Article

AAV manufacturing

Prepare for progress: streamlining the transition to clinical trials

Gene therapy manufacturers looking to progress from research and development (R&D) to clinical trials face a range of challenges and key considerations. Collaborating with a contract development and manufacturing organization (CDMO) that has strong supplier relationships can significantly streamline transition from the bench.

At Thermo Fisher Scientific, we choose to work closely with CDMOs who share our passion for driving valuable gene therapies to the clinic. We spoke with Dr. Artur Padzik, AAV technology manager at Biovian, a CDMO, to answer commonly asked questions about scaling up for clinical trials.

Gene therapy development is still a relatively new area. Why is it important to consider scale-up and prepare for clinical trials during initial development stages?

For any gene therapy developer, progression to clinical trials is a critical stage in a biologic's journey to approval, and preparing for scale-up is vital. However, manufacturing large volumes of a safe, effective, and regulatory-approved biotherapeutic can present challenges that developers may not fully appreciate in the early development stages. Optimizing and scaling up a workflow in preparation for clinical trials comes with key considerations, such as ensuring raw material supply, choosing a cell line, and understanding the challenges of different vector production techniques. It may not always be clear which factors should be prioritized; therefore, preparing early can help streamline the process. Fortunately, there is a wide range of experience and expertise that can be utilized to increase the chance of success.

The production of viral vectors is a complex process affected by many variables and parameters. Can you describe these key considerations in more detail?

To produce a chosen viral vector at scale, developers will need to evaluate their current cell line and consider whether it is suitable for GMP manufacturing. Adeno-associated virus (AAV) vectors are currently among the most used viral vectors for gene therapy [1], and mammalian HEK293 cells have been used in AAV production for many years. This has led to well-established cell expansion protocols and a production method that is widely accepted and uses helper-free triple transfection. Alternative approaches use insect-derived Sf9 cells. This is a less common production method; however, it can help developers perform AAV production at a larger scale. Relevant expertise is vital to understand cell line options, limitations, and growth requirements to enable a successful scale-up.

While considering cell lines, developers will also need to decide whether to utilize transient transfection or a packaging/producer cell line through stable integrations. Transient transfection works sufficiently on a small scale as it is well understood, flexible, and cost-effective. However, the success of transient transfection

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techniques can be variable, particularly at scales larger than 200 L. Developing a stable workflow using packaging or producer cell lines may improve overall AAV manufacturing efficiency but is less flexible and more complex to implement. However, swift technological advancements in the miniaturization of screening large cell populations are becoming a promising alternative and the direction in which AAV manufacturing is likely to progress.

While the regulatory landscapes of some biologics—such as recombinant proteins and monoclonal antibodies—are well established, the gene therapy industry is still relatively immature and does not have the breadth of knowledge to drive standardization of processes. Therefore, establishing relationships with CDMOs and experienced suppliers can ensure developers have the right expertise before and during scale-up.

Speaking of suppliers, what advice do you have for gene therapy manufacturers looking to source raw materials for scale-up?

AAV vectors are generally manufactured at relatively low production volumes, with the majority produced in bioreactors below 500 L [2]. Therefore, when scaling up a gene therapy workflow, such as AAV production, it is critical to effectively source, qualify, and store a greater amount of raw materials, at the cost, quality, and quantities needed for clinical manufacturing. For this, understanding options is key to achieving supply security and batch-to-batch consistency, while avoiding bottlenecks and delays. A CDMO can provide the required storage and manufacturing capabilities for a developer. But choosing a CDMO partnered with a reliable supplier can also offer the expertise and troubleshooting experience to meet the unique demands of transitioning to clinical trials. There are organizations that offer clinical-focused technology transfer services that collaborate closely with suppliers that can also advise on the challenges specific to this phase.

Partnering with a CDMO that has a strong catalog of qualified products and audited suppliers with excellent supply reliability credentials will help to secure consistent, high-quality raw materials, and reduce the risk of delays or stoppages. There could also be the opportunity to take advantage of supplier services, such as in-depth raw material characterization to optimize workflows. The raw materials used at smaller scales may not always be suitable for larger-scale manufacturing. With the right expertise, developers can be educated on their options, where different formulations or formats such as the Gibco™ Advanced Granulation Technology (AGT™) media format may be more suited to clinical-scale manufacturing.

How can CDMOs help developers finalize their scale-up strategy?

As the production of viral vectors is multifaceted, opting for a CDMO with extensive capabilities to conduct large design of experiment (DoE) projects can accelerate clinical progression. This allows for the testing of multiple variables concurrently and can define key factors affecting a process—providing a faster, data-driven approach to understanding complex biological processes, which can significantly impact costs [3]. DoE methods can investigate the use of different cell lines, culture media, and transfection reagents, as well as other parameters such as bioreactor temperature and dissolved oxygen, all of which can contribute to the productivity of a process. By leveraging collaborative supplier relationships and expertise, CDMOs can then help identify optimal formulations for the target cell line with media optimization and analysis services. Access to tools such as the Gibco™ Viral Vector HEK Media Panel—which offers a range of nutritionally diverse media formulations to evaluate with HEK293 cultures—can rapidly accelerate gene therapy process optimization and media selection.

CDMOs with a strong supplier relationship can work to support developers and help them understand their many options. By utilizing our shared expertise and reliable supply, we can provide the necessary components to enhance a gene therapy workflow and progress to the clinic.

Biovian is a Nordic CDMO providing one-stop-shop services in GMP manufacturing of biopharmaceuticals and "Manufacturing Happiness". Learn more at: biovian.com

References

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