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Optimising Viral Vector Manufacturing by Building Scalable Platforms from Early Research to GMP Production

Cell and gene therapies (CGTs) are redefining what is possible in modern medicine, offering innovative and potentially curative treatments for diseases that were once considered untreatable. Scientific innovation across adeno-associated virus (AAV), lentivirus (LV) and retrovirus (RV) viral vectors has accelerated rapidly, driving a growing and increasingly diverse clinical pipeline.

While science and CGT innovation have moved quickly, manufacturing often still remains a critical rate-limiting step. High-quality viral vectors are the backbone of CGTs, and the ability to scale their production reliably, reproducibly and compliantly is key to determining how quickly and efficiently a promising therapy reaches patients.

Scaling a viral vector from early research to good manufacturing practice (GMP) production is a multi-step journey that transforms innovative science into viable, commercial-ready processes and products. From plasmid sourcing to analytical design, each decision made along the way creates either friction or momentum for the future. The most successful CGT programmes are those that start with the end in mind, building scalability, quality and regulatory confidence into development from the outset.

This article explores the key stages of viral vector scale-up and examines how early technical and strategic choices can strengthen quality, protect timelines and set the foundation for long-term success.

Viral Vector Challenges and Opportunities

The CGT sector is maturing with a growing number of approved therapies, alongside a surge in clinical programmes targeting both rare and more prevalent diseases. As of the end of 2025, 38 gene therapies, 36 RNA therapies and 71 non-genetically modified cell therapies have been approved globally for clinical use.1 This reflects increasing regulatory confidence and technical progress. For small and mid-sized biotechs, this momentum presents a significant opportunity but also new operational pressures.

Viral vectors sit at the heart of the challenges associated with CGT development and manufacturing but also offer the potential for strategic opportunities. Demand for AAV, LV and RV vectors continues to rise across therapeutic areas such as oncology, neurology and rare genetic disorders. Although all the vector types share common manufacturing processes, each specific type has its own set of unique challenges. Developers must also navigate increasingly complex expectations around manufacturing consistency, analytical rigor and GMP compliance.

The viral vector manufacturing landscape has evolved to meet this demand. Contract development and manufacturing organisations (CDMOs) now offer end-to-end services and advances in platform processes and analytics are improving yields and reproducibility while helping reduce the cost of goods. However, this expansion has been uneven. Industry consolidation is accelerating, with some CDMOs narrowing their focus or exiting viral vectors entirely, and commercial-scale experience remaining limited.

For emerging and mid-size biotechs with finite resources and tight financial budgets, selecting the right manufacturing partner has become as strategically important as the science itself. Capacity alone is no longer enough. Partners must be able to translate early innovation into scalable, commercial-ready manufacturing.

Start with the End in Mind by Scaling as a Design Principle

Scaling a viral vector is often framed as a later-stage development problem or something to address once clinical proof of concept has been achieved. In practice, scalability is a design principle that should be embedded from the earliest stages of development.

Early planning begins with understanding the target patient population. A rare disease programme may only require a 50 L GMP run, while broader indications can demand bioreactor volumes of up to 2,000 L. Processes that can flex across this range are better positioned to avoid costly reinvention later.

While AAV, LV and RV vectors share common manufacturing fundamentals, each presents unique scale-up challenges:

- AAV: Scaling AAV production can lead to declines in yield and consistency if transfection efficiency is not carefully maintained. Early optimisation of transfection parameters, such as enhancers, sensitisers and reagents, helps preserve performance as volumes increase. For very large-scale programmes, alternative production systems, including packaging or producer cell lines and Sf9 baculovirus platforms, can further improve reproducibility and volumetric productivity.
- LV and RV: These vectors are more fragile than AAV vectors, making them particularly sensitive to processing time and shear stress. Scale-up strategies must prioritise streamlined, shear-aware downstream workflows. Appropriately sized filters, well-tuned chromatography systems and simplified processing steps help protect vector integrity and maximise recovery across scales. For *in vivo* applications, additional development complexity can arise when envelope modifications are introduced to achieve specific tropism, requiring careful consideration of process compatibility and consistency as programmes scale.

Additionally, embedding Quality by Design (QbD) principles early allows developers to overcome technical hurdles and treat scale-up as an opportunity to strengthen process robustness and accelerate the path to patients.

Upstream Decisions That Define Downstream Success

Some of the most consequential scale-up decisions are made long before GMP manufacturing begins. Early material choices directly influence manufacturability, comparability and regulatory risk include:

- Plasmids: GMP-grade plasmids are critical, with production timelines measured in months rather than weeks. Engaging plasmid vendors early can

prevent missed manufacturing slots and downstream delays.

- **Cell lines:** Access to licensed master cell banks reduces supply risk and supports smoother technology transfer as programmes advance. Early alignment on cell substrates also simplifies later comparability assessments.

- **Starting materials:** Choosing scalable, GMP-compatible materials from the outset reduces the likelihood of rework and re-qualification in later phases.

In contrast, a speed-first, "quick and dirty" approach to early development may enable rapid entry into first-in-human trials but frequently creates challenges when processes must later be uplifted to support late-phase or commercial manufacturing. When early processes are not designed with GMP and QbD in mind, additional optimisation is often required, along with additional cost, time and risk.

Analytical Rigor as a Foundation for Regulatory Confidence

As viral vector programmes progress, robust analytics become the backbone of both process understanding and regulatory success. Regulators, including the FDA and the EMA, expect validated, phase-appropriate methods capable of accurately measuring potency, infectivity, purity and safety.

The greatest advantage for biotech developers comes when these analytical tools are embedded early rather than retrofitted later. Fit-for-purpose assays aligned with QbD principles allow teams to track critical quality attributes (CQAs) throughout development, ensuring that each scale-up decision is grounded in meaningful data.

This continuity is essential as programmes move from first-in-human studies toward commercial readiness. Analytical methods should evolve alongside the process, supporting comparability, consistency and the generation of strong chemistry, manufacturing and controls (CMC) documentation for Investigational New Drug (IND) or Investigational Medicinal Product Dossier (IMPD) submissions. Early investment in analytical rigor not only de-risks scale-up but also builds regulatory confidence and preserves optionality as programmes advance.

The Twin Constraints of Speed and Cost

Even with strong technical foundations, two pressures consistently shape viral vector development: speed and cost. Legacy production processes remain a major contributor to high therapy costs and prolonged timelines, while rising prices for GMP-grade plasmids and transfection reagents can further strain early-stage budgets.

For small and mid-sized biotechs, speed is often non-negotiable. Advancing to first-in-human trials quickly can unlock funding, partnerships and validation. However, moving too fast without sufficient planning frequently results in inefficiencies and rework that ultimately slow progress.

Cost and speed are tightly linked. Poorly optimised processes increase cost per dose, while delays in materials or analytics can cascade into missed milestones. When combined, these two factors can significantly impact the delivery of CGTs to patients who need them. Balancing these pressures requires strategic efficiency rather than shortcuts.

Practical levers for balancing speed and cost include:

- Running process development, analytical method development and plasmid procurement in parallel
- Initiating GMP plasmid production as early as possible in development
- Designing processes at the right scale for the intended patient population
- Applying a single, commercial-ready

quality system in a phase-appropriate way

When executed well, these strategies can help compress timelines without compromising quality or compliance.

Partnerships That Enable Viral Vector Progress

Given the complexity of viral vector scale-up, collaboration has become a defining strength of successful CGT programmes. Strategic CDMO partnerships now play a central role in development, enabling biotechs to combine innovation with the manufacturing expertise needed to progress confidently toward the clinic and beyond.

A true value-adding CDMO partner brings more than manufacturing capacity. Commercial manufacturing experience, regulatory fluency and analytical depth allow early decisions to be informed by late-phase realities. Equally important are transparency, flexibility and communication.

For emerging biotechs, their programme is often their entire company. Effective partnerships are built on trust, clear escalation pathways and consistent project management. Dedicated project managers, regular steering meetings and direct access to technical experts and leadership help ensure alignment and minimise surprises.

Flexibility is another differentiator. Programmes evolve, funding cycles shift and priorities change. Partners who can structure work in stage-gated phases, adapt technical approaches and explore creative financial models help biotechs maintain momentum without overextending resources.

Looking Ahead and Building the Next Generation of Viral Vector Platforms

The future of viral vector manufacturing lies at the intersection of technical innovation and collaborative execution. Emerging approaches, including synthetic DNA, stable producer cell lines, advanced transfection enhancers and digital analytics, promise improvements in productivity, consistency and scalability.

However, technology alone is not enough to realise the full potential of CGTs. The most successful programmes will be those that integrate these tools into thoughtfully designed platforms, guided by data and aligned with long-term commercial goals.

Equally, partnership models must continue to evolve. Transparency, shared ownership of risk and early alignment on end goals will define the collaborations that turn promising science into approved therapies.

From Scale-Up Challenges to Strategic Opportunities

Optimising viral vectors is rarely just a question of increasing production volume. It is about designing processes that can stand up to scale, scrutiny and regulatory expectations. When scalability, quality and analytics are built in early, developers can carry innovative science forward into GMP manufacturing with greater confidence.

In an increasingly competitive CGT landscape, these early decisions determine both the speed to clinic and also the likelihood of long-term success. With the right strategy, the right data and the right partners, viral vector scale-up becomes less of a bottleneck and more of a catalyst for delivering life-changing therapies to patients.

REFERENCES

1. https://www.asgct.org/uploads/files/general/Landscape-Report-2025-Q3.pdf

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