CASE STUDY: SELECTING THE RIGHT FACILITY DESIGN AND TECHNOLOGY TO SUPPORT AAV PRODUCTION AT SCALE

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ABOUT

Dave Backer has been in the cell and gene therapy (CGT) industry for over 20 years, giving him a long-term view of the differences and similarities of manufacturing CGTs vs monoclonal antibodies (MAbs) and how that plays out in terms of tech transfer and scale-up.

In this case study, Dave shares his experiences and necessary considerations when scaling up AAV manufacturing.

SITUATION

The company in question was at a very early stage and had just been funded via preclinical studies and was set to enter clinical trials in the next 18-24 months.

The product is AAV-based, with orphan drug potential in a rare disease.

CHALLENGES

The biggest challenge was that the technology came out of academia and the process that had been used for early studies involved adherent processes, cell factories upstream and ultracentrifugation as part of the purification process in the downstream process. The unique issue with AAV relates to how complete the virion is during the manufacturing process; it is classed as 'full' if it's a complete infectious particle and 'empty' if not. Ultracentrifugation can be used to filter the full particles from the empty particles but is very difficult to scale, and that can be a bottleneck to late-stage development and commercialisation. It was necessary to evaluate alternative processing methods both up and downstream before entering the clinic.

Additionally, the continued challenge that we all face (but maybe exacerbated in the gene therapy and rare disease space) is that trials are usually condensed, with phase I/II involving 10s of people rather than 100s. The intent is then to go straight into a phase III pivotal, which often is not going to allow conversion to a new process.

Another dimension to the barriers we faced was somewhere in the cross-section of investors and pressure on timescales. The investors wanted to start clinical trials as soon as possible and their preference was to stay with the academic process, get it good enough to go into the trial and see if it works. At the same time, finding a CDMO that could also accommodate these timescales for a newly financed company was a significant hurdle so there was a discussion about building a manufacturing facility in addition to using a CDMO partner.

SOLUTIONS

First, we tackled the process design challenges. There are several ways to manufacture AAV; the two main options were to continue with the adherent process using cell factories and transient transfection or transfer to one of the available suspension technologies. For example, suspension bioreactors with transient transfection and plasmids could be used. The other options are to use baculovirus as a system or a use helper system, such as herpes virus or a wild-type adenovirus to provide some of the information that you'd normally get from plasmids.

When we examined the initial commercial need and the productivity of the process, it was clear that the maximum reactor size was needed to be able to meet the potential need. So, the next question was how to scale. One option is the use of suspension bioreactors with transient transfection all the way up to the max scale of 2000L. However, it's important to note that the phase I/II trials wouldn't require close to that, this was purely aspirational.

The adherent processes already in use by the academic institute weren't easily scalable and it wasn't possible to continue to use cell factories. This method would be enough for the phase I/II trial, but it would not meet the needs for a phase III pivotal trial or commercial levels. Another option to scale was to remain in an adherent process but move to a fixed bed reactor, and there are a few companies that use these with AAV products on the market right now.

These different options were investigated, including a study as to the merits of each. The results allowed us to come up with the decision:

to move to a 50L suspension system at, transient transfection and a downstream process that didn't involve ultracentrifugation – instead, we would adopt use some alternative steps to help with the full: empty ratio.

In terms of the challenge of finding a CDMO partner we eventually identified a CDMO that could deliver the product in nine months at the 50L scale. The selection criteria for the CDMOs also involved their ability to go up to 500L, so there were bids for 50L and 500L. The facility design on the build vs buy-side also only went up to 500L, the decision was made not to go up to the maximum scale of 2000L. This was primarily due to the large distance between the initial academic process and 2000L, it was felt that multiple batches of 500L were less risky and easier to get to from the 50L scale.

LESSONS

It wasn't enough to just focus on the demand-supply balance and the fastest way to get into the clinic, it really made more sense to take more time. Even though there was approximately a 9-month delay on the initial clinic timelines, it meant there was time to develop the best process and the best chance to be able to scale up to 500L. Other organisations have stayed with the adherent and moved to fixed bed bioreactors, which is a viable alternative, but for this product and the opportunity it ended up being optimal to move to suspension.

The other surprise was the CDMO landscape. As there are many ways to make AAV, not every manufacturer has expertise in all the different areas, for example, some CDMOs are AAV manufacturers but are pure baculovirus players. Other companies claim to have 2000L capability but 100s of litres was the actual experience that these companies had.

But we ended up with a good solution and the product came from the CDMO on time at a moderate 50L scale. Now, in the covid era, the timeline of getting to 500L is unsure but it has proven to be a good solution at least for the initial phases.

This case study was presented at a recent virtual event 'Pharma Shifts to Biologics', which included six in depth case studies and networking sessions.

Details of future events can be found here.

You can watch Mark's case study in full and on demand here

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