# Accelerating cell and gene therapy development

**As cell and gene therapies show increasing promise for improving patient care, the need to overcome the complex manufacturing and delivery model is vital if the pharma industry intends to keep pace with market demands**

## Inside this report:

- How to accelerate the timeline to commercialize cell and gene therapies and deliver to patients in need.
- Actions pharma companies can take to improve resiliency and efficiency in their supply chains.
- How to navigate crisis recovery from the Covid-19 pandemic and continue developing cell and gene therapies at scale.

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# An introduction to cell and gene therapy



Cell and gene therapies (CGTs) have advanced since US-based National Institutes of Health undertook the first gene therapy clinical research in 1990. While the **concepts initially arose** in the late 1960s and early 1970s, developments in CGTs have accelerated in the past three decades as big pharma increased its involvement, giving rise to new clinical trials and facilities to manufacture these therapies at scale.

"Important advances in our understanding of disease biology and major innovations in gene editing, protein engineering and cell culture technology have created a highly fertile scientific environment in which cell therapy research is flourishing," explains Regina Fritsche Danielson, Senior Vice President and Head of Research and Early Development, Cardiovascular, Renal and Metabolism, BioPharmaceuticals R&D at AstraZeneca.

**Novartis** defines cell therapy as aiming to treat, prevent or potentially cure diseases by "restoring or altering certain sets of cells or by using cells to carry a therapy through the body", with cells originating from patients or donors. The company defines gene therapy as aiming to treat, prevent or potentially cure diseases by "replacing, inactivating or introducing genes into cells" either inside or outside the body. Some treatments can be defined as CGTs when genes are altered in specific types of cells and inserted into the body.

Arianna Kalkandis, Field Applications Engineer at Entegris says that gene therapy is "the introduction and removal or change in a person's genetic code" and within CGT there are many "overlapping factors".

A study on **delivering cellular and gene therapies to patients** found at least 95 per cent of people received medicines only through commercial delivery, however, stakeholders have struggled to develop and sustain successful business models for CGTs.

There are four contributing challenges facing stakeholders in the pharma arena when seeking to accelerate CGT development - industrialization (developing reliable, robust manufacturing processes); manufacturing (providing infrastructure and expertize to innovate, scale up and commercialize therapies at a reduced risk); regulation (understanding the sector's constant evolution, actions and processes); and clinical trial delivery (getting the right data to demonstrate efficacy and safety).

If pharma companies can leverage their breadth and depth to develop new, personalized therapies, run new trials and further scale up their manufacturing processes, CGTs will drive increased benefits to patients and cure conditions at a faster rate.

In this report Pharma IQ tackle the key challenges the pharma industry is facing in the development of CGTs. The report will also identify solutions from Entegris, AstraZeneca and PPD to accelerate the approval of projects, making the development of CGTs safer, more effective, scalable and affordable.

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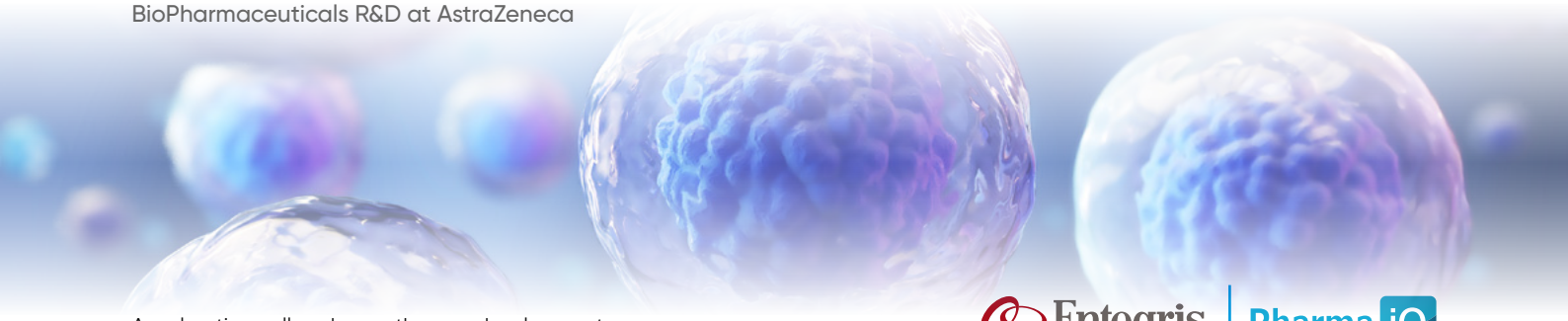
**Regina Fritsche Danielson**

Senior Vice President and Head of Research and Early Development, Cardiovascular, Renal and Metabolism, BioPharmaceuticals R&D at AstraZeneca



# Challenges in bringing cell and gene therapies to market

The twin challenges of scalability and manufacturability are related – the ability for CGTs to reach their clinical potential safely, quickly and affordably is vital to achieve widespread access.

Inefficiencies highlight a need for process standardization. Adherent upstream processing, cell line expansion and current packaging methods are inefficient, and given the **high viral titer numbers** (the concentration of viral particles that can transduce cells) indicated in recent approvals, scaling up is difficult.

In order for CGT to thrive in the market, technology providers and suppliers need to join the development process so treatments can come to market quickly and safely. Their role should include automating systems and understanding the contribution of labor, overheads and economies of scale from reducing processes.

Dr Panteli Theocharus, Global Vice President and CGT Strategy Lead, for contract research organization, PPD, says manufacturing is complicated by personalized therapies in a complex, multi-step process of generating autologous products with a risk of production failure, delays and patients being denied access to treatment.

"Failed manufacturing or human error remind us that this is personalized medicine and cannot be replicated under urgent circumstances," Theocharus says.

The fragmented market can make CGT delivery complex, time-consuming and expensive. In some cases, pharma companies have to negotiate terms with every regional authority.

The Covid-19 pandemic has also exposed additional vulnerabilities in CGT supply chains, where challenges already existed in getting new treatments to patients. Kalkandis gave the example of government approval in the US being required for commercial flights to deliver bags of high-value, sensitive products as a challenge during the pandemic.

"We have seen the single-use industry lead times at an all-time high, so it makes accessibility to these life-saving products a challenge," Kalkandis says. "We have learnt to prioritize stock supply and forecasting, and make sure our lead times are always as competitive as possible; one delay can shut down an entire site."

Data privacy is another concern. In Europe, data protection and privacy regulations require patients to consent every time their data is used unless it is anonymized. This protects patient privacy but increases clinical trial costs and adds to run-times.

PPD's Theocharous points out that the sheer volume of trials is not comparative to the number of accredited centers globally.

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Field Applications Engineer at Entegris

"While the treatment of cell therapy products must be mandated in certified centers by trained healthcare providers who adhere to risk evaluation and mitigation strategies guidelines, procedures such as leukapheresis now overwhelm centers due to the volume of cell therapy trials," he says. "Standard procedures contribute to the operational burden on institutions and staff participating in autologous therapies."

The fragmented market can make delivery of CGTs complex, lengthy and costly with added bureaucracy from negotiating with countries or different regions within countries. This is where governments can help to reduce red tape.

# Solutions for treatment manufacture and delivery

As well as technical solutions, there are major projects and consultative processes underway aimed at improving CGT processes. In areas such as cell culture components, production chemicals, single-use technologies, sterile-fluid transfer and excipients, technology partners can help ensure greater efficiencies. Value can also be added by improving collaboration wherever possible and trying new solutions to optimize manufacturability and scalability.

PPD's Theocharus for example emphasizes it is important to balance accelerated testing times and frequency with enhanced caution on small deviations, data entries and calculations when manufacturing CGTs as batch errors and delays in treatment can otherwise occur.

"In-house manufacturing, rather than an outsourced contract manufacturing organization, can provide additional oversight into the manufacturing process itself, which allows for increasing readiness of products as well as control over logistical challenges that come with the vein-to-vein process," he says. "Many logistical challenges associated with the complex manufacturing process of current autologous cell therapies will likely get addressed with allogeneic, off-the-shelf products."

AstraZeneca has sped up time to market and improved genome-engineering precision in human cells by using a bacterial toxin-based selection with the development of the Xential method. This reduced the time it takes to create a new clonal cell pool to one week, rather than four to six weeks with traditional cell enrichment processes.

"We are seeing our portfolio of CGTs therapies grow, which focuses on regeneration of tissues and organs using either a patient's own cells or donor cells, and modulation of the immune system with removal of diseased cells so that healthy cells can take their place," says AstraZeneca's Fritsche Danielson. "Alongside our pre-clinical research, we are already exploring the production and analytical processes to scale up manufacturing for promising future therapies."

Creating a regulatory environment that balances removing inefficient bureaucracy with maintaining safety is essential for CGTs to progress.

In the UK, regulatory change is likely after a **combined review** into clinical trials for medicinal products by the Medicines and Healthcare Products Regulatory Agency, Research Ethics Services and Health Research Authority, starting in January 2022.

The Northern Alliance Advanced Therapies Treatment Centre (NA-ATTC), a UK-based consortium of industry and academic organizations is developing systems and infrastructure to support CGT delivery to increase patient access to Advanced Therapy Medicinal Products (ATMPs) nationally. NA-ATTC released **guidance** in June 2021 on regulatory, health economy and commissioning processes and pathways. Additionally, the National Institute for Health and Care Excellence CGT process is being reviewed.

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The **Alliance for Regenerative Medicine** (ARM) praised the German parliament for approving legislation in June 2021 to accelerate patient access to CGTs by removing a bureaucratic barrier that delayed hospital availability. Inquiries for new ATMP examination and treatment methods will take place twice a year rather than annually.

"ARM applauds this action to reduce a bureaucratic hurdle that stood in the way of patient access to durable, and potentially curative, ATMPs," Paige Bischoff, Senior Vice President, Global Public Affairs at ARM says. "The legislation makes it easier for German hospitals to provide life-changing CGTs to patients, many of whom have few other treatment options."

European data protection laws can lengthen clinical trials, but the European Union (EU) has taken steps toward expediting clinical trials across the bloc. The **EU Clinical Trials Regulation** is slated to replace the EU Clinical Trials Directive by 31 January 2022. The EU Portal and Database will support a new regime for clinical trials in Europe, speed up authorization applications, improve transparency, simplify safety reporting, and require clinical trials taking place outside the EU but submitted for EU marketing authorization to follow similar provisions of the directive, effectively setting an international standard.

PPD's Theocharous says clinical trials can be improved by implementing CGT-specific education programmes for sponsors and institutions, training existing staff to specialize in CGTs, and assessing the necessary end-to-end expertise and comparing it to current internal proficiencies to highlight strengths and shortfalls.

## **Entegris case study:** A manufacturing solution in practice

Entegris worked with a large Covid-19 vaccine manufacturer to overcome supply chain challenges caused by the global pandemic such as shortages of raw materials and finished goods, which heavily disrupted manufacturing as a result.

Entegris' Kalkandis says: "The project helped us improve our knowledge on scaling up to meet demand with short notice, increase shipping requirements among multiple sites, and adapt our single-use technology designs for customers' ever-changing processes.

"Sometimes the pace of change for qualified products can take a long time due to the handling of quality risk management aspects, but with a laser focus and working more closely with our customers as a unified team we have been able to speed up the process."

A technical solution to a CGT manufacturing challenge is the **Aramus™ 2D single-use assembly by Entegris**. It protects high-value fluids and reduces the risk of product loss, contamination or compromised quality. The high-grade, gamma-stable fluoropolymer bags are universally compatible with chemicals and durable in frozen applications, with a temperature range of -85°C to 40°C. The single-layer construction has no binders or adhesives, reducing potential contaminants in the final product.

Kalkandis explains that for CGT, this technology protects patient material and improves workflow at different stages, such as sterile fluid transfer, freezing, shipping, storage and thawing.

"The Aramus bags are an industrialized cold chain solution that can adapt to the different steps, different products, different temperature requirements and different shipping requirements," says Kalkandis. "So that ability to adapt, manage, scale and provide speed will help improve that supply chain process."

"By implementing the higher-order, higher- end solutions via assessing different freezing methods… we have created a complete, robust cold chain packaging solution that goes beyond just the bag," she adds.

Real-world shipping and ASTM International standard studies evaluated the Aramus bag in a range of cold-chain distribution solutions, demonstrating the robustness of the bag to withstand thermal and mechanical stress in a variety of solutions. Across all trials the temperature was maintained during shipping. Drop tests ensured strength and confirmed that patient material would not be damaged in shipment. Final real-world shipping and drop tests showed the bags could withstand cryogenic temperatures.

# Cell and Gene therapy:
## The next frontier in pharma

Industry-wide collaboration and a facilitative regulatory environment are needed to bring products to market quickly and safely via efficient supply chains. Market fragmentation is less of an issue when processes are efficient, clinical trials optimized, technology valued and regulations balance safety with reducing bureaucracy.

Overcoming inefficiencies along the value chain is crucial for scaling up and ensuring quality treatments make it to market. Cell therapies, and some gene therapies, are personalized medicines, which a complicating factor in ensuring drug availability, but steps to eliminate human error, standardize systems, reduce waste, share knowledge and promote collaboration will improve the success rate from clinical trials to delivery.

Clinical trials will benefit from identifying training needs to optimize skills. Transparency in data-sharing and keeping patients and their families informed helps to boost confidence in the process from development to market. Back-up and mitigation plans are essential because of the fragile, unpredictable nature of trials involving cells and genetic material.

Technologies to improve monitoring, data-gathering and data-analysis are important, along with solutions that seem simple, such as Entegris's Aramus bags, but meet CGT trials' complex needs.

"By creating standardized, streamlined solutions, sometimes there are trends where we can develop products that solve multiple pain points for multiple customers with varying applications," says Kalkandis. "If a customer wanted to use Aramus for storage of a downstream intermediate for CGT and then wanted to use it for high-density cell banking, the efforts to see through qualification and regulatory approval are more efficient, because they are assessing one bag for multiple processes."

Encouragingly, 2021 has seen positive steps toward meeting CGT challenges, such as multiple industry collaborations and regulatory progress in Germany and the EU, with wider international implications. In 2022, the UK will launch a combined review into clinical trials for medicinal products, including CGTs, and a CGT consortium based in the north of England and Scotland aims to set high standards for the UK. Despite supply chain issues which affected the entire pharmaceutical industry in the wake of the Covid-19 pandemic, the CGT sector has the potential to emerge stronger than ever in a post-pandemic world.

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Field Applications Engineer at Entegris

# About Entegris

Our 50+ years of proven materials science experience in the most complex manufacturing environments positions us to serve as a trusted strategic partner to companies in the life sciences industry. Our solutions, which are among the cleanest, most scalable, and most reliable currently available, reduce your validation time, development costs, and time to market.

We combine product innovation with quick-turn customization to deliver critical solutions for your upstream and downstream needs. Our comprehensive set of bag solutions, bioreactors, mixing systems, and microcarrier separation systems meet the emerging requirements of fast-growing, single-use bioprocessing applications.

Entegris

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