Article

AAV manufacturing

# Straight from the source: streamlining scale-up with quality raw materials

Manufacturing adeno-associated virus (AAV) vectors and the necessary plasmids for gene therapies is complex, with media alone sometimes requiring more than 100 different raw materials [1]. As processes increase in scale, the greater raw material volumes and stricter quality requirements can make it challenging to deliver an effective and economically feasible product. In this how-to guide, we discuss the common challenges that developers face when moving through process development and outline the essential steps for streamlining scale-up through effective raw material sourcing.

The main challenge of scaling up a workflow is maintaining affordability while maximizing yields and product quality. As a rule of thumb, when it comes to a biotherapeutic manufacturing process, variability in equals variability out. So, if the quality and consistency of incoming raw materials can be maximized, then the chances are higher of producing a more consistent AAV vector. This is important when scaling up to commercial volumes and trying to meet critical quality attribute targets, as negligible inconsistencies early on can quickly cause issues as production increases. By considering how to source raw materials—in the volumes and quality classifications that are required—you can streamline the scale-up process, future-proof your workflow, and deliver a gene therapy that will meet regulatory and clinical requirements. Below we have outlined the five most important factors to consider when sourcing raw materials for scale-up.

## 1. Balancing cost and quality

While the best-quality materials can be used at smaller scales, costs can compound with scaling. On the other hand, inconsistencies that may not have an impact at smaller volumes can be amplified when a process is scaled up. This makes scaling a delicate balancing act between staying within budget and maximizing the standard of incoming materials. As media quality is a big driver of cell culture performance [2], raw material decisions are particularly important when it comes to media development and optimization. Raw materials manufactured using GMP quality systems are more likely to be consistent. Non-GMP materials may demonstrate comparable performance in early stages but can pose troubleshooting challenges later due to a relative drop in consistency.

## 2. Mitigating risk

Hundreds of components are needed during the AAV manufacturing process, and it may not be cost-effective or logistically feasible to source each one at GMP-grade at scale. Certain raw materials carry a higher risk of adding variability, so by identifying, characterizing, and understanding which materials pose the most risk, you can make informed sourcing decisions. For example, mined materials such as ferrous sulfate and iron salts can introduce impurities in the form of trace elements. These may have a limited impact during research and development but can lead to significant differences in batch-to-batch product yield and quality at larger scales.

With a risk-based approach, it is possible to use historical data to analyze which components have the greatest likelihood of affecting process consistency and product quality. Then the decision can be made to either use the highest quality classification, or proactively monitor incoming materials. At this stage, you may also choose to conduct a more in-depth characterization to gain a better understanding of specific components.

## 3. Planning for the future

In addition to optimizing raw material quality, maximizing supply assurance should also be a primary consideration for AAV manufacturers. This is particularly important when scaling up production, as increasing raw material demands can put additional pressure on suppliers, potentially resulting in supply disruption and delays. To reduce this pressure, it is recommended that you begin forecasting your future raw material requirements as soon as possible. As a guide, you should be aiming to begin this process at least two years before starting to scale up.

Implementing a forecasting system during early development can be advantageous, even though inaccuracies could be possible at this stage, because it will allow you to refine and optimize your system over the course of process development. As you then start to scale up your process, you will be able to communicate your raw material needs to your suppliers in a timely manner, which will give them an opportunity to assess their own raw material supplies, manufacturing capacity, and supply chains. By validating their ability to meet your projected needs, they can give you confidence that they can plan to scale with you and continue to fulfill your raw material requirements into the future.

## 4. Managing lead times

Although collaborating closely with your supplier to forecast future requirements can reduce the risk of raw material shortages, there is still the potential for unforeseen supply chain disruption. This has become an increasing focus over recent years, following a number of global crises that extended lead times for many critical bioproduction raw materials.

To safeguard against this, manufacturers can invest in maintaining a safety stock of critical raw materials above their forecasted requirements. In addition to protecting against supply chain disruption, this strategy can also be advantageous to mitigate any internal challenges caused by raw material qualification variability and overall production variability.

## 5. Taking a holistic approach to process consistency

While having a strong focus on raw materials is important, it is also necessary to keep an eye on the bigger picture. A thorough knowledge of the whole cell culture system can facilitate an understanding of which factors have the greatest impact on process consistency and therefore are critical to process success. Some cell lines and workflows are more sensitive to certain parameters or raw material impurities, so by taking a targeted approach, it is possible to control the variables most important to your process. It is also important to make sourcing decisions as soon as possible, as establishing raw material choices early will lessen the risk and complexity of the unavoidable late-stage process changes.

## Choosing a raw material supplier

The supplier you choose will be just as important as the raw materials themselves. A supplier that can contribute knowledge and expertise from a range of biotherapeutic areas will greatly help with process development. In this regard, Thermo Fisher Scientific can leverage its wide international network and strong service offerings to help streamline your scale-up. In particular, our raw material program can help with in-depth material characterization and media development and optimization.

Furthermore, field application scientists and technical sales specialists from Thermo Fisher understand the Gibco™ AAV production portfolio in depth and can point you in the direction of other resources and services if necessary. They can also provide assistance with demand forecasting for raw materials, helping you to maintain a consistent supply of critical materials as you scale up.

On the manufacturing side, look for a supplier with robust quality systems for their own raw materials. Thermo Fisher makes sure to conduct strict qualification and validation of all incoming materials, including in-depth characterization and testing; and with its multiple qualified production sites and separate animal origin and animal origin–free facilities, you can scale up your process with confidence. Ultimately, by being proactive about your raw materials and the validation of your suppliers, you can lock in your process as early as possible. This will give you the best chance of a successful scale-up and delivering your therapeutic to the people who need it.

### References


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