



Adapting to the Ever-evolving Cell and Gene Therapy Landscape

Over the past 10 years, the cell and gene therapy (C>) space has grown rapidly, with the number of innovative medicines entering the development pipeline steadily rising year on year.

The potential of C>s continues to expand as our understanding of molecular biology and genetic engineering techniques grows and manufacturers adopt innovative technologies. As well as improving the safety, efficacy and manufacturability of these therapies while helping to broaden patient access, advancements in the C> space are driving trends and introducing new challenges. From meeting changing regulatory requirements to adopting strategies to minimise manufacturing costs, C> developers must adapt to navigate these novel difficulties and continue to provide life-changing medicines to current and future patients.

In this article, Andelyn Biosciences examine the drivers behind current trends in the C> space and the obstacles developers and manufacturers face on their journey to market. Leveraging its unique insight, Andelyn Biosciences emphasizes the importance of implementing specific strategies to quickly adapt to changing C> needs as they emerge.

Three Decades of Rapid Expansion

Following the success of the first approved gene therapy procedure in 1990 to treat a patient suffering from severe combined immunodeficiency (SCID), the biopharma industry has seen a steady increase in resources dedicated to unlocking the potential of C>s.¹

Over the last decade, the biopharma industry has intensified its focus on next-generation technologies such as C>s and precision medicines. There are now 26 gene therapies and 63 non-genetically modified cell therapies approved for clinical use globally.² These revolutionary therapies target a wide variety of indications, from rare diseases to cancers and neurological disorders.²

Prominent factors driving the demand for C>s include the rising prevalence of cancer worldwide and the expanding population of chronic disease patients.³ This growing demand is reflected in the projected expansion of the global C> market from US\$13 billion in 2022 to US\$62.5 billion by 2032 at a compound annual growth rate of 22.8%.⁴

Many of the therapeutics behind the recent growth in the C> market require an extremely skilled workforce, state-of-the-art technologies and advanced consumables, including plasmids and viral vectors. As a result, meeting the expanding demand for C>s has increasingly relied on outsourced development, manufacturing and testing organisations offering

the necessary capacity, technical capabilities and expertise to support production.

Navigating the Challenges of a Novel Therapeutic Space

Although the C> market has grown immensely in the last 30 years, it is still relatively new compared with other therapeutic areas. Our understanding of the treatments' mechanisms of action and delivery has rapidly transformed in this time. As a result of this transformation, novel challenges have also surfaced in the development and manufacturing of these new medicines.

A Lack of Necessary Expertise and Experience

Staffing has been a persistent challenge in the biopharma industry and it has been felt strongly in the burgeoning C> space. Even now, few companies possess the technologies needed to scale commercially, and even fewer have experience working with multiple vectors and different serotypes in those systems. As a result, finding staff with relevant C> experience is a significant challenge for developers.

To attract talent with a breadth of late-stage and commercial experience across different geographies, development and manufacturing organisations supporting C>s must carefully design recruitment and retention models.

A Need for Clarity from Regulatory Bodies

The rapid advancement of C>s has forced regulatory bodies to quickly adapt guidance to meet the changing requirements of their production. Although various agencies including the FDA and EMA have created regulatory frameworks for C> development and manufacture, there are still some areas where clarification may be needed to avoid delays as projects progress toward the market. In part, this has been attributed to the predominant familiarity of regulators with assessing processes used to make traditional biologics like monoclonal antibodies (mAbs) as opposed to novel therapies.⁵

With the increasing demand for C>s globally, it is critical developers and manufacturers build strong relationships with the relevant regulatory bodies to ensure smooth delivery to market. Worldwide, various regulatory agencies have shown they are willing to work with innovator companies creating programs designed to improve interactions between the agency and therapeutic developers.

Adopting and Adapting Technologies to Scale Production

Initially, many of the systems and tools utilised in developing, manufacturing and testing C>s were derived from academic settings. It quickly became apparent that many of these techniques and technologies were unsuitable for scaled production, especially when aiming to provide enough material for a global patient population.

As a result, industry leaders have focused on designing advanced instruments to enable drug developers to improve



the manufacturability of these innovative medicines. In the past five years alone, there have been significant advances in the techniques and technologies used throughout C> development, from molecule screening to purification. For example, in viral vector production, suspension cell culture platforms have gradually replaced adherent processes as the favoured cell type to enable scalability.

Additionally, many of the technologies used in C> development and manufacturing have shifted to single-use systems to limit cross-contamination and improve safety. Although single-use options have the potential to shorten timelines by reducing the cleaning and sterilisation burden, they have also complicated the raw material supply chain, driving extended lead times for C>s.

There's Still Change to Come in the C> Space

As production needs of C>s have risen, developers, manufacturers and supporting organisations have adjusted

their models to provide the flexibility needed to serve both relatively small-batch manufacturing and larger indications. However, there is still a long way to go to fully realise the potential of these cutting-edge therapeutics. Looking to the horizon, C> producers must continue to demonstrate flexibility, adapting to overcome the challenges ahead. This includes:

- **Integrating Automation**

Although there are areas where automation has been widely adopted within today's C> manufacturing environment, the industry still has a long road ahead to match the level seen in the production of traditional biologics like mAbs and recombinant proteins.

A key driver behind the integration of enhanced processing and automation in C> manufacturing is the need to provide broader patient access to potentially life-changing treatments. As viral vector technologies continue to expand



from targeting rare diseases to treating more prevalent indications, automation will need to be embraced to meet demand.

Additionally, the extensive costs of gene therapies can benefit from the integration of automation. With gene therapies costing between \$1 million and \$2 million on average per dose, automation will play a key role in driving down manufacturing costs and providing broader patient access.⁶ Automating the manufacturing process will reduce the need for highly specialised labour, helping to reduce costs while improving process reproducibility and predictability.

- **Further Improving Manufacturability**

In addition to adopting automation technologies, C> developers and manufacturers must implement other strategies and tactics to enhance the manufacturability of these revolutionary medicines.

One strategy is the use of producer cell lines where there has been an increasing interest. These producer cell lines are equipped with genes needed for viral vector protein expression that are stably integrated into their genomes. In contrast to relying solely on transient transfection processes, stable producer cell lines can improve product yields and quality by reducing batch-to-batch variability and simplifying upstream culture and harvest. Over time, these advances can reduce the cost of goods (COG) significantly and, consequently, lower manufacturing costs.

As well as cell line improvements, the incorporation of manufacturing methods designed to improve cost-efficiency can further boost patient access in disease areas where the price of therapeutics is a limiting factor.

- **Centralisation for Robust Supply Chains**

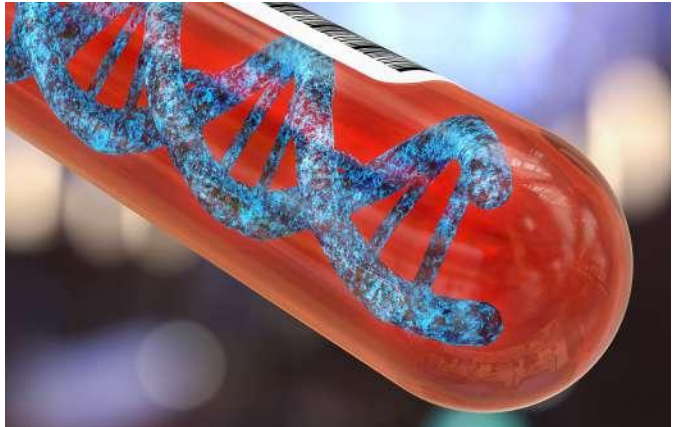
A robust supply chain is critical to avoid potential delays and to ensure the reliable and secure delivery of C>s to key milestones and subsequently, the patients who need them.

As well as developing a robust supply chain, C> developers and manufacturers should focus on adopting a centralised model to minimise delays, particularly when striving to meet growing demand. A centralised manufacturing hub can reduce the time surrounding tech transfer, as well as enable transparent and swift communication between all groups involved in production.

By consolidating their analytical repertoire and bringing critical assays in-house through centralisation, developers and manufacturers can also reduce timelines and strengthen control of vital lead times.

Preparing to Embrace Tomorrow's C> Challenges

The C> space has changed rapidly following the success of the first approved gene therapy over three decades ago. Developers, manufacturers and all organisations offering support services in the production of these innovative therapies have had to demonstrate flexibility and agility to adapt to the quickly evolving C> landscape.



However, we have only just begun to understand the potential of C>s. As new trends emerge, producers must consider adopting tactics to further improve therapy manufacturability. This, in turn, will broaden patient access and continue changing patients' lives. Finding the support of development and manufacturing partners adopting these techniques will be critical in meeting the rising demand for C>s anticipated on the horizon.

REFERENCES

1. Anderson WF. September 14, 1990: The beginning. *Hum Gene Ther.* 1990 Winter;1(4):371-2. doi: 10.1089/hum.1990.1.4-371. PMID: 1981846.
2. Gene, Cell, and RNA therapy landscape report. Q2 2023. American Society of Gene and Cell Therapy.
3. <https://www.globenewswire.com/en/news-release/2023/04/11/2644248/0/en/Gene-Therapy-Market-Revenue-to-Cross-USD-49-3-Bn-Globally-by-2032-CAGR-of-25.html>
4. <https://www.bloomberg.com/press-releases/2023-05-03/cell-and-gene-therapy-market-projected-to-grow-at-a-cagr-of-22-8-and-reach-us-62-5-billion-by-2032>
5. <https://bioprocessintl.com/bioprocess-insider/regulations/cell-and-gene-sector-needs-regulatory-clarity-says-andelyn/>
6. <https://www.genengnews.com/insights/cell-and-gene-therapy-manufacturing-costs-limiting-access/#:~:text=Cell%20and%20gene%20therapies%20are,and%20%24%20million%20per%20dose.>

Andelyn Biosciences, Inc.

Andelyn Biosciences is a full-service cell and gene therapy CDMO focused on the development, characterisation and production of viral vectors for gene therapy. With more than 20 years of experience, Andelyn's deep scientific expertise has resulted in the production of cGMP material for more than 450 clinical batches and 75 global clinical trials. Operating out of three Columbus, Ohio facilities, Andelyn supports its clients in developing curative cell and gene therapies from concept through plasmid development and manufacturing, process development, and cGMP clinical and commercial manufacturing. Andelyn's versatile capabilities include cGMP manufacturing capacity for both adherent and suspension processes up to a 2,000-liter capacity. An advanced digital model, quality system, full regulatory support and supply chain vertical integration help Andelyn accelerate the development and manufacturing of its clients' innovative cell and gene therapies. For more information, visit andelynbio.com.