Regulatory requirements and product attributes for cGMP viral vector production

Scott Cross, Dark Horse Consulting Group, and **Shikha Mishra**, Thermo Fisher Scientific

Scott Cross and Shikha Mishra share their insights on regulatory compliance throughout the therapeutic development lifecycle, and best practices for producing high quality viral vectors at scale, for clinical and commercial applications.

Navigating the constantly evolving regulatory landscape in cell and gene therapy manufacturing can pose critical challenges for developers and manufacturers. Failure to meet requirements can significantly raise costs, motivating the implementation of robust, reproducible, and compliant processes.

From a regulatory angle, there are a few common mistakes during process development that affect the transition into clinical and commercial manufacturing phases that people may not anticipate.

Scott Cross: The most common issues from the CMC perspective include teams lacking an understanding of their manufacturing process. The rush to the clinic may come at the expense of having a well thought out process. Organizations tend to focus on getting the highest possible titer out of their vector, without paying enough attention to residuals. Regulators look at whether a process is producing a high titer vector at the expense of clearing residual DNA or protein, as this can complicate things down the road.

Another common issue is teams who move forward with an academic process that may not be feasible at a commercial scale. A classic example of this is ultracentrifugation. This can produce high titer and purity vectors, but it is not a highly scalable option. The early lots of some products can have a completely different purity profile to the more commercial and scalable process. This will require a great deal of optimization work to resolve. These considerations need to be made ahead of time.

How do you develop a scalable process that ensures product quality is maintained?

Shikha Mishra: When starting out, it is important to develop a strategy whilst keeping your end goals in sight. When looking to produce AAV vectors at 100+ L scale, you will not be completing your initial process optimization at those volumes. However, the practical logistics of whether the initial process can be translated to commercial scale must be considered. For example, if your production method involves a complexation step between plasmid DNA and a transfection reagent, there may be a logistical timing issue related to transferring large volumes from one place to another. There are scientific factors contributing to liquid movement that you may not appreciate at a large commercial scale. Poor complexation could translate to a low transfection efficiency and low vector quality which can affect the viral vector empty to full ratio.
How do you avoid this? You must understand the existing scalable technologies before you begin your process. Hindsight is 20/20; you should adapt your process to be scalable early on.

The CTS™ AAV-MAX and CTS LV-MAX systems use the suspension cell platform, which lends itself to scalability. The Advanced Granulation Technology™ (AGT) media format is manufactured according to regulatory guidelines and also allows high scalability. At small-scale, it is possible to have reagents in small packing configurations, but if they are not available in larger ones, this can add a dimension of potential contamination risk when scaling up. As you transfer to process development and large-scale commercial manufacturing, you need to choose tools that can optimize for scale. Choose solutions that can grow with you all the way from A to B to Z. Growing pains are inevitable, but taking away the major failure risks to support a high quality end product is possible.

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