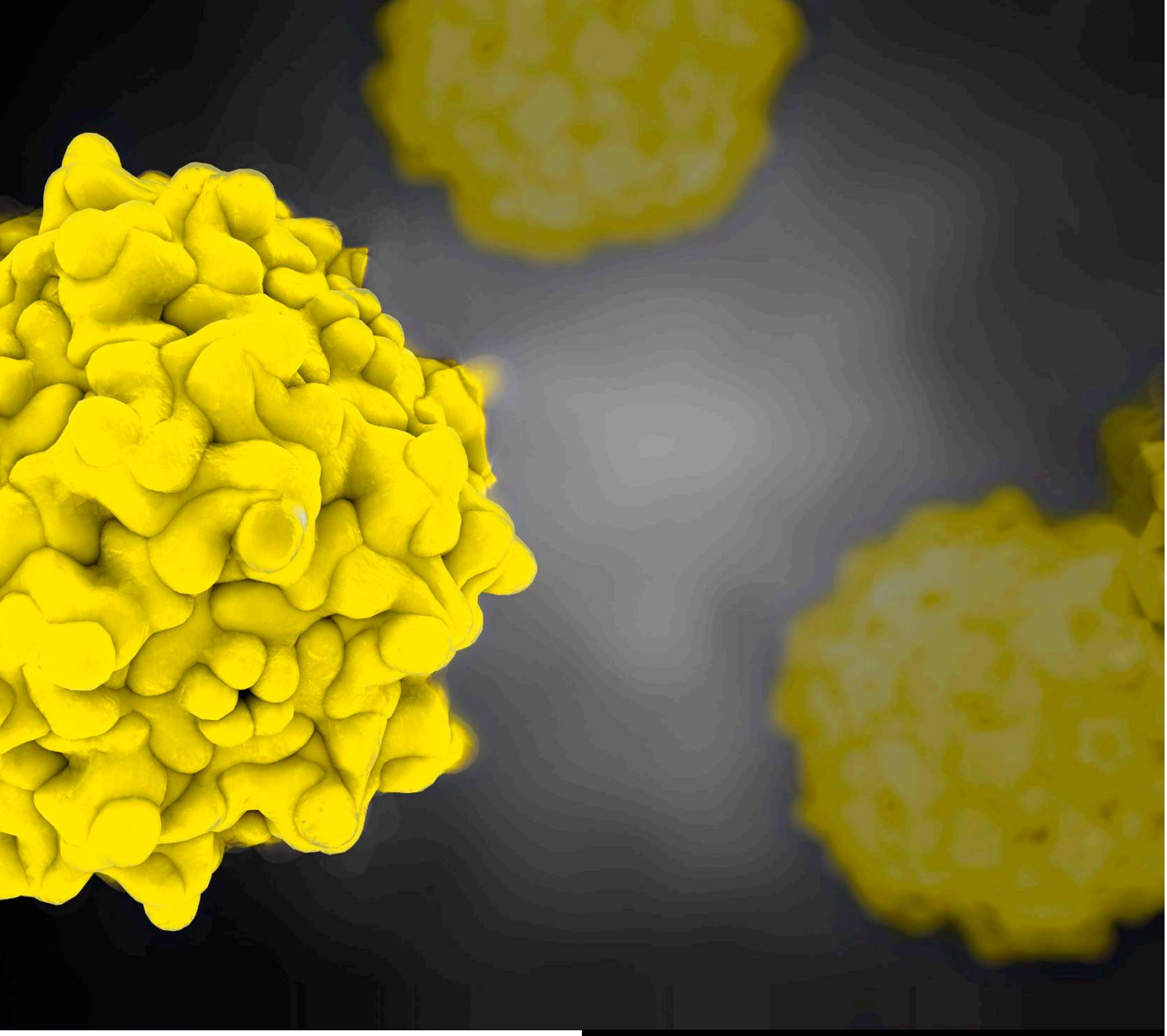

Simplifying Progress

Navigating Upstream AAV Production: A Checklist for Efficient and Reliable Gene Therapy Manufacturing

May, 2023 | Catherine Buchere, Kathrin Teschner, David Ede, Katy McLaughlin

Keywords or Phrases:
Adeno-associated virus, cell and gene therapy, viral vector processes

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Introduction

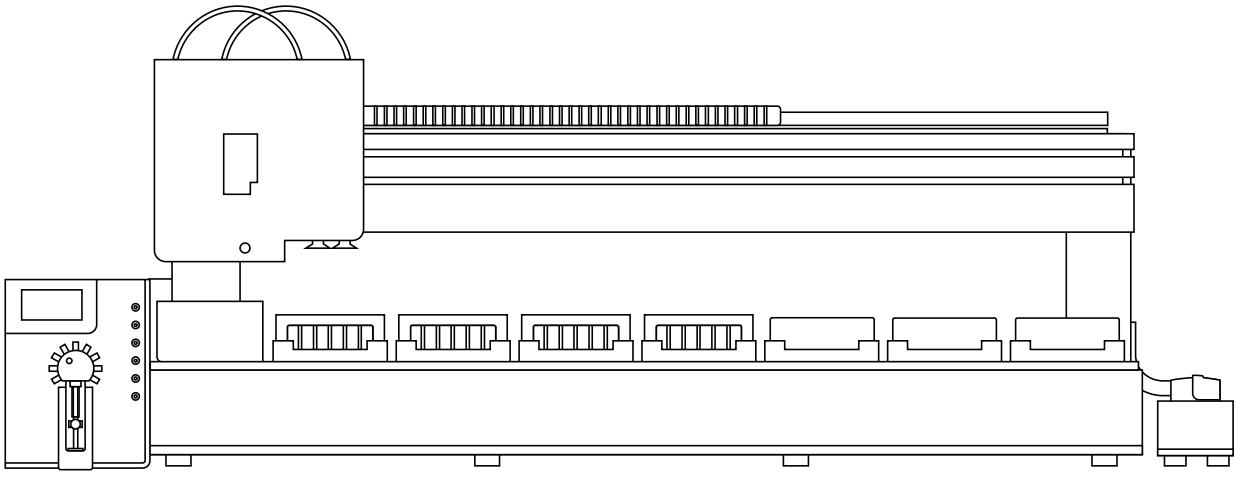
The demand for advanced therapies, including viral vector-based gene therapies, is expanding in both scope and scale. Initially developed for rare and ultra-rare disease, there is now increasing interest in the development of gene therapies for more common indications. This shift requires biomanufacturers to adopt new tools and strategies that support higher yielding, larger scale, and traceable processes that generate high-quality products.

Adeno-associated viruses (AAVs) are the leading platform for in vivo gene therapy delivery. There are currently at least three FDA-approved AAV-based advanced therapies in human embryonic kidney (HEK293) cells[1] and over 235 candidates in the pipeline.[2] Therefore, the establishment of reliable AAV production processes would be of considerable clinical value.

The rapid pace at which the market moves and the fierce competition between players mean that minimizing time-to-clinic is a top priority for gene therapy manufacturers. While it may be tempting to speed through process development activities in favor of progressing into production, some key principles must be considered at each developmental phase.

Upstream AAV process development (particularly cell line development) is a costly and time-consuming process. From plasmid preparation to clarified harvest, there are many decisions to make and process parameters to optimize. Therefore, successful expansion and production require careful consideration from early research to clinical production.

This white paper provides guidance for designing and executing an efficient upstream AAV production process. We provide a checklist for drug developers to ensure they have investigated the appropriate factors at each phase to mitigate risks throughout AAV process development.



Upstream AAV Production

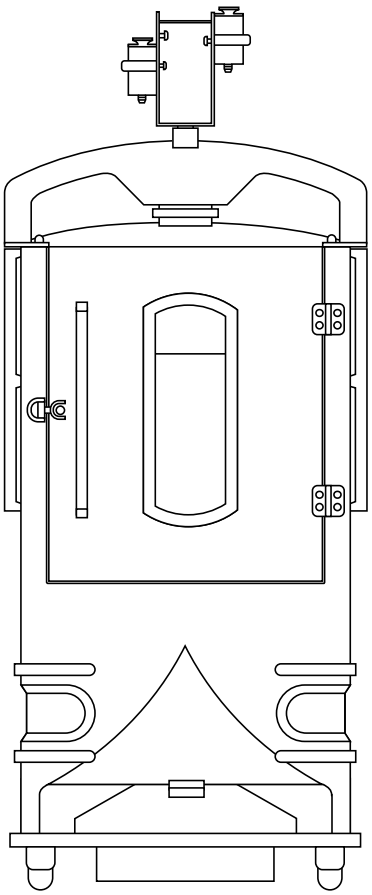
AAVs are relatively small, non-enveloped viruses. They possess low pathogenicity in humans and require helper-virus functions to replicate, creating a robust safety profile. Additionally, there are multiple serotypes possessing different tissue tropisms, making them suitable for varied applications. These features, along with their capacity for long-term transgene expression, make AAVs the vector of choice for in vivo gene therapy. Host HEK293 cells possess adenovirus sequences (E1A/B), providing helper functions and improving AAV titers.[3]

Table 1: *Key Features of Three Commonly Used Viral Vectors*

	Adeno-Associated Virus (AAV)	Adenovirus	Lentivirus
Size [nm]	~25	~90	~100
Enveloped?	No	No	Yes
Genome	Single-stranded DNA	Double-stranded DNA	Positive-strand RNA
Insert Size [kb]	5	8	8
Use-Case	In vivo gene therapy	Vaccines	Ex vivo gene therapy and gene-modified cell therapy

A significant bottleneck in the production of AAV-based therapeutics is the low efficiency of upstream process steps. Low yields, expensive reagents, and challenging scale-up processes can limit manufacturing efficiency and create batch-to-batch inconsistencies that regulatory agencies will not look upon favorably.

The industry requires robust and reproducible AAV production platforms to maintain progress toward increased accessibility for advanced therapeutics. However, as a relatively new modality, AAV production processes lack standardization and are not yet entirely optimized.



Upstream AAV Production Challenges

Complex Cell | Media Interactions
Designing and implementing cell culture conditions that support efficient transfection and AAV production is challenging. The complex interplay between host cells, transfection reagents, media, process parameters, and viral packaging processes is almost impossible to untangle and navigate. As a result, high-throughput screening and design of experiment (DoE) approaches are essential to finding the HEK clone and culture conditions that deliver sufficient yields of a high-quality product.

Sourcing Regulated Raw Materials
Sourcing high-quality and compliant raw materials, including transfection reagents, media components, and other consumables, is essential to ensuring batch-to-batch consistency, achieving regulatory approval, and safeguarding patient safety. Moreover, securing a robust supply chain is crucial to avoid costly production delays.

High Development and Production Costs
AAV vector production reagents are expensive and can represent a significant financial burden for drug developers, especially where production processes are in their infancy. Additionally, gene therapy is dynamic and fast-moving and lacks the standardization that exists in more established modalities. AAV manufacturers must keep up with evolving technologies, consumer demands, and a changing regulatory landscape.

Navigating Regulatory Hurdles
The way gene therapy products are regulated is complex and multifaceted. Advanced therapy medicinal products (ATMPs) encompass a broad range of products, from manipulated cells and tissues to gene therapies. Understanding how regional and global regulations impact new and established production processes is crucial, especially as regulatory standards are still evolving.[4] Two key guidance documents issued by the FDA[5] and EMA[6] can be used to determine product characterization.

Fierce Competition
The gene therapy market is unique and crowded. Biopharmaceutical developers must carefully consider their target indication and appropriately prioritize speed, efficacy, scale, and patient outreach.[7]

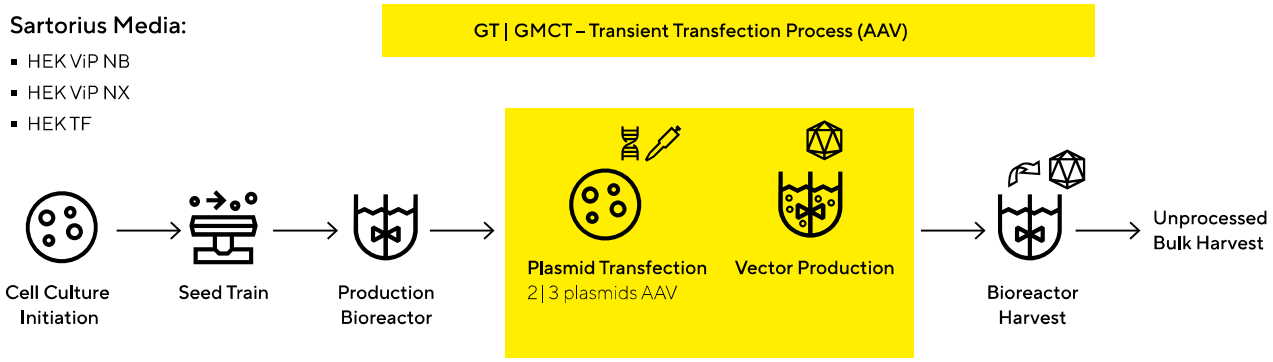
Dissecting Upstream AAV Production From Research to Clinic

Process parameters do not act in a vacuum. Each parameter must be considered within the complex web of cell metabolism, media components, and culture conditions when developing an AAV production process. Further confounding this complexity is the uniqueness of every AAV process: many potential variables impact the interactions between cells, media, and culture environment. For instance, AAVs are diverse in nature (more than 13 serotypes and variants exist), which makes developing standardized platform processes challenging. Additionally, different cell lines and production clones differ in their metabolism of nutrients and media components.

As a result, a significant amount of cell line development activities and process optimization may be required to build a high-performing HEK293 cell line that produces a significant AAV yield possessing the necessary critical quality attributes (CQAs).

The following sections provide guidance for drug developers at each phase of their project to maximize the chance of success. We outline important considerations across stages, from selecting a cell line during research and early development to process development activities and into pre-clinical production and beyond.

Figure 1: *Overview of Transient Transfection for Viral Vectors*



Note. Gene therapy (GT) and gene-modified cell therapy (GMCT) processes typically involve transient transfection of HEK293 cells with plasmid DNA. Sartorius has a broad HEK media portfolio (including HEK ViP NB, HEK ViP NX, and HEK TF) to suit all upstream viral vector process steps and applications.[8,9]

Stage 1 | Research and Early Development

Production Scale

A fundamental factor to consider early in production is the potential patient population. What production scale is envisaged based on factors such as disease incidence, cost, competitive landscape, and patient access?[7] Designing the process with the final scale in mind will avoid additional optimization experiments later. Additionally, the final production scale will strongly impact the technology selection and whether some process development and/or manufacturing activities must be outsourced due to facility capacity.

Fostering Collaborations

Once the production scale is determined, it might shed some light on whether development or production activities will be in-house, outsourced, or a hybrid model. Each of these approaches is associated with its own advantages, and the decision of which route to take is entirely facility- and process-dependent.[10,11]

Facility capabilities and capacity are fundamental drivers of this decision. Key considerations will include access to the necessary technologies, floor space, and skilled personnel to perform proper process characterization. For upstream AAV production, manufacturers require suitable cell culture media, transfection reagents, plasmids, and protocols. They must also have relevant experience selecting and optimizing them for the process, including suitable feeding strategies and process parameters (i.e., pH and dissolved oxygen [DO]). These features are an important part of a comprehensive cell line development process. In terms of expertise, experience with clone selection and cell banking will be essential.

Identifying CQAs

Understanding the product features necessary for AAV product efficacy is essential. While this understanding is likely to evolve during process development, it is critical to understand the key product features and the process parameters required to achieve those parameters. For AAV vectors, likely CQAs include genomic titer, product-related impurities (e.g., empty capsids, non-infectious particles, and aggregates), process-related impurities (e.g., host cell proteins and host cell DNA), and adventitious agents (e.g., endotoxins and adventitious viruses).[12] These attributes can be ranked according to their risk, helping scientists prioritize their focus from early development and select manufacturing strategies that facilitate the production of high-purity, high-efficacy AAV products.

Once the CQAs have been determined, the production variables that may influence these features should also be considered. Narrowing down the process ranges will accelerate the identification of critical process parameters (CPPs).

Choosing a Production Strategy

The adopted manufacturing approach will also affect early decision-making and vice versa. It is important that the tools and strategy chosen can be scaled up to the final production scale without any significant operational changes.

Traditionally, HEK293 cultures are grown in adherent cultures supplemented with animal-derived serum. However, in the biopharmaceutical industry, serum-free suspension cultures are increasingly favored owing to their more straightforward scale-up,[15,16] ability to reach higher densities, reduced lot-to-lot variability, and simplified regulatory approvals. Simple protocols exist for adapting adherent HEK cells to suspension culture.[13] AAV production in adherent and suspension cultures is compared in Table 2.

Table 2: *Comparing Adherent and Suspension Culture Modes in AAV Production*

Feature	Adherent	Suspension
Applications	Almost all cell types	Most cell lines must be adapted to suspension (except non-adherent or primary cells)
Phase	Often used in research and development for fast material generation	Often used in process development and production
Passaging	Cells must be detached from the cell culture dish enzymatically or mechanically	Easy passaging, enabling seed train expansion
Scale-Up	Capacities are limited due to surface area restrictions	Suspension cells can grow in three dimensions, increasing titer output
Culture Equipment	Requires an incubator and specially treated culture vessels	Treated vessels are not necessary, but agitation is usually needed for gas exchange
Process Analytical Technologies (PAT)	No control of process parameters like pH or DO (use of PAT is challenging for some equipment)	Full application of PAT is possible
Animal-Derived Serum	Required	Not typically required

Several more technical and methodological factors must also be considered. Will cells be cultured in batch or fed-batch mode? How will this affect the downstream process? What culture vessels will be implemented (stainless steel or single-use equipment)? These decisions strongly affect the culture environment, media strategy, and the day-to-day running of the facility, meaning they should be considered as early as possible in process development.

Variations in the upstream manufacturing process (as well as the AAV serotype) will strongly impact the impurities present in the sample that enters downstream steps.

- AAVs typically require cell lysis to be released prior to harvest, introducing host cell proteins and DNA into the harvested sample.
- Different manufacturing protocols affect the proportion of empty AAV capsids produced.
- Media additives are required to limit the aggregation of some AAV serotypes.
- The biological activity of AAVs can vary depending on process parameters such as the HEK cell line, plasmid, and process design.

Therefore, selecting an AAV production strategy that limits the introduction of high-risk impurities can be beneficial.

Stage 2 | Process Development

High-Throughput Screening Tools

The more clones that are evaluated, the higher the chance of finding a high-performing one. Therefore, AAV process development is accelerated if high-throughput screening is performed. Scaled-down, automated platforms such as the Ambr® 15 cell culture system facilitate the evaluation of multiple cultures in parallel (48 in the Ambr® 15), making it ideal for identifying the top clones and optimizing culture conditions. The environment in the microbioreactors is predictive of conditions in larger bioreactors, meaning clone performance remains consistent across scales.

As well as the instruments required for clone selection, AAV therapeutic developers can leverage data analytics software to simplify their decision-making and rank their clones based on custom selection criteria. For instance, Ambr® Clone Selection (powered by Umetrics®) is an integrated software that facilitates data-driven decision-making to improve consistency and speed up process development.

Finding the Best Cell Culture Media

Choosing the right cell culture media is critical to maximizing efficiency in any AAV production process.[9] Different clones and AAV serotypes can behave very differently in culture. Additionally, the composition of the media also has significant implications for the product's CQAs and downstream processing requirements.

As well as assisting with clone selection and determining culture conditions, high-throughput tools can also be used for media selection and optimization. While AAV developers might have some media in mind based on research and experience, fine-tuning the selection process could pay dividends in terms of titers and quality. A DoE approach allows the creation of an optimized, streamlined approach to testing several parameters at once, meaning various media attributes can be assessed in a minimal number of runs. Taking advantage of 'try before you buy' schemes (such as the HEK Media Sample Kit from Sartorius) can grant access to a broad range of media without significant expense or commitment.

Finally, spent media analytics (SMA) provide valuable insights about cell metabolism, including how the cell uses the nutrients in the media and what byproducts are released. The information gathered by SMA can reveal opportunities for improvements in the media formulation that could support more robust cell cultures.[9]

Choosing the Right Partner

By now, manufacturers will likely know whether they will outsource all or part of their development and production process. For example, if they require external access to high-throughput screening tools or AAV expertise. If they decide to outsource their process development activities, selecting the right partner is essential.[11]

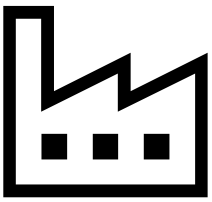
A service provider with a comprehensive offering (like Sartorius) can grant support through the entire cell line development pipeline, which means benefiting from a complete service with knowledge both up- and downstream of the outsourced operations. An experienced provider with knowledge of the entire workflow can provide more reliable and tailored advice, avoiding hurdles later down the line.[9–11]

Measuring CQAs

During early development, the CQAs of the AAV vector should have been established. It is also important to consider the methods most appropriate to measure these CQAs during process development and production to ensure quality is continually monitored.

To maintain product quality, improve consistency, and simplify regulatory approvals later, process development scientists should have access to tools that provide fast insights into product quality attributes. This will form an important part of process development activities as the information used can help to inform any modifications required to achieve the target product profile.

Process analytical technologies (such as the sensors and analyzers in the BioPAT® toolbox) offer deep insights into the AAV production process to fulfill quality-by-design (QbD) principles and track process deviations to ensure CPPs are maintained. These analytics must be supported with software that facilitates the fast interpretation of results to allow quick, data-driven decision-making.



Stage 3 | Clinical and Commercial Production

Scaling-Up

Once the process has been developed, scaling up the process to a clinical or commercial scale becomes a reality. Hopefully, this phase has been heavily factored into early decision-making to ensure that production scenarios are appropriate at larger scales. Important considerations include the suitability of the cell culture mode, the feasibility of the media strategy, and security of the supply.

It is also important to recognize that scaling calculations are complex. For many process parameters, scaling is not linear, posing a challenge for progressing to clinical or commercial scale, and especially challenging if the cell line is adherent. Bioreactor scaling is particularly complex and often poorly understood; the biological nature of cells also makes them inherently stochastic and challenging to control.[14] However, manufacturers can access tools designed to simplify the scaling process and accelerate the transition to clinical manufacturing. The BioPAT® Process Insights software allows users to simultaneously evaluate various parameters across multiple scales to identify high-risk transfers earlier in process workflows, saving significant work hours.

Single-use products can offer flexibility and modularity when it comes to process scale-up. Having the same film used for different types and sizes of single-use containers is important to maximize process robustness and reduce regulatory challenges. Not all suppliers can offer end-to-end single-use solutions with the same film across scales and from Upstream to Downstream.

Assurance of Supply

Ensuring you have a robust supply of high-quality materials is essential to maintaining consistent production and meeting targets. Developing a robust supply chain is also a key concern in the modern biopharmaceutical arena. A 2022 survey by BioPlan Associates Inc. found that almost 20% of respondents noted that the most important area where they thought innovation was required was "Materials Sourcing/Raw Materials Management," a significant jump from 5.3% in 2021.[12] Additionally, the majority (84%) of respondents indicated that "Increased focus on supply chain security" was "much greater" or "somewhat greater" compared to previous years.[12]

Building a robust supply chain for upstream AAV production starts with choosing a media supplier that has forged relationships with raw material providers to ensure the supply chain is not interrupted. Dual sourcing of reagents can also be an effective risk mitigation strategy. Finally, it is essential to select media that can be manufactured in large quantities in the desired format (liquid in bags or powder) to manage at least 1,000 L and up to 5,000 L per batch.

Regulatory Approvals

Navigating a complex regulatory landscape can be daunting. AAV production scientists must keep up to date with industry regulations and consider what resources are necessary to accelerate and retain regulatory approval.

Regulatory agencies require an increasing level of transparency in the process. Live data monitoring can help maintain tight control and avoid process deviations. To ensure regulatory requirements are met, reliable data acquisition, visualization, and storage should be employed to keep accurate records and simplify data interpretation, facilitating data-driven decision-making. This type of monitoring and recording is offered by PATs, which can record features such as biomass and nutrient levels to limit process deviations and batch-to-batch variability.

Continuous Process Improvements

Finally, as process knowledge increases, opportunities may come to light. As part of continuous process improvements, manufacturers may want to incorporate new strategies to improve production efficiency. Such strategies could include adopting intensified production strategies such as seed train intensification or perfusion culture.[17] They may also include harnessing automation technologies or analytic solutions to generate data to support increased process control.

AAV Testing Assays

As with any product for human use, AAV-based products for gene therapy should be extensively evaluated for CQAs, purity, potency, and safety. Every stage of the product lifecycle requires at least some testing to demonstrate that the quality attributes required by the regulatory bodies have been achieved.

Biological products derived from mammalian cell lines pose an inherent risk for the introduction of microbial or viral contaminants. In addition, the manufacturing process or product itself may introduce impurities that must be characterized and removed where necessary.

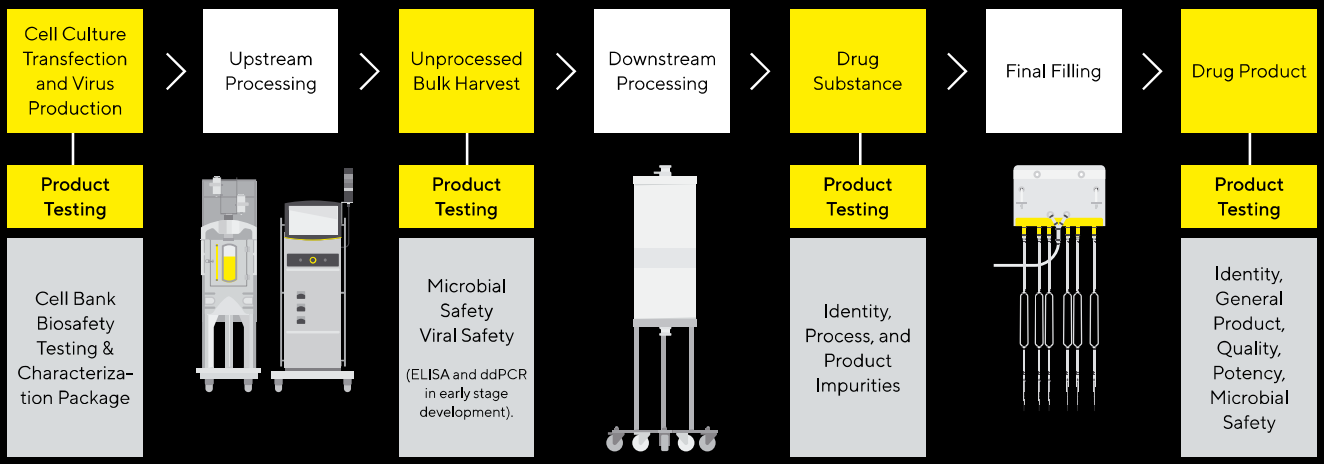
Testing Needs by Phase

During research and development, AAV testing methods are necessary to evaluate the manufacturing process and confirm satisfactory yields. Good manufacturing practice (GMP) compliance is not a priority at this stage. Nevertheless, when development is completed for investigational new drug (IND) filing, and later biologics license application (BLA) filing, biosafety and toxicology should be verified by GMP-compliant methods.

Testing Needs by Process Step

Over the production process of an AAV therapeutic, there are several stages where samples are taken, and testing is performed to ensure a safe and efficacious product is available for the patient (Figure 2).

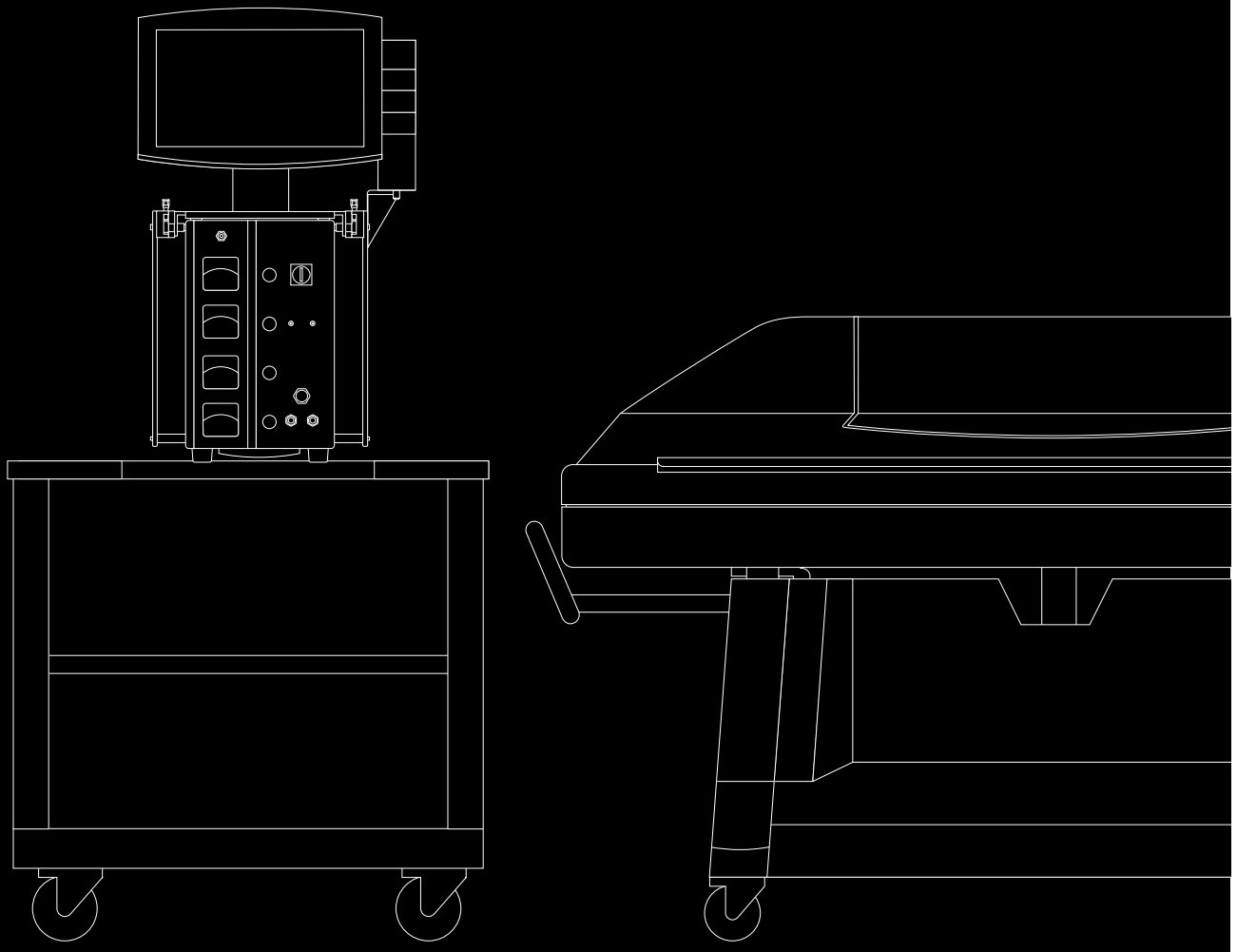
Figure 2: *Biosafety and Characterization Testing Methods Are Required at Every Stage of AAV Product Manufacturing*



Upstream Production
During upstream production, the cell bank undergoes rigorous biosafety testing to ensure there are no contaminants that may have adverse effects on the patient. Once certified, this cellular expression system is transfected to produce the AAV drug candidate, which is tested predominantly for microbial and viral safety at the bulk harvest step.

Once the product has been shown to be free from any microbiological or viral contaminants, downstream processing is carried out, and the drug substance is tested for identity and product and process-related impurities. Finally, after fill | finish, representative samples of the drug product are tested for product quality, identity, safety, and potency.

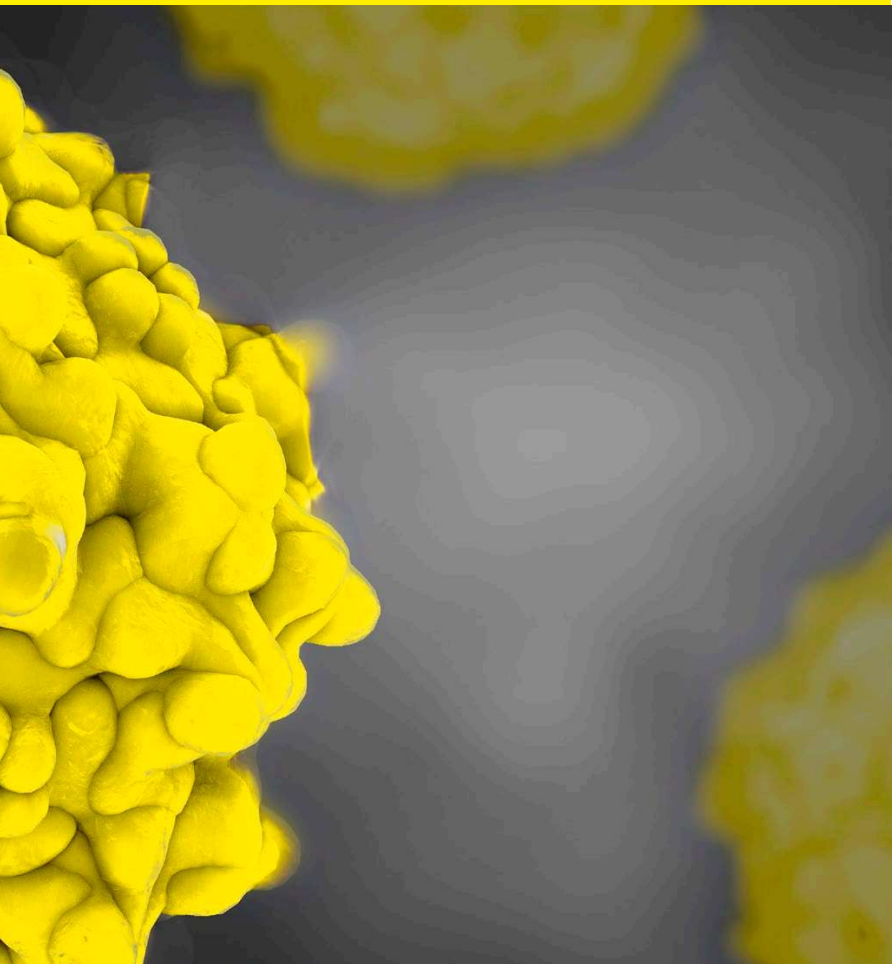
Sartorius now offers a complete set of assays with appropriate GMP-compliant qualification or validation to appropriately characterize the AAV product for its current stage of development. Visit AAV Testing Services | Sartorius to learn more.



Conclusion

Complex interactions underpin the relationship between cell metabolism, process parameters, and AAV production efficiency. Therefore, deep process and product understanding are essential to establish an effective AAV production strategy. Part of this includes truly knowing your methods and precisely what they measure to ensure you make informed decisions when designing and optimizing your process.

Priorities might change along the pipeline, but taking a holistic approach and considering these factors early in process development will avoid unwelcome surprises during scale-up and commercialization. Choosing a partner with demonstrated expertise across the AAV production pipeline is favorable, whether simply sourcing media or outsourcing much of your process.



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Catherine Buchere has been working for Sartorius since 1998, where she is today Product Manager for viral-based therapies for Vaccines and Gene Therapy. She holds a Master of Science in Polymer Analysis & Structure in Medical and Food & Beverage purpose from Paris XI Pharmacy university.

She was leading during the 8 last years the team of Custom Product Development (ETO), focused on Single Use Product from Upstream Process until Fill Finish Step. She joined Marketing as Product Manager for Flexboy® product in 2018 and moved in 2020 to the newly created Sartorius division Cell line, Media & Testing Solutions (CMTS) – Viral-based Therapies.

She has been supporting the adoption of Sartorius portfolio and more specifically today on developing MDCK, BHK-21, Vero, Insect & HEK293 production platforms

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Katy is part of the Marketing Communications team at Sartorius, where she supports the creation of a variety of written pieces, from published articles to web content.

Before joining Sartorius in 2021, Katy was employed as a Post-Doctoral Research Associate at the University of Edinburgh, where she also completed her doctoral studies. Here, she carried out research in genetics and cellular biology and began taking on writing projects, eventually entering into a career as a freelance writer for various biotech companies and agencies.

Kathrin Teschner
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Kathrin joined Sartorius in 2021, where she is part of the product development team focused on process and media optimization to produce viral vectors.

Before joining Satorius, Kathrin was employed as a Post-Doctoral Research Associate at the University of Bielefeld, where she also completed her doctoral studies, which were focused on the use of AAV in cancer gene therapy.

David Ede
Process Technology Manager,
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In his current role as Process Technology Manager at Sartorius, David supports viral-based biotechnology stakeholders to bring their full bioprocess from research and development to commercial scale. He has 5 years' experience in process development and manufacturing for viral vectors.

David is a biomedical and chemical engineer graduated from the University of Utah and Oklahoma State University in the USA.

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