The Use of a Proven AAV Platform to Drive Down Program Costs and Maximize Speed

By **Andy Moreo**, Head of Process Development and Preclinical Manufacturing, Andelyn Biosciences

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Cell and gene therapies are increasingly popular vehicles for treating rare and devastating diseases. As their foothold grows, sponsors are beginning to explore how these technologies can treat more common indications as well. Though the potential is extremely promising for patients across the biopharma space, regulatory bodies are still working to catch up and craft guidance to help sponsors navigate their way through development and current good manufacturing practice (cGMP) protocols. When a sponsor is beginning their adeno-associated virus (AAV) development and manufacturing journey, much of their success will be tied to the expertise of the contract development and manufacturing organization (CDMO) they choose to partner with.

For an AAV sponsor, it may seem as though all CDMOs have relatively similar AAV platform approaches and manufacturing capabilities. This, however, is far from true in practice. A CDMO with robust AAV manufacturing experience and expertise — from research and development to clinical and commercial scale — is a rare find. While many CDMOs may have the capacity, equipment, and space to manufacture, they may not necessarily have the applied technical know-how or functional understanding to deliver a high-quality product according to timeline. As you begin your search for the ideal AAV manufacturing partner, consider the defining characteristics of an experienced and efficient CDMO.

Identify the Right Questions

When meeting with potential CDMO partners, it is important to ask directly about previous AAV manufacturing experience. It is critical to determine what the CDMO has already accomplished, including how many GMP batches they have produced and released for Phase 1 or Phase 2 trials, and how many clients they have that are moving into project performance qualifications (PPQ) and onto biologics license applications (BLAs). Though some CDMOs may reference their previous commercial experience, there are currently only five AAV products on the market; as a result, commercial AAV manufacturing experience is inherently hard to come by.

Once you have assessed a CDMO's experiential knowledge, don't be afraid to get technical. Ask potential partners to discuss their average yields out of suspension and/or adherent cell culture. Implore them to speak to their regulatory knowledge and chemistry, manufacturing, and controls (CMC) panel experience. From there, ask if they are willing to provide examples of previous panels they have done. From a performance standpoint, it is important to know how a CDMO defines success, i.e., is it on-time delivery, high yields, or something else entirely?

To determine whether a CDMO is agile and experienced, you might also evaluate the questions they bring to you. Their number one goal should be understanding the product and associated analytics as thoroughly as possible. This should include questions about the route of administration, the serotype, the transgene sequence and folding, and any other factors that might be relevant to manufacture and test the product. A CDMO's subject matter experts should also seek to understand a sponsor's previous experience with the product and any goals and expectations.

Establish a Strong Partnership

Beginning your CDMO relationship early in development can yield high benefits and a mutually positive, long-term partnership. At Andelyn Biosciences, a CDMO experienced in AAV manufacturing, our roots are in the proof of concept and development phase. However, we find that we have strong outcomes when we work with a client at any point in their product lifecycle, from proof-of-concept through to research and development, toxicology, Phase 1, Phase 2, and finally, commercial production. In a long-term partnership, we gain both data and experience with the vector, allowing for a far more streamlined process and CMC panel going into commercialization.

Regulatory experience is another critical aspect tied directly to the success of a project. Though a client will ultimately decide how best to approach their interactions with the FDA and other regulatory authorities, Andelyn imparts insight into what the FDA might be looking for based off our previous experience with clients. Since regulatory guidance for AAV manufacturing is still very much in flux, there is a long way to go in terms of standardizing processes. One effective strategy to help alleviate these unknowns is working with a partner with a proven platform that has conducted FDA-approved, cGMP-grade runs. When a client mentions to the FDA that Andelyn is their manufacturing partner and references our drug master file (DMF), regulators already know our capabilities.

Communication and transparency are also crucial to the success of a manufacturing partnership. Andelyn is built upon a wealth of commercial manufacturing and core scientific knowledge with nearly two decades of continuous operations in gene therapy. Our process experts maintain a scientific and collaborative mindset throughout the relationship. As a result, we place a high premium

on scientist-to-scientist and scientist-to-manufacturing collaboration. By building this communicative culture, it is easier to establish agreed-upon outcomes, efficient timelines, and a mutually beneficial partnership. Furthermore, Andelyn provides clients with continuous guidance and transparent updates about obstacles that come up along the way. Finally, Andelyn clients have direct access to key decision makers as needed. Andelyn prioritizes all of these touchpoints to ensure client satisfaction and a high-quality product to help bring life-saving treatments to patients.

Leverage Optimization to Improve Timelines

It is vital to consider how potential partners are building optimization into their workflows. Particularly, what programs do they have in place to help platforms run smoother, faster, and more productively? At Andelyn, we understand that process optimization can have an enormous impact on your project timelines and budget. By applying design of experiment (DOE) principles to optimize both the upstream and downstream processes, we can increase productivity up to eight-fold and decrease losses in purification by as much as 50%.

The result is that with a relatively small investment in strategic optimization and one cycle of DOE, we can potentially see up to an 80% gain in efficiency and a process that requires fewer materials and less labor, dramatically reducing costs and increasing speed.

Recognize the Pillars of an Established AAV Platform

At Andelyn, we have supported 75+ investigational new drug (IND) applications and successfully completed 450+ cGMP clinical batches and 2,000+ research-grade batches. Our reliable, proven model is built on four pillars: (1) speed and efficiency, (2) high-quality products, (3) configurability, and (4) predictable performance.

Development is built into our platform, thus there is no need for outside tech transfers, helping to shorten our timelines. Our materials are standardized, allowing us to drive down costs and save additional time in development. Since the platform remains the same from the start, this helps us to be expeditious in terms of regulatory and CMC requirements. At the outset of a client's program, we identify the platform and downstream purification methods that are best suited for the indication and maintain it throughout a product's life cycle. By the time a client reaches their regulatory filing and CMC phase, all data is streamlined and applicable to the cGMP production platform, including data from the research phase.

In terms of architecture, our manufacturing platform is a base scaffold consisting of interchangeable and configurable building blocks. Supporting the platform is an underlying methodology of characterization, optimization, and assembly based on decades of data. Depending on a client's CMC needs or indication, we fit together the platform configuration best suited to produce a product within budget that conforms to the highest quality standards with components that lend themselves to performance predictability and efficiency.

Seek a High-Quality AAV Partnership

As you work to identify the right CDMO partner to manufacture your AAV therapy, start early and place a major premium on previous experience. The field is young, regulatory guidance is limited, and robust viral vector expertise can be hard to

come by. At Andelyn, we have a long-standing commitment to developing innovative gene therapies that improve and elongate patient lives. When it comes to our partnerships, we place an emphasis on how we can bring their products to market rapidly via predictable platform performance. As a result, we ensure that innovative therapies reach patients in need and improve their lives.

About the Author

Andy Moreo oversees process development as well as preclinical plasmid and viral vector production at Andelyn Biosciences. He leads a diverse organization of interdisciplinary scientists specializing in process development of new vector production platforms and offers solutions to clients for accelerating gene therapy products to the patients who need them.

Andy has over two decades of experience in genetic and molecular research with roles at Syngenta and The Ohio State University. He joined Nationwide Children's Hospital and Andelyn in 2007, focusing on the production and development of gene therapy products.

About Andelyn Biosciences

Andelyn Biosciences is a full-service cell and gene therapy CDMO focused on the development, characterization, 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. Andelyn supports customers developing curative cell and gene therapies from concept through plasmid development and manufacturing, process development, and cGMP clinical and commercial manufacturing. Its 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.

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