Construct Viability: A Hidden Challenge in Viral Vector Manufacturing

Minaris Viral Vectors

Article

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Consider a common scenario in cell and gene therapy: a development team spends years perfecting the biology, target binding, and expression of an adeno-associated virus (AAV) or lentiviral vector (LVV) candidate. They move through discovery with a clear lead, optimized for clinical efficacy.

Then, they hit a wall.

As the program approaches the Investigational New Drug (IND) filing, the focus shifts from the bench to manufacturing. It is here that developers often discover their construct, the heart of their therapy, possesses significant manufacturability "red flags."

"A company does not want to hear that the 'baby' they have been working on for years has design problems that will prevent them from hitting their target titers at scale," says **Francesca Vitelli, VP Global Head, Process Development and Innovation at Minaris**. Having seen this play out both as a development scientist and a consultant, she adds: "It is a difficult conversation to have. You must either invest additional time and resources to optimize the process to achieve target titers, or redesign the construct and repeat development, since once the IND is filed, the construct is locked and cannot be easily changed."

"It's a vital conversation that often doesn't happen until a developer speaks to a CDMO later in the process," says **Richard Parker-Manuel, Head of Plasmid Engineering at Minaris.**

While the science may be sound, manufacturability remains a notable blind spot in construct design—one with hazards that stay hidden until it is too late.

THE PRESSURES DRIVING THE MANUFACTURABILITY BLIND SPOT

The forces shaping cell and gene therapy in 2026 help explain why this blind spot persists. Investors no longer reward promising science alone; they demand disciplined execution and a credible path to market and patient access, which is often tied to costs of therapies.

"In this economy, speed to clinic for proof-of-concept is essential," Vitelli stresses. "To secure the next round of funding, teams often optimize designs by engineering out attributes that are not immediately milestone critical. That pressure often tempts early-stage teams to defer manufacturability consideration to later stages."

Competition has also intensified. Multiple programs often race toward the same targets, increasing the appeal, and often the risk, to making tradeoffs to increase development speed. Simultaneously, the industry recognizes that manufacturing costs directly impact patient access. While meaningful reductions in Cost of Goods (COGS) are essential, developers frequently triage these considerations as a lower priority during the high-pressure race to IND and clinical proof of concept.

Yet these calculations are risky. When the FDA published Complete Response Letters between 2020 and 2024, 74% cited quality or manufacturing issues as the main driver.[1] And the issue didn't only affect later stage applications. A recent report in Drug Discovery News estimated that 40% of cell and gene therapy INDs also experience delays with the FDA due to Chemistry, Manufacturing, and Controls (CMC) issues.[2] As more therapies seek approval, regulators are raising the bar for the data, and product understanding, required to advance with efficiency. Construct viability is foundational to that data package.

A VIABILITY "HEALTH CHECK" FOR CONSTRUCT DESIGNS

Are developers simply caught in a trap then, forced by limited resources to deprioritize their construct's viability for manufacturing? Not necessarily. Addressing construct viability may be less resource-intensive than many assume.

Many innovators hesitate to engage a CDMO early on, fearing "Cadillac" services they cannot afford. Consequently, early construct evaluation feels out of reach. However, addressing viability can be a low-cost, high-speed intervention—an agile "Health Check" conducted before the program is locked, when small changes can yield major benefits.

"We view it like a car service report—using red, yellow, and green lights," says Parker-Manuel. "Based on our expertise, we provide recommendations and identify risks where simple changes or swapped elements can significantly increase the probability of success." Even if changes are not possible or chosen immediately, the sponsor has still gained the ability to weigh the risks and make better decisions.

Such a Health Check analyzes elements that developers may feel pressured to overlook. For example, an evaluation might flag ampicillin-resistant backbones—which are increasingly discouraged by regulators—and suggest a move to kanamycin resistant backbones instead. It might examine the WPRE (Woodchuck Hepatitis Virus Post-transcriptional Regulatory Element) for sequence integrity and safety or predict how promoters and codon optimization will impact viral vector titers when transitioning from a small-scale experiment to a larger-scale bioreactor. Or it may find that using a proprietary off-the-shelf solution, such as Minaris's SnapFast™ AAV and LVV backbones, presents a ready fix for their specific application.

While developers often fear optimization will cause delays, a Health Check usually takes only a few days. Fixes identified early are measured in weeks. Left until closer to process lock, the resulting problems may lead to months of troubleshooting.

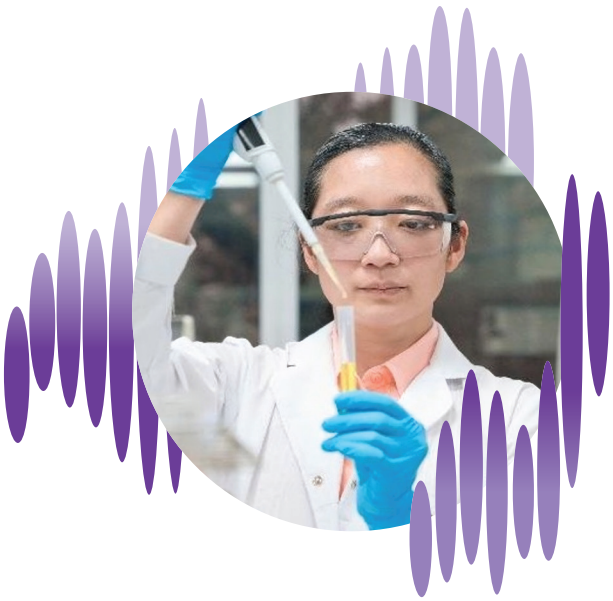
EARLY INTERVENTION, LONG-TERM BENEFITS

Are developers simply caught in a trap then, forced by limited resources to deprioritize their construct's viability for manufacturing? Not necessarily. Addressing construct viability may be less resource-intensive than many assume.

When construct viability for manufacturing is ignored, every dollar of capital already invested is at risk. Programs may reach a point where, after years of work, they must spend an undetermined amount of time and money re-engineering for manufacturability.

"Increasing your titer by threefold early on could save immense pain during process development and help improve consistency and scalability" Parker-Manuel emphasizes.

Early optimization also transforms the therapy's commercial profile. Higher yields lead to fewer required batches, making clinical development more efficient and the final therapy more accessible to patients. Proactively managing construct viability offers a vital lever for reducing COGS and, ultimately, the cost-per-dose.





BUILDING A ROBUST PATH TO THE CLINIC

As the industry matures, innovators recognize that the fastest path forward is one of strategic foresight. Success belongs to those who view construct viability not as a hurdle, but as an accelerator. By verifying early, teams transform their journey from reactive firefighting to a controlled, integrated path.

At Minaris Viral Vectors, we believe early-stage evaluation should be a standard part of the development journey. By optimizing construct design for both biology and the bioreactor, the transition to IND happens with maximum momentum, helping life-saving therapies reach patients faster and more reliably than ever before.

Talk to one of our experts about a rapid health check for your construct design.

References

1. Wright, A. "FDA's CRLs reveal 74% of applications rejected for quality, manufacturing issues." Pharma Manufacturing. 2024.
2. Goldsmith, B. "Why gene and cell therapies are stalling at the FDA." Drug Discovery News. 2024.



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