Streamlining Advanced Therapy Medicinal Product Manufacturing: A Platform Approach for Accelerating Gene Therapy Commercialization at Viralgen

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Abstract

Viralgen Vector Core, S.L.U. specializes in the manufacturing of Advanced Therapy Medicinal Products (ATMP), specifically adeno-associated viruses (AAVs) for gene therapy applications. Their manufacturing process utilizes a state-of-the-art triple transfection method with a HEK-293-derived suspension cell line (Pro10™ cell line), enabling the production of various AAV serotypes while maintaining consistent quality attributes. The unique nature of gene therapy presents challenges in establishing a cost-effective manufacturing process. Viralgen proposes a platform approach that leverages shared characteristics across different AAV serotypes to streamline operations and reduce variability. This strategy unfolds in three stages: Establishing a platform control strategy; generating experimental data to refine this strategy; and verifying it through specific studies.

By adopting this approach, Viralgen aims to enhance the robustness, reliability, and predictability of its manufacturing process, from pilot to clinical to commercial scale, by leveraging process knowledge between different AAV serotypes and various drug products ensures consistency, robustness, process, and provide high-quality output with limited data. Ultimately, this methodology has the potential to address unmet medical needs, shorten development timelines, and improve accessibility and affordability of gene therapies.

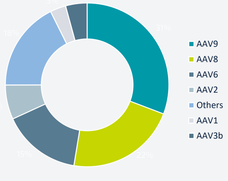
Platform Approach for Accelerating Gene Therapy

Viralgen Vector Core, S.L.U. (Viralgen) is a CDMO dedicated to the manufacture of Advanced Therapy Medicinal Product (ATMP). The manufactured product is a sterile suspension of adeno-associated virus (AAVs) for human use, which contains the therapeutic transgene in between ITR (inverted terminal repeat) sequences. The company employs a technology for manufacturing a wide range of AAV serotypes with different genes of interest (GOI). Gene therapy requires a very limited number of doses, being probably in most cases a single dose. This feature together with the possibility of targeting rare/ultrarare diseases (limited number of patients) or diseases requiring very low doses (e.g. ocular diseases) created a new paradigm in the world of drug manufacturing. The limited number of batches required to treat a given population makes it very difficult to establish a robust and cost-effective manufacturing process.

A platform approach for gene therapy could consider the transgene as a unique difference and the specific capsid as a common structural element that shares physico-chemistry characteristics within the same serotype. The manufacturing process at Viralgen is based on a triple transfection of a unique Master/Working cell bank of a HEK-293-derived suspension cell line (Pro10™ cell line), which includes common Rep/Cap and helper plasmids in between programs and the specific gene targeting the disease. Regardless of the GOI, Viralgen's manufacturing process includes common features throughout the process concerning raw material such as cell culture media, transfection reagents and matrix for purification as well as manufacturing equipment and facilities. Process parameters, material release specifications and in process controls (IPC) remain constant across the process. The manufacturing technology is also based on the use of identical single-use bioreactor vessels, operational parameters, nutrient media and feed strategies, and cell culture targets applied, which substantially reduces the variability and allows streamlining the manufacturing process. Viralgen has manufactured more than 90 GMP batches with the process described for a wide range of AAV serotypes (Figure 1). All AAV products generated share common quality attributes to ensure the product quality and allow the study of limit, range or distribution independent of the GOI. The data obtained have generated extensive knowledge of the GMP scale process, established safe operating ranges and identified potential critical process parameters that may have an impact on product quality, with which Viralgen has established a preliminary process and product control strategy.

Figure 1. Batches produced at Viralgen at different quality levels and by serotypes

Viralgen (2018-Today)	Batches Produced
Research Batches (2L)	1335
Toxicology Batches (50L)	129
Clinical cGMP Batches (250L | 500L)	104
Engineering Runs in Commercial Facility (2000L)	14



This common production system for all AAV produced to date could be mapped in several manufacturing operational units similar to those followed for production of conventional biologics (Figure 2). The level of development, understanding and control of these operational units progressively increases in a phase-appropriate manner. However, for gene therapy products, the number of batches and experience gained at each stage is likely to be substantially less than that gained for other product modalities. Our historical data along with published knowledge have shown us that some of these operating units share common physical and chemical characteristics beyond a given GOI. Thus, Viralgen is considering applying a partial platform-based approach following the principles of Quality by Design, through which it is defined what knowledge can be used to support platform-, serotype- or product-specific processes.

DNA Provision	Upstream Process	Downstream Process
Helper	Cell Line Development and Banking	Clarification
		Affinity Chromatography
Rep/Cap	Cell Thaw and Expansion	Ultracentrifugation
	AAV production and Triple Transfection	AEX
GOI	Cell Lysis	TFF
		DS Formulation

Figure 2. Viralgen manufacturing process operational units.

Results

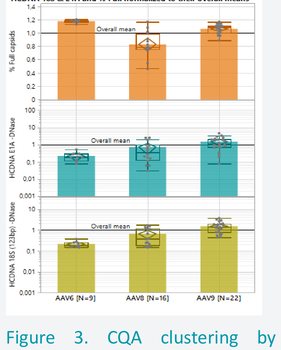


Figure 3. CQA clustering by serotype. Distributions for AAV6, AAV8 and AAV9 serotypes are depicted for host cell DNA 18S ribosomal RNA, host cell DNA E1A oncogene and percentage of full capsids.

As an example, quality attributes such as host cell DNA 18S, host cell DNA E1A and full capsids are distributed differently in different serotype groups: These CQAs have a clear serotype-dependent variation in their values accompanied by a significant difference in the respective means. As seen in Figure 3, for a given CQA the mean diamonds indicating the location of the mean and its 95% confidence interval for each serotype do not overlap vertically, thereby giving grounds for grouping CQA values by serotype. This facilitates the development and manufacture of more than one drug through a standardized production or manufacturing process or processes. As an example, quality attributes such as host cell DNA 18S, host cell DNA E1A and full capsids are clustered by serotype. Distribution results for AAV6, AAV8 and AAV9 serotypes show that they are comparable between serotypes.

The technology employed by Viralgen represents a substantial innovation in the field of ATMPs manufacturing, particularly for adeno-associated virus (AAV) therapies. This platform-based approach allows a different perspective compared to traditional CMC approach where product specific experiments are needed to generate sufficient data to demonstrate product characterization and validation, where each new product might require a bespoke manufacturing setup. By clustering products with the same serotype and leveraging historical data on impurity profiles, Viralgen can standardize its production processes, enabling faster development times and ensuring consistent quality. This consistency not only enhances efficiency but also facilitates regulatory approval processes, as it aligns with the FD&C Act's Platform Technology definition. The ability to produce multiple AAV drugs through a standardized process significantly accelerates the timeline from development to market, making these advanced therapies more accessible and affordable for patients. Figure 4 represents how the different validation activities can be grouped as platform, serotype- specific and product specific, enabling to leverage the body of data for the platform and serotype-specific operational units and the reduction of product specific experiments.

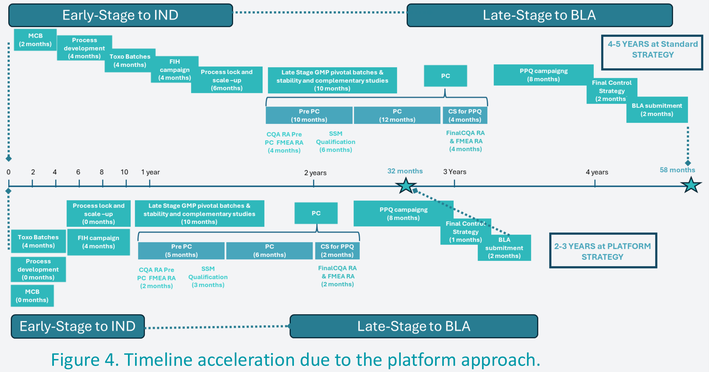


Figure 4. Timeline acceleration due to the platform approach.

Conclusion

This platform approach would allow us to acquire adequate knowledge to feel confident of providing a high-quality material manufactured in a robust manner even in the absence of exhaustive product- specific knowledge. Additionally, it would allow us to establish all the parameters, limits and ranges to accomplish a Process Performance Qualification to demonstrate that the commercial manufacturing process performs as expected and deliver a product with the defined quality in a robust manner.

In conclusion, the described approach has the potential to offer treatment to patients in areas of unmet medical needs, to reduce development timelines and to enhance product accessibility and affordability, demonstrating a clear advancement in the field of ATMP manufacturing.