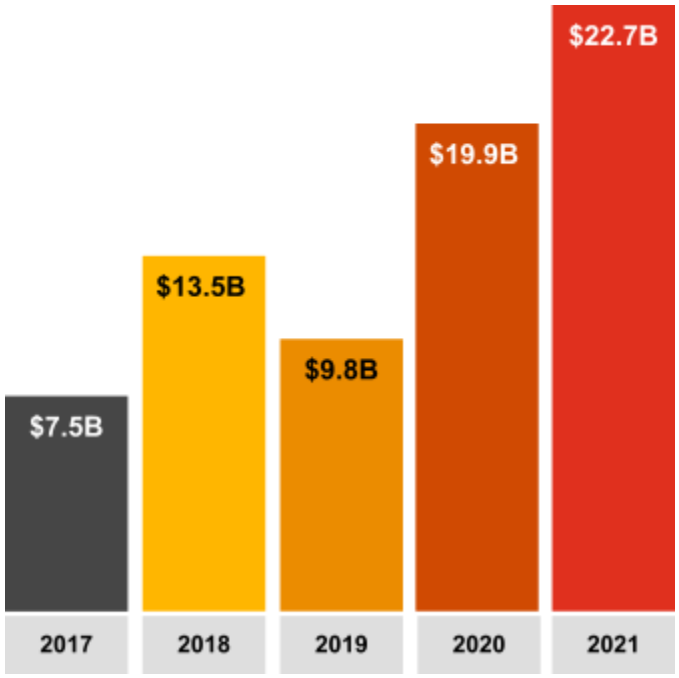
- **Embrace digital transformation**. Companies need to assess their current digital infrastructure and determine where connectivity could be improved between their manufacturing network, healthcare providers and the patient population. Digital platforms can deliver value by providing seamless interaction between parties, plus clear accountability, insight development, transparent processes and improved security.

- **Redesign your operating model to support outpatient care:** Interest is growing in community-based treatment approaches. It is critical that outpatient support systems are put in place to ensure patient safety and to optimize outcomes. As the standard of care transitions to outpatient procedures, coordination will become more important to ensure that vein-to-vein time is minimized and safety remains uncompromised.

3. Expanding investment and pipeline growth have created a war for talent

Research and development of cell and gene therapies has benefited from increased investment in the regenerative medicine sector in recent years. According to the Alliance for Regenerative Medicine (ARM), investment for cell and gene therapy reached $22.7B in 2021, surpassing the 2020 record of $19.9B. 2021 was also the second best year for new product approvals, with six new therapies globally (including three new CAR-T approvals).[17] The number of developers of gene, cell and tissue-based therapeutics globally surpassed 1,300 in 2021, up by 19% from 2020, according to the ARM. The public markets have been challenging for small biotechs in general and gene therapy developers in particular, but the ARM concluded that the sector continues to rest on a strong scientific foundation. Investment has more than tripled since 2017, when the total amount was $7.5B.

Figure 1: Money raised by the regenerative medicine sector by year (based on data provided by the Alliance for Regenerative Medicine)

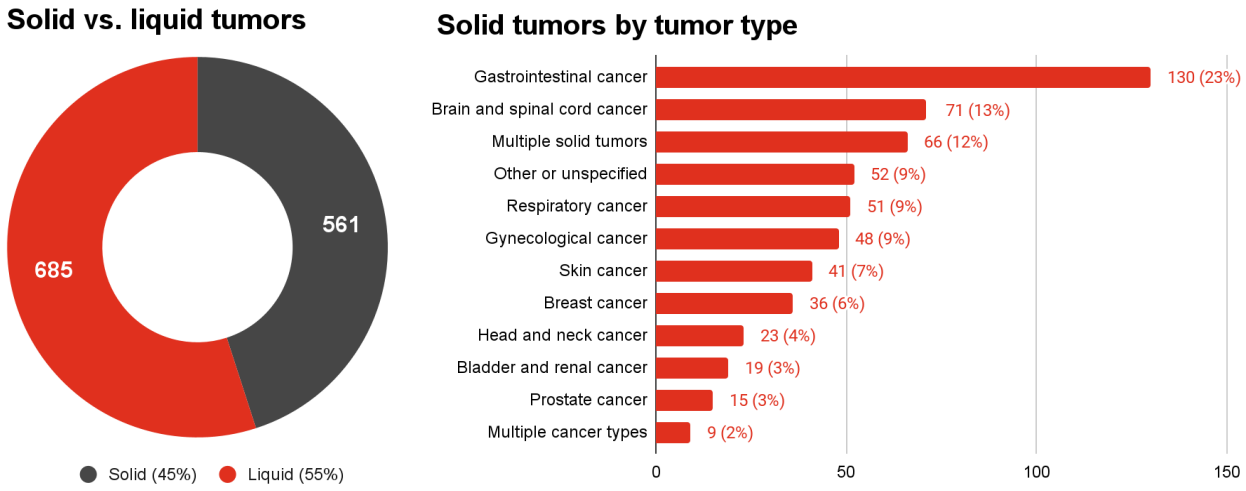


Source: alliancerm.org

At the end of 2021, there were 2,406 clinical trials in regenerative medicine sponsored by industry, academia and government, according to the ARM.The oncology therapy area is the most active, accounting for 52% of ongoing trials. The remaining 48% of trials are spread fairly evenly across central nervous system (CNS), infectious diseases, immunology, monogenic diseases, hematology, musculoskeletal diseases and cardiovascular diseases.

Solid tumors are increasingly a focus of development activity, whereas traditionally the cell therapy field has been dominated by development of therapies for hematologic cancers. Solid tumor trials now make up 45% of total oncology trials, with gastrointestinal cancers acting as the main target (23% of solid tumor trials) followed by brain and spinal cord cancer (13%).

Figure 2: Solid tumors are now a significant portion of ongoing clinical trials



Source: alliancerm.org

Both the United States and European Union government authorities have shown a continued interest in promoting CGT therapies. The FDA's reauthorization of the Prescription Drug User Fee Act (PDUFA VII) provides increased funding for the agency's Center for Biologics Evaluation and Research (CBER) to develop, review, and approve cell and gene therapies.[18] The FDA renamed the Office of Tissues and Advanced Therapies as the Office of Therapeutic Products,[19] a new entity that will be elevated to super-office status in the CBER and will have capacity to handle the growing number of applications, according to the agency.

Meanwhile, the FDA is expanding its reviewing capabilities of the increasing number of cell and gene therapies in the pipeline, another positive development for the field.[20]

Through the 2018 Beneluxa initiative, Belgium, the Netherlands, Luxembourg, Austria and Ireland agreed to streamline the pricing and reimbursement negotiation process for innovative therapies, including CGTs. One strategy called for mutual recognition of health technology assessments.[21]

The continued excitement in this space has launched an industry-wide "war for talent," pitting companies against each other as they fight to attract the small number of individuals with the appropriate skills. A 2021 report from the UK's Cell and Gene Therapy Catapult (CGT Catapult) estimates that the country will require 15,100 CGT professionals (117% more than today) by 2026, including 10,000 bioprocessing jobs (151% more than today).[22]

The greatest areas of concern have been related to manufacturing and quality, followed by supply chain, logistics and process development. At the annual meeting of the International Society for Cell & Gene Therapy (ISCT) in May 2022, President Bruce Levine emphasized the need for CGT training and education to combat the shortage of workers in the industry.[23] Groups like the ISCT and academia are investing in these initiatives, but they will take years to show results. Likewise, automation technology will provide similar relief to the industry, but in the short run processes are still highly manual.[24]

In addition to human capital concerns that may limit growth, CGT companies must ensure that they are correctly projecting the manufacturing capacity required to fully satisfy the market for their therapeutics. A number of CGT manufacturers have underestimated their needs due to poor demand planning, which has forced them to pull back on global expansion efforts and deprioritize important market launches due to the lack of available product.

J&J and Legend, for example, recently described themselves as being in a “supply-constrained environment” partially driven by a lack of slots to produce T-cells. They announced in October 2022 plans to double investment to $500 million in a New Jersey manufacturing facility in order to satisfy newly projected demand for the multiple myeloma CAR-T treatment Carvykti (ciltacabtagene autoleucel) in the US.[25] As pipelines and commercial portfolios grow, companies need to ensure they will have enough supply in the future, either by building their own facilities in advance or through outsourcing agreements.

How companies can address growth in the short term:

- **Increase investment in talent identification and retention.** Competition for talent means that not all companies will be properly staffed to ensure timely product development and commercialization. Companies must ensure they have staffing scale-up and retention strategies in place to match their future growth projections and minimize turnover. Companies must also reinforce their relationships with leading universities to ensure new, highly skilled graduates can easily transition into the workforce.

- **Upskill your employees.** Leaders at larger companies should develop the capability to transition workers from small molecule and/or biologics workforces into cell and gene therapy. Companies must ensure they have the proper programs in place to train talent, or they’ll risk putting their clinical and commercial programs at risk.

- **Implement proven demand forecasting and planning approaches.** Teams must ensure that their current manufacturing network can support both the current portfolio and future drugs undergoing clinical development. Construction plans and contract development and manufacturing organization (CDMO) contracts must be built with enough optionality to adjust to the growing pipeline.

4. Allogeneic therapies will disrupt the current supply chain paradigm

Allogeneic therapies represent a particularly disruptive advance on the horizon for the CAR-T market. These “off-the-shelf” treatments use donor cells or induced pluripotent stem cells to create a standardized target cell therapy for the general population, instead of a highly individualized batch made from a patient’s own cells. Allogeneic therapies have the potential to significantly improve costs with shorter treatment timelines, simplified supply chains and economies of scale during the manufacturing process. Research suggests that the costs of manufacturing an autologous CAR-T gene therapy product are $95,780 per dose compared to $4,460 for an allogeneic product.[26]

In theory, allogeneic therapies could also elicit a superior efficacy and safety profile when compared to autologous therapies due to the standardization and improvement of the cell starting materials. Unfortunately, progress has been slowed by clinical holds.

In January 2022, the FDA removed a clinical hold on all five of Allogene Therapeutics’ AlloCAR T clinical trials.[27] The hold had been in place since October 2021 after a report of a chromosomal abnormality detected post-administration in a single patient. In August 2022, the FDA lifted another hold that had been imposed in March 2022 on a Phase 1B trial for Celyad Oncology’s CYAD-101 after two fatalities prompted a voluntary pause.[28]

At present, most allogeneic CAR-T and CAR-natural killer (CAR-NK) therapies are in preclinical or early clinical development stages. However, a few allogeneic therapies are in advanced stages of development. Atara Biotherapeutics’ Ebvallo (tabelecleucel), a T-cell immunotherapy, was approved in Europe in December 2022.[2930] Precision BioSciences (PBCAR0191), Allogene Therapeutics (ALLO-501) and CRISPR Therapeutics (CTX110) are contenders to become the first allogeneic therapies approved in the United States[31]

While allogeneic CAR-T therapies have shown promise, there are challenges associated with manufacturing them. One important factor is that the materials required to manufacture allogeneic therapies differ from those required to manufacture autologous therapies. In particular, primary cell suppliers will become increasingly essential as the market shifts toward allogeneic therapies in the coming years.

The challenges currently faced by the CGT market in regard to the supply-constrained viral vector marketplace could emerge in the cell supplier space. Current suppliers include Charles River Labs (which purchased Cellero in 2020 and HemaCare in 2019), Be The Match and the American Red Cross.

Another important factor is the design of the manufacturing and supply network. Autologous therapies are generally outsourced at early stages, but in-sourced during commercial production. Given the scale advantages and fewer logistical challenges that allogeneic products present, companies may decide to shift toward a more outsourced model during all stages of development. In addition, the current ecosystem of manufacturing technology and processes designed for autologous therapies has not been designed to embrace scaled-up manufacturing and automation.

How companies can continue to address the network as science evolves:

- **Perform a gap analysis to ensure your existing infrastructure will support new therapies.** The supply chain of an allogeneic therapy is completely different from the supply chain of an autologous therapy. Companies will have to conduct a gap analysis of their existing autologous suppliers, workforce, capabilities and technology to determine what components need to be phased out or brought in to fit the new paradigm.

- **Pressure test all guiding principles and planning parameters.** The flexibility of allogeneic therapeutics will allow companies to ask questions they would not have contemplated when working with autologous therapies.[32] Where should one position product inventory and distribution channels for delivery as you wait for patients to enter the clinic? What logistical costs can be minimized when chain of identity is no longer required for an “off-the-shelf” product? Can a manufacturer shift back to a model with a single manufacturing site when vein-to-vein is no longer a key differentiating factor?

5. Subpar quality control can derail development, risk lives

Robust quality control is important for all pharmaceutical products to ensure successful outcomes and build trust in the patient and provider community. Strict quality controls are necessary to ensure patient safety, but navigating the quality challenges for CGTs will be critical to ensure timely access to these novel therapies. Doctors also have concerns about long-term safety and efficacy, issues that can dampen interest in trying complex new therapies.

Trials supporting new cell and gene therapies typically include a small number of participants due to the low availability of sick patients and the rarity of many of the target diseases. Furthermore, safety risks have often slowed down or derailed development.[33] For this reason, clinical activity in the cell and gene therapy space requires especially close communication and collaboration between the R&D and quality functions.

Recent quality control issues have highlighted the risks of manufacturing for CGT products. Failures in detecting byproducts while engineering personalized cells have led to patient deaths during clinical trials, emphasizing the importance of well-developed quality control methods.[34] Handling the inspection of incoming material is risk-based, and when dealing with incoming apheresis materials, companies should include risk management of materials originating from hospitals classified as non-good manufacturing practice (GMP) environments.

As the industry — and its regulators — ramp up knowledge and experience in this new field and technologies, all major players agree there will be a learning curve. Companies and inspectors must understand and standardize guardrails for product development and analytical method development, making it challenging to define a single compliance goal.

As CGT companies begin handling one-time treatments in a pressured time window, it's critical to create an efficient process for handling out-of-specification (OOS) results and the potential release of a confirmed OOS batch based on a thorough risk-benefit analysis in line with regulations. While the European Medicines Agency (EMA) allows exceptional administration of confirmed OOS batches of cell-based advanced therapy medicinal products with a marketing authorization after risk-benefit assessment and involvement of treating physicians, the FDA only allows this for investigational new drug products.[35]

To accelerate delivery to patients while safeguarding product quality and patient safety, it is important for CGT organizations to set up a quality management system (QMS) that's fit for purpose to drive efficient and on-time delivery to patients. The traditional QMS needs to be reshaped to handle new situations with a risk-based approach and an eye for the best outcome for patients.

CGT companies must consider their ability to deliver a quality product. Traditional drug manufacturers can replace faulty batches with good ones, but autologous cell therapy producers of individualized therapies can't always do the same. A poor-quality autologous cell therapy product could result in restarting the entire process — and with patients waiting for cancer therapy, delays in treatment may mean the difference between life and death, and also could undermine outcomes-based contracts with insurers and government payers. Digital platforms can help set up industry players in this field for success by allowing end-to-end visibility and transparency throughout the supply chain, and monitoring the chain of custody and chain of identity.

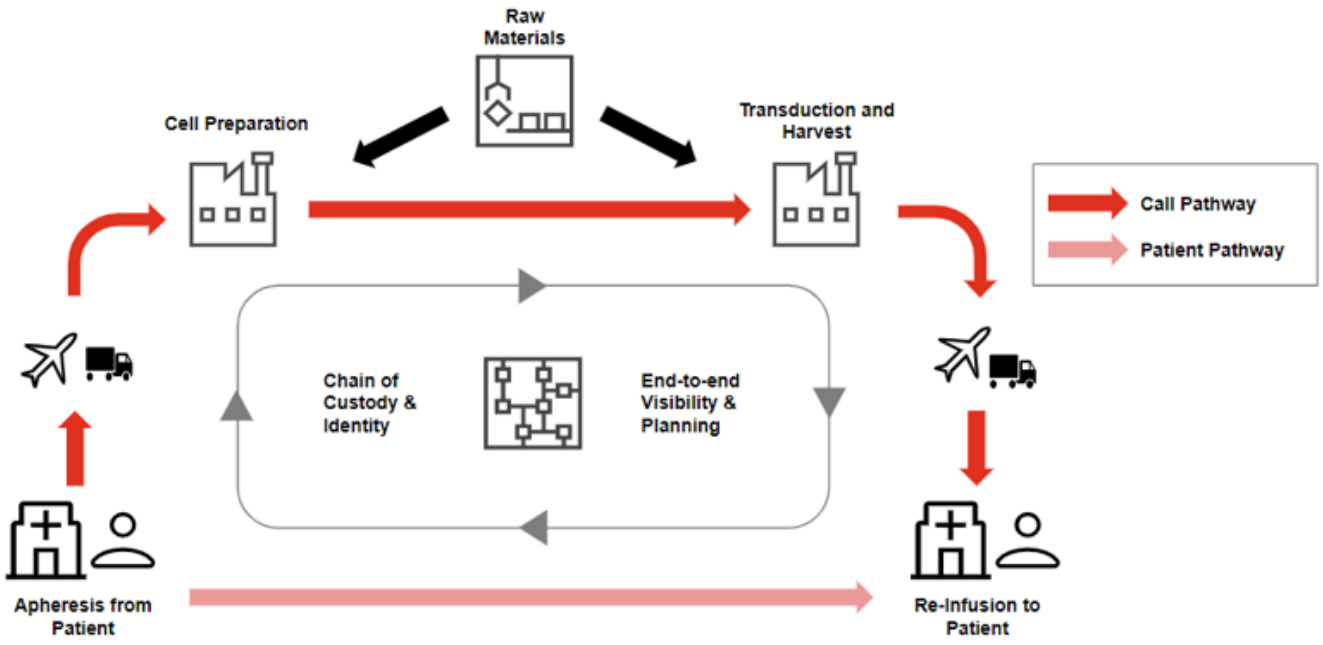
How the quality unit can position itself as a key enabler:

- **Establish a fit-for-purpose QMS** to accelerate delivery to patients while safeguarding product quality and patient safety, it is important for CGT organizations to set up a Quality Management System fit for purpose to meet new needs of novel therapies.
- **Develop deviations and OOS management procedures** to accelerate handling of OOS results and allow release of product supported by a risk based approach.
- **Accelerate learning.** As the industry – and consequently its regulators – ramp up knowledge and experience in this new field and technologies, standardizing definitions, measurements and applicability of parameters such as CQA, CPP, purity, potency of viral vectors, standardization of labeling and platform technology for CoI and CoC will be important to harmonize and assure speed to market with minimal error.
- **Drive collaboration with regulators** to address the learning curve on quality parameters, analytical method development and assays for CGTs.
- **Take advantage of digital enablers to drive quality.** Platforms for quality control, end to end traceability, chain of identity and chain of custody support integration of players along the value chain end to end and create transparency for batch status and tracking at all times.
- **Include QA functions in establishing strategic relations with external parties** such as CMOs and suppliers of starting materials or hospitals for apheresis materials to support a robust supplier quality management program.

6. Decentralized manufacturing will force organizations to rethink network design

The complexity of the supply chains required for autologous cell therapy manufacturing needs to be simplified. Providers and pharmaceutical companies need to extract cells from the patient, tag them with a resilient and foolproof tracking system to ensure chain of custody and chain of identity, ship them under specific conditions to one or more manufacturing facilities, ship the cells back to the same administration site and coordinate an appointment with the original patient within a specific timeframe.

Figure 3: Autologous Cell Therapies Rely on Complex Supply Chains with Many Potential Sources of Error



Source: PwC analysis

Every step in this process provides abundant opportunities for human error, timeline delays and quality disruptions that could impact the efficacy and safety of the product. The time in transit and the technology required to minimize risk drive up the total cost of administration significantly.

The possibility of flexible modular manufacturing (GMP-in-a-box solutions) has driven significant interest in regional therapy production. Many companies have already established regional manufacturing hubs to minimize the distance between patients and the factory, such as Bristol Myers Squibb's new facility in Leiden.[36] But truly decentralized manufacturing could be distributed to the state, province or even clinic level, circumventing many of the current logistical challenges.

In theory, GMP-in-a-box technology condenses all steps of the CAR-T manufacturing process into an automated, closed system that can be installed within a clinic. A number of major players have targeted the GMP-in-a-box market in recent years, with Miltenyi Biotec (CliniMACS Prodigy) as the first mover and Lonza (Cocoon), ThermoGenesis (CAR-Txpress), Cellares (Cell Shuttle) and Thermo Fisher Scientific (Rotea) providing competitive alternatives.

Recent clinical successes have shown the value of using a modular, decentralized manufacturing approach. A point-of-care CAR-T therapy manufactured at the University of Colorado showed encouraging efficacy for refractory B-cell non-Hodgkin lymphoma patients in a phase 1 study.[37] The CliniMACS Prodigy was used to develop the clinical supply on campus, allowing for a vein-to-vein,

apheresis-to-infusion time of two weeks. In December 2021, Leucid Bio announced that it had agreed to collaborate with Lonza to use the Cocoon for phase 1 clinical through commercial manufacturing of CAR-T cells for the company's lead candidate LEU-011.[38] This CAR T-cell therapy is intended to treat both tumors and hematological malignancies. Earlier in 2021, Lonza and the Sheba Medical Center had announced successfully dosing multiple patients with a CAR-T cell therapy using Lonza's Cocoon automated manufacturing platform.[39]

In addition, Cytiva recently announced that it was collaborating with Bayer to develop the first modular end-to-end manufacturing platform for allogeneic cell therapy.[40] Cytiva will be supplying end-to-end manufacturing solutions, and Bayer will bring expertise in technology and process development for complex therapeutics.

These platforms aim to decrease manufacturing costs, simplify logistics, reduce the footprint and minimize vein-to-vein time for the patient populations. Although not widely available at the moment, in the near future, decentralized manufacturing networks could disrupt cell therapy supply chains as much as, if not more than, allogeneic therapies.

How companies can continue to build flexibility in operations as new technology emerges:

- **Quantify the benefits of implementing decentralized manufacturing.** Supply chain professionals may be underestimating the speed at which modular cell therapy manufacturing suites will be widely available at the clinic level. The potential impact on supply chain paradigms should encourage companies to reevaluate their current portfolio to see which products or geographies could be improved by a transition away from traditional network designs with centralized manufacturing sites.

- **Establish partnerships with GMP-in-a-box providers.** It is important to integrate modular manufacturing partners early in the clinical development process and facilitate their access to the provider sites that give patients access to therapeutics.

7. New technologies will add further complexity to the viral vector marketplace

The most important raw ingredients required to manufacture cell and gene therapies are viral vectors. Although CDMOs have expanded capacity in recent years, they have yet to meet the demand for this critical input. Viral vectors are required for a wide range of therapeutic products beyond CGT — including COVID-19 vaccines — so it is a competitive marketplace for companies in both the short and long term.

Recent analysis suggests that there are less than 90 viral vector contract manufacturing sites worldwide, with the vast majority located in the United States and Europe (primarily the United Kingdom).[41] The marketplace is responding accordingly, with a number of large projects recently announced to increase capacity both for CDMOs and drug companies, including a new $40 million Fujifilm viral vector manufacturing site in Boston and Gilead's new 67,000-square-foot viral vector facility in Oceanside, California.[42,43]

The market for acquiring viral vector manufacturing has also seen significant activity, highlighted by Thermo Fisher's $1.7 billion deal for viral vector manufacturer Brammer and Catalent's $1.2 billion acquisition of Paragon Bioservices, a gene therapy CDMO.[44,45] Companies are aware that lack of access to viral vectors will lead to delays in clinical trials. Wait times were approximately 16 months in 2018 and may have grown as high as three years more recently.[46,47] Even worse, for an established commercialized product, a break in supply continuity for viral vectors could prevent a patient from accessing life-saving medicine.

Several innovations could alleviate the pressure on viral vector markets in the short term. The first is a focus on improving and standardizing manufacturing processes and methods. Today, vectors derived

from adeno-associated virus (AAV) and lentivirus are the most prevalent in the industry. AAVs are the leading viral vector for gene therapy, while lentivirus is the primary vector for cell therapy products.

Various upstream factors can impact the vector titer of both AAV and lentivirus processes, including plasmid design, conditions for cell cultures and other raw ingredients, while key downstream steps such as chromatography also have an impact on yield and cost. But many of the existing processes were developed to serve small patient populations or clinical trials, neither of which are suitable for the higher demand associated with more indications and vaccines. [48]

For example, many of the cells used to generate viral vectors today are adherent cells that are limited by the size of the surface area of the device in which they are grown, thereby forcing the manufacturer to increase the size or number of growing devices. Alternatively, cells that can be grown in suspension can enable the use of large-tank bioreactors, which often have additional benefits in the form of reduced production units, increased automation and less contamination risk. [49]

Unfortunately, some manufacturers may be too far along in the path toward commercialization to adjust their production process and adapt to the latest optimized viral vector technology. Transitioning from an adherent to suspension-based system could necessitate significant comparability testing and regulatory filing hurdles to measure and report any biological differences between the two viral vector processes. Further optimization is required at early stages of development to avoid this process development trap.

In the long term, there is great interest in finding substitutes for viral vectors that could help to lessen the pressure on the supply constrained industry. Although these alternative gene delivery mechanisms may not be suitable for all therapies, an alternative for a subset of products could divert demand away from the constrained resources and provide more access for the rest of the industry. These non-viral vectors include both physical and chemical strategies, including but not limited to: lipid-based nucleic-acid-delivery systems, naked plasmids, electroporation, ballistic DNA, sonoporation and photoporation.[50]

How to stay ahead of viral vector supply bottlenecks:

- **Lock-in supply commitments early.** Solidify contracts with CDMO suppliers many years prior to clinical and commercial launches or through in-house viral vector manufacturing capacity.
- **Invest in resources to survey the viral vector technology landscape.** Product development teams must remain vigilant of the newest viral vector production technology on the market to ensure that this key raw material does not cause constraints or delays on the integrated product development plan.
- **Improve your production process as early as possible to avoid longer delays.** Companies must transition their portfolios toward lower-cost vector supply by integrating both short-term (e.g., suspension cell-based manufacturing) and long-term (e.g., naked plasmids) opportunities. Waiting until the product is already commercialized will add significant delays and risks.

Smart companies can prepare for long-term success

As interest in the CGT market continues to grow, companies throughout the industry must find solutions to address these challenges. In this article, we reviewed a broad range of topics that should be top of mind, including: slower than anticipated sales, barriers to administration, greater competition for workers, supply chain and network design disruptions, quality risks and viral vector technology disruptions.

Anticipating and creating strategies to prepare for these and other scenarios can help ensure that biopharma companies are able to go to market, drive pipeline growth and ultimately find success. We hope that this overview can spur some productive discussions about how company executives and other decision-makers can best prepare their organizations for the years ahead in this exciting new area of development and commercialization.

Authors:

Greg Rotz,
Partner, Pharmaceutical and Life Sciences Transformation Leader, PwC US
greg.rotz@pwc.com

Shaguna Punj,
Partner, Strategy&, PwC US
shaguna.punj@pwc.com

Rohit Harve,
Managing Director, Strategy&, PwC US
rohit.harve@pwc.com

Alvin Tam,
Director, Strategy&, PwC US
alvin.tam@pwc.com

Brendon Pezzack,
Senior Manager, PwC US
brendon.e.pezzack@pwc.com

Caroline Kustermans,
Manager, PwC US
caroline.k.kustermans@pwc.com

Endnotes

[1] Office of the Commissioner “FDA approval brings first gene therapy to the United States.” U.S. Food and Drug Administration, FDA, 30 Aug. 2017, https://www.fda.gov/news-events/press-announcements/fda-approval-brings-first-gene-therapy-united-states.

[2] CAR T-cell therapy total cost can exceed $1.5 million per treatment.” Healio, 29 May 2019, https://www.healio.com/news/hematology-oncology/20190529/car-tcell-therapy-total-cost-can-exceed-15-million-per-treatment.

[3]Kansteiner, Fraiser. “Bluebird Bio's $2.8M gene therapy Zynteglo wins FDA backing. Will Its US launch take flight?” Fierce Pharma, 17 Aug. 2022, www.fiercepharma.com/pharma/bluebirds-28m-gene-therapy-zynteglo-gets-fda-backing-beta-thalassemia.

[4] Bluebird Bio reports second quarter financial results and provides operational update.” Business Wire, 9 Aug. 2021, www.businesswire.com/news/home/20210809005334/en/bluebird-bio-Reports-Second-Quarter-Financial-Results-and-Provides-Operational-Update.

[5] The global use of medicines 2022.” IQVIA, 9 Dec. 2021, www.iqvia.com/insights/the-iqvia-institute/reports/the-global-use-of-medicines-2022.

[6] Tunis, Sean, et al. “Variation in market access decisions for cell and gene therapies across the United States, Canada, and Europe.” Health Policy, vol. 125, no. 12, Dec. 2021, pp. 1550–1556., doi:10.1016/j.healthpol.2021.10.003.

[7] “ICER publishes evidence report on gene therapy for Beta thalassemia.” Institute for Clinical and Economic Review, 2 June 2022, icer.org/news-insights/press-releases/icer-publishes-evidence-report-on-gene-therapy-for-beta-thalassemia/.

[8] Faylor, Gordon. “Bluebird's $2.8M gene therapy opens door to pricing questions.” MM+M - Medical Marketing and Media, 19 Aug. 2022, www.mmm-online.com/home/channel/bluebirds-2-8m-gene-therapy-opens-door-to-pricing-questions/.

[9] CMS issues final rule to empower states, manufacturers, and private payers to create new payment methods for innovative new therapies based on patient outcomes.” Centers for Medicare & Medicaid Services, 21 Dec. 2020, www.cms.gov/newsroom/press-releases/cms-issues-final-rule-empower-states-manufacturers-and-private-payers-create-new-payment-methods.

[10] Ledford, Heidi. “Last-resort cancer therapy holds back disease for more than a decade.” Nature, vol. 602, no. 7896, 2022, pp. 196–196., doi:10.1038/d41586-022-00241-0.

[11] Kelly, Cathy. “Zynteglo could be gene therapy test case for viability of outcomes-based Contracts – UHC EXEC.” Pink Sheet, 21 June 2022, pink.pharmaintelligence.informa.com/PS146370/Zynteglo-Could-Be-Gene-Therapy-Test-Case-For-Viability-Of-Outcomes-Based-Contracts — UHC-Exec.

[12] Jostz, Laura. “Car T offers clinical hope but reimbursement, access hurdles remain.” AJMC, 1 Apr. 2022, www.ajmc.com/view/car-t-offers-clinical-hope-but-reimbursement-access-hurdles-remain.

[13] Godwin, John E., et al. “Outreach: Results from a phase 2 study of lisocabtagene maraleucel (Liso-Cel) administered as inpatient (INPT) or outpatient (Outpt) treatment in the non-university setting in patients (PTS) with R/R large B-cell lymphoma (LBCL).” Blood, vol. 138, no. Supplement 1, 2021, pp. 1762–1762., doi:10.1182/blood-2021-148792.

[14] Amorosi, Drew. “Outpatient therapy: Bringing Car T cells closer to home.” Healio, 20 Dec. 2021, www.healio.com/news/hematology-oncology/20211220/outpatient-therapy-bringing-car-t-cells-closer-to-home.

[15] Alexander, Maurice, et al. “Chimeric antigen receptor T cell therapy: A comprehensive review of clinical efficacy, toxicity, and best practices for outpatient administration.” Transplantation and Cellular Therapy, vol. 27, no. 7, 2021, pp. 558–570., doi:10.1016/j.jtct.2021.01.014.

[16] Zaloga, Steven. “Revolutionizing cell and gene therapy with a frictionless experience.” LinkedIn, PwC, 12 Aug. 2021, www.linkedin.com/pulse/revolutionizing-cell-gene-therapy-frictionless-steven-zaloga/.

[17] Alliance for Regenerative Medicine. 2021, alliancerm.org/wp-content/uploads/2022/03/ARM_AR2021_FINAL-singles.pdf.

[18] Marks, Peter, and Patrizia Cavazzoni. “FDA user fee reauthorization: Ensuring safe and effective drugs and biologics.” U.S. Food and Drug Administration, 3 Feb. 2022, www.fda.gov/news-events/congressional-testimony/fda-user-fee-reauthorization-ensuring-safe-and-effective-drugs-and-biologics-02032022.

[19] Gingery, Derrick. “New name, old problems: US FDA's cell and gene therapy office still facing growth challenges.” Pink Sheet, 5 Oct. 2022, pink.pharmaintelligence.informa.com/PS147080/New-Name-Old-Problems-US-FDAs-Cell-And-Gene-Therapy-Office-Still-Facing-Growth-Challenges.

[20] Wechsler, Jill. “FDA expands oversight of cell and gene therapies.” PharmTech, 12 Oct. 2022, www.pharmtech.com/view/fda-expands-oversight-of-cell-and-gene-therapies.

[21] Cline, Helen. “Evolving EU policy on cell and gene therapies needs views of business.” Pinsent Masons, 17 June 2022, www.pinsentmasons.com/out-law/analysis/evolving-eu-policy-on-cell-and-gene-therapies-needs-views-of-business.

[22] 2021 UK Cell and Gene Therapy Skills Demand Survey Report. 2021, www.atskillstrainingnetwork.org.uk/app/uploads/2021/12/2021-Skills-Demand-Survey-Report.pdf.

[23] ISCT president calls for cell and gene therapy education, training amid 'talent shortage'.” The Science Advisory Board, 6 May 2022, www.scienceboard.net/index.aspx?sec=rca&sub=isct_2022&pag=dis&ItemID=4228.

[24] Pillar, Matthew. “Taking on the talent crunch in biopharma, cell & gene manufacturing.” Bioprocess Online, 1 Mar. 2021, www.bioprocessonline.com/doc/taking-on-the-talent-crunch-in-biopharma-cell-gene-manufacturing-0001.

[25] Liu, Angus. “J&J, Legend double Car-T manufacturing investment to $500m as Carvykti eyes wider myeloma use.” Fierce Pharma, 6 Oct. 2022, www.fiercepharma.com/manufacturing/legend-jj-double-down-car-t-manufacturing-500m-carvykti-eyes-wider-myeloma-use.

[26] Harrison, Richard P., et al. “Chimeric antigen receptor–T cell therapy manufacturing: Modelling the effect of offshore production on aggregate cost of goods.” Cytotherapy, vol. 21, no. 2, 12 Feb. 2019, pp. 224–233., doi:10.1016/j.jcyt.2019.01.003.

[27] Allogene Therapeutics announces removal of FDA clinical hold across all AlloCAR T clinical trials.” Allogene, 10 Jan. 2022, ir.allogene.com/news-releases/news-release-details/allogene-therapeutics-announces-removal-fda-clinical-hold-across.

[28] Celyad Oncology SA. “Celyad Oncology announces FDA lifts clinical hold of CYAD-101-002 phase 1b Trial.” GlobeNewswire News Room, Notified, 1 Aug. 2022, www.globenewswire.com/news-release/2022/08/01/2489100/0/en/Celyad-Oncology-Announces-FDA-Lifts-Clinical-Hold-of-CYAD-101-002-Phase-1b-Trial.html.

[29] “European Medicines Agency (EMA) validates Atara Biotherapeutics' marketing authorization application for tabelecleucel for the treatment of Epstein-Barr virus-positive post-transplant lymphoproliferative disease.” Atara Bio, 30 Nov. 2021, investors.atarabio.com/news-events/press-releases/detail/254/european-medicines-agency-ema-validates-atara.

[30] Schloesser, Paul. “EC approves first allogeneic T-cell therapy for rare post-transplant complication,” 19 Dec. 2022, https://endpts.com/ema-approves-first-allogeneic-t-cell-therapy-for-rare-post-transplant-complication/.

[31] DeArment, Alaric. “Precision's Allo Car-t inches closer to filling post-auto Car-T niche.” Scrip, 9 June 2022, scrip.pharmaintelligence.informa.com/SC146529/Precisions-Allo-CAR-T-Inches-Closer-To-Filling-Post-Auto-CAR-T-Niche?vid=Pharma.

[32] Reed, Carla. “Recalibrating the supply chain for allogeneic cell therapies.” Recalibrating The Supply Chain For Allogeneic Cell Therapies, 25 Feb. 2019, www.cellandgene.com/doc/recalibrating-the-supply-chain-for-allogeneic-cell-therapies-0001.

[33] Arnold, Carrie. “Record number of gene-therapy trials, despite setbacks.” Nature Medicine, vol. 27, no. 8, 5 Aug. 2021, pp. 1312–1315., doi:10.1038/s41591-021-01467-7.

[34] Nawrat, Allie. “Patient death following CAR-T therapy highlights serious manufacturing issues.” Pharmaceutical Technology, 24 Mar. 2022, www.pharmaceutical-technology.com/news/patient-death-following-car-t-therapy-manufacturing/

[35] Questions and answers on the use of out-of-specification batches of authorized cell/tissue-based advanced therapy medicinal products.” European Medicines Agency, 24 Apr. 2019.

[36] Bristol Myers Squibb starts construction of its European therapy facility, at Leiden Bio Science Park.” Bristol Myers Squibb, 28 Oct. 2021.

[37] Amorosi, Drew. “Point-of-care Car-T shows 'promising' efficacy, safety for B-cell non-Hodgkin lymphoma.” Healio, 9 Apr. 2022, www.healio.com/news/hematology-oncology/20220408/pointofcare-cart-shows-promising-efficacy-safety-for-bcell-nonhodgkin-lymphoma.

[38] Pharmaceutical Technology Editors. “Leucid Bio to use Lonza's Cocoon platform for automated manufacturing of CAR T cells.” PharmTech, 9 Dec. 2021, www.pharmtech.com/view/leucid-bio-to-use-lonza-s-cocoon-platform-for-automated-manufacturing-of-car-t-cells.

[39] Editors Pharmaceutical Technology. “Lonza and Sheba Medical Center demonstrate successful cell therapy results with Cocoon automated platform.” PharmTech, 12 Aug. 2021, www.pharmtech.com/view/lonza-and-sheba-medical-center-demonstrate-successful-cell-therapy-results-with-cocoon-automated-platform.

[40] Nelson, Millie. “Cytiva and Bayer partner to develop allogeneic platform - Bioprocess Insider.” BioProcess International, Informaconnect, 7 July 2022, bioprocessintl.com/bioprocess-insider/deal-making/cytiva-and-bayer-partner-to-develop-allogenic-cell-therapy-platform/.

[41] GlobalData Healthcare. “Few contract manufacturing sites exist to supply world's viral vectors.” Pharmaceutical Technology, 18 July 2022, www.pharmaceutical-technology.com/comment/few-contract-manufacturing-sites-exist-to-supply-worlds-viral-vectors/.

[42] Weintraub, Arlene. “Fujifilm triples down on viral vector manufacturing with new $40m Boston site.” Fierce Pharma, 5 Jan. 2021, www.fiercepharma.com/manufacturing/fujifilm-triples-down-viral-vector-manufacturing-new-40m-boston-site.

[43] Weintraub, Arlene. “Fujifilm triples down on viral vector manufacturing with new $40m Boston site.” Fierce Pharma, 5 Jan. 2021, www.fiercepharma.com/manufacturing/fujifilm-triples-down-viral-vector-manufacturing-new-40m-boston-site.

[44] Palmer, Eric. “Thermo Fisher shoulders into gene therapy ,manufacturing with $1.7B deal for Brammer.” Fierce Pharma, 25 Mar. 2019, www.fiercepharma.com/manufacturing/thermo-fisher-shoulders-into-gene-therapy-manufacturing-1-7b-deal-for-brammer.

[45] https://www.catalent.com/catalent-news/catalent-to-acquire-gene-therapy-leader-paragon-bioservices-inc-for-1-2-billion/

[46] Lo, Chris. “Can the Gene and Cell Therapy Revolution Scale up?” Pharmaceutical Technology, 23 Mar. 2022, www.pharmaceutical-technology.com/analysis/can-gene-cell-therapy-revolution-scale/.

[47] Zamecnik, Adam. “A perfect storm: Covid-19 viral vector manufacturing adds further burden to Car-t development.” Pharmaceutical Technology, Verdict, 7 June 2022, www.pharmaceutical-technology.com/analysis/a-perfect-storm-covid-19-viral-vector-manufacturing-adds-further-burden-to-car-t-development/.

[48] Mirasol, Feliza. " Driving manufacturing improvements through viral vector advances." Biopharm International, Aug. 2022, www.biopharminternational.com/view/driving-manufacturing-improvements-through-viral-vector-advances.

[49] Pettit, Steve, et al. "Upstream manufacturing of gene therapy viral vectors." Cell Culture Dish, 26 Apr. 2021, cellculturedish.com/upstream-manufacturing-gene-therapy-viral-vectors/.

[50] Kanvinde, Shrey, et al. "Non-viral vectors for delivery of nucleic acid therapies for cancer." BioTech, vol. 11, no. 1, 2022, p. 6., doi:10.3390/biotech11010006.

Thank you

www.pwc.com