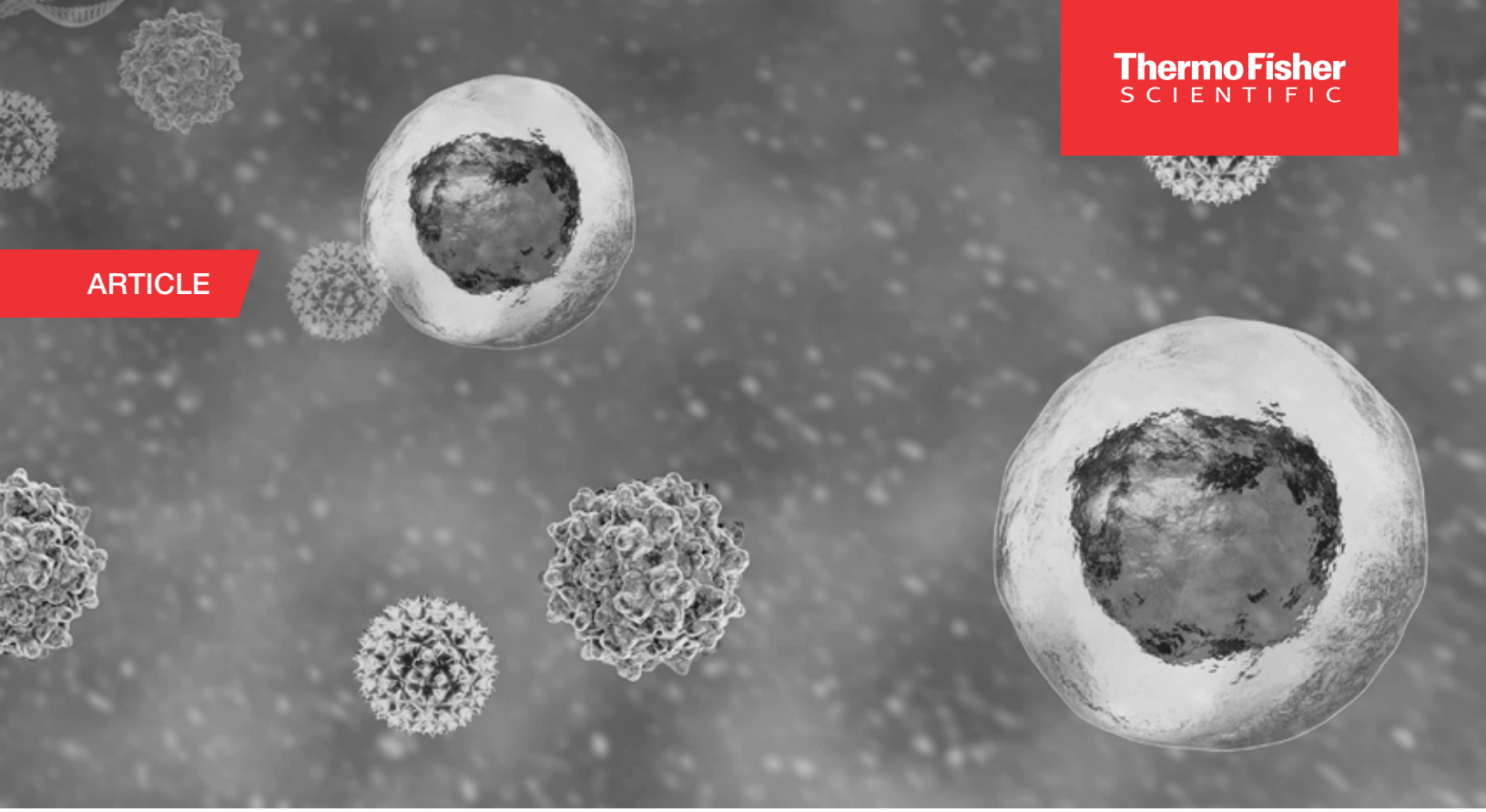


ARTICLE

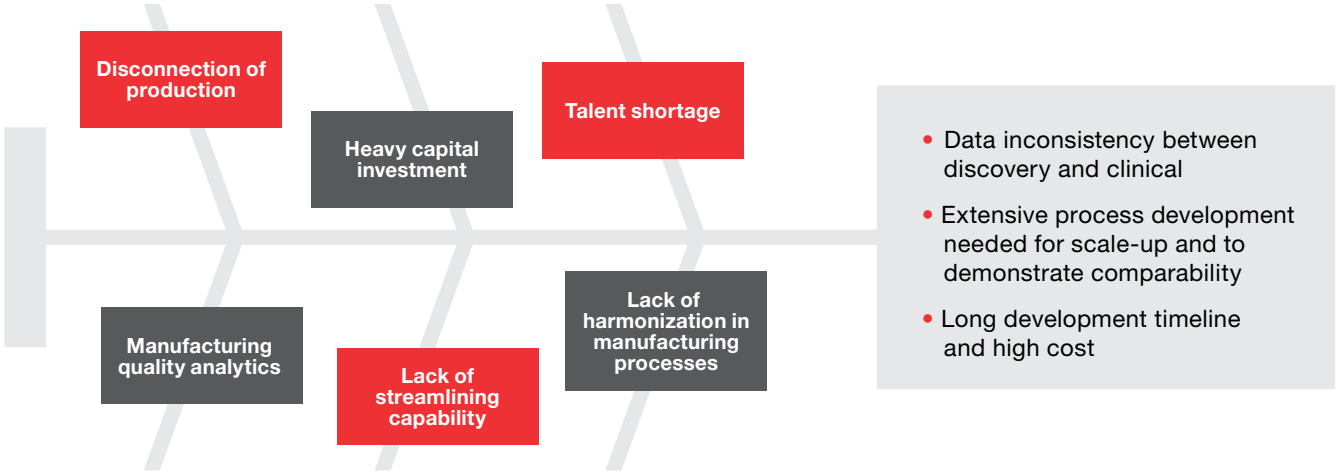
Strategies to accelerate drug development through harmonization of early and late stage processes

In the advanced therapies industry, adeno-associated viral (AAV) and lentiviral (LV) vectors have emerged as essential tools for gene delivery in cell and gene therapy applications. The complex biological manufacturing systems that produce these viral vectors face the challenge of establishing and maintaining product consistency throughout the different stages of drug development.

For drug developers with limited in-house manufacturing capabilities, there is a strong motivation to outsource services to contract development and manufacturing organizations (CDMOs) for viral vector production. CDMOs have the potential to support customers all along the drug development value chain, including lead candidate screening and selection, process development, and Good Manufacturing Practice (GMP) clinical through commercial manufacturing. Unfortunately, there is minimal harmonization between the at-scale processes utilized in GMP manufacturing and the processes used to produce small quantities of research-grade materials to support lead screening. This frequently results in challenges with technical transferability, data consistency, and product performance predictability across different drug development stages that lead to unnecessary delays and escalating costs. See Figure 1 for more on common advanced therapy industry challenges.

Here we present a harmonized and streamlined approach established at Thermo Fisher Scientific for manufacturing AAV and LV vectors for discovery research using technologies and processes mirroring current GMP platforms with fit-for-purpose raw materials, starting materials, and qualifiable assays to yield high quality products at small scale (>1 L). Our platform is scalable to enable a seamless technical transfer, with minimal need for process development and demonstration of comparability, as the lead molecule is identified and moves into the clinic. Our approach is to leverage the turnkey 50–200L scale GMP Quick-to-Clinic™ platform's upstream and downstream production processes and minimally modify them for small-scale production.

Figure 1. Challenges within the advanced therapies industry that are important to consider when selecting a CDMO



A need for harmonization and decision-making

The advanced therapies market continues to expand with several new treatments now commercially available. However, several challenges exist in the field that hinder developers' ability to bring products from discovery to the clinical phase at the desired pace. For example, data inconsistency results from using different manufacturing platforms for early discovery studies and GMP manufacturing (i.e., shifting from an adherent platform to a suspension platform or switching from manual to semiclosed processes for clinical/commercial manufacturing), differences in raw materials and starting materials, and using different analytical assays. Tight funding can lead to pressure to quickly generate data to show results and launch first-in-human clinical trials. As the industry matures, innovators must comply with evolving regulatory requirements and develop strategies to vet critical and raw materials to ensure supply chain continuity and CMC compatibility. As one moves through the different phases of clinical development, it becomes increasingly difficult to make changes. Furthermore, limited qualified personnel with an understanding of all aspects involved in moving a drug from concept to clinic brings additional challenges.

Implementing quality and process controls at the lead discovery/identification stage can save time and allow for a better understanding of product performance. This is a pivotal point at which to engage with an experienced CDMO that can identify the lead product configuration and demonstrate proof of concept with the lead candidate. In the academic research setting, a plethora of catalog and home-brew products are available for use, such as cell lines, media, and analytical assay measurement kits. However, one should consider the suitability of raw materials and processes, intellectual property, and the regulatory landscape during early stages of development. The ideal CDMO can influence its suppliers to ensure a robust supply chain and/or guarantee that ample stock materials are readily accessible.

Manufacturing process alignment

The pathway from lead candidate selection to manufacture for clinical use can involve many different handoffs and technical transfers. At each of these junctions, there is an increased risk for miscommunication and incongruities, such as changes in starting materials and raw materials, which lead to longer lead times, frustration for those involved, drug candidate performance inconsistencies, and increased costs. These increased risks can be exacerbated during a critical point in the process, including at scale-up. With the different factors necessary to consider while going from small-scale lead identification to clinical and commercial-scale manufacturing, having different parties involved can make drug development more challenging.

It is beneficial to work with a CDMO that has alignment from beginning to end and has the ability to maintain complete oversight to mitigate the pitfalls found in critical junctions. Working with one CDMO for the entire drug lifecycle ensures that all parties are in alignment from the beginning, eliminating unnecessary risks and saving time.

Best-in-class analytics for manufacturing capabilities

If a drug developer is contemplating working with multiple vendors to outsource analytics, there is also the potential for discontinuity in the data received, leading to inconsistent results and possible ramifications that will affect decision-making. Performing comparability studies is one possibility, but this requires time and resources, and potentially introduces new challenges. It is important to have the most up-to-date, reliable analytics coming from one trustworthy source to instill trust in the data, and ultimately support regulatory and manufacturing strategies.

When evaluating potential CDMOs, it is important to consider whether the partner can align the manufacturing platform with analytics during the lead identification/proof-of-concept stage through to cGMP transition. This not only will expedite the process, but also will provide confidence that results are predictive throughout product development. Knowing the results obtained at the early stages will be measured using the same analytical methods in subsequent stages helps mitigate analytical method concerns. Not only should analytics be aligned throughout product development, but as new technologies become available, the CMDO should be using fit-for-purpose, best-in-class analytical assays to evaluate critical quality attributes. This approach streamlines the process of producing high quality products while saving time and capital with a quick turnaround time.

Quality and material alignment

In the early stages of drug development, emphasis on quality may not be critical, but quality is of paramount importance at the GMP manufacturing stage. As the process is further defined, raw material requirements may change to ensure a higher quality, more robust supply chain and clean-room compatibility. Failure to take these issues into account at the early stages of development may require small to significant changes to the process and affect drug product performance.

Risk and timelines can be reduced if a CDMO incorporates quality at the start by implementing a “begin-with-the-end-in-mind” approach and producing vectors at the lead identification stage under a quality management system (QMS). If a CDMO is able to initially assess raw and starting materials to ensure a path to GMP-compatible materials, potential hurdles arising from quality and performance inconsistency can be avoided. This allows drug developers to utilize phase-appropriate raw materials to control costs while keeping future expectations in mind.

About Translational Services powered by Patheon

Patheon Translational Services provides its advanced therapies clients with small-scale, high quality, research-grade viral vectors and molecular biology services that seamlessly connect to Patheon’s advanced therapies GMP manufacturing services. Clients have direct access to our highly experienced multidisciplinary team of technical, bioprocessing, regulatory, legal, and quality experts. With laboratories based in Alachua, FL and San Diego, CA, our goal is to accelerate clients’ transition to GMP manufacturing by utilizing best-in-class standardized processes and a path that identifies lead product configurations and de-risks the journey to clinic.

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