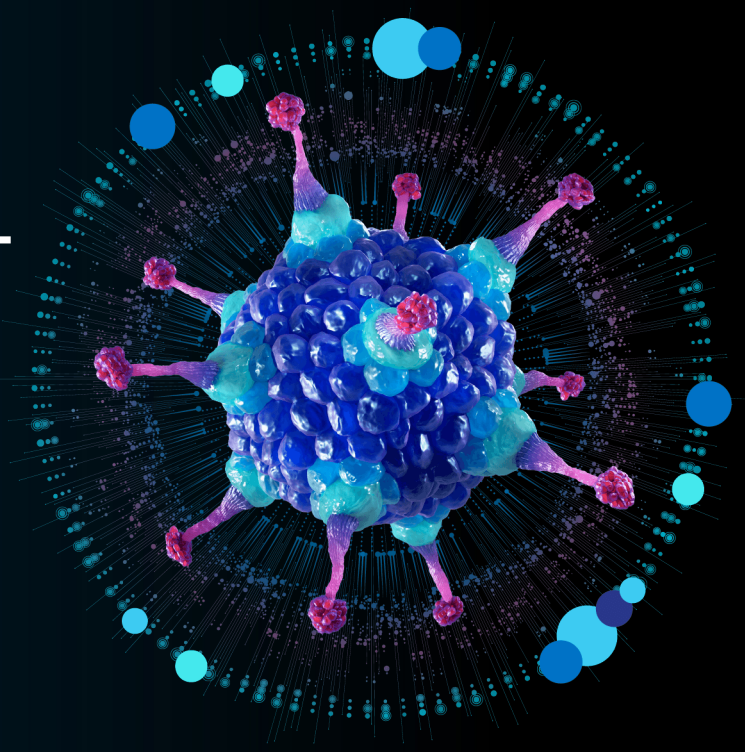
CONSIDERATIONS IN VIRAL VECTOR ANALYTICAL DEVELOPMENT TO ENABLE SMOOTH TRANSFER TO QUALITY CONTROL



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Viral vector manufacturing remains a relatively new field. Consequently, there is little standardization of analytical assays and a lack of clarity in regulatory requirements as pertains to the characterization and release of these products, which directly impacts analytical method development. Biopharma companies developing viral vectors should seek outsourcing partners that can help reduce development timelines and regulatory uncertainty by providing analytical method development, process development, quality control (QC), and manufacturing services under one roof. As important, their analytical development and QC groups should collaborate closely, and the same equipment, reagents, quality systems, policies, and procedures should be employed across both groups. This approach has been implemented at Avid Bioservices' new viral vector facility, ensuring the rapid and seamless transfer of analytical methods from research and development (R&D) to QC.

Analytical Assays are a Key Component of Project Success

Analytical development, the technology transfer to a QC setting, and then ultimately the qualification of the developed methods comprise what is most likely a critical path activity for any viral vector chemistry, manufacturing, and controls (CMC) program. The quality and depth of the analytical program can enable process development and the transfer of a manufacturing process, or it can become a hindrance effectively slowing progress as analytical methodologies and capabilities come online. An effective contract development and manufacturing organization (CDMO) partner can assist in transforming an analytical program from a slow-moving headache to a streamlined program, which supports process development and good manufacturing practice (GMP) manufacturing. Avid Bioservices has integrated analytical development and QC capabilities to ensure the timely success of viral vector programs.

The ideal solution for a biopharmaceutical company developing viral vector–based therapies or vaccines is to form a strategic partnership with a CDMO that can provide an integrated approach to analytical method development, process development, manufacturing, and QC.

Process and Analytical Method Development Should Be Interconnected

Analytical method development for viral vectors should ideally begin as early in a project timeline as possible. That can be challenging, however, because material must be produced for use in method development work. Ideally, material from a robust process will be available. The development of a robust process, however, requires analytical methods.

Consequently, analytical method development and process development are intertwined and should be initiated at the same time. As the process evolves, the analytical method is refined so that it becomes fit-for-purpose for a specific process. It would be too late to perform major analytical method development when performing engineering or GMP runs.

Having analytical method and process development closely integrated facilitates communication between all parties involved (e.g., process development, analytical development, and the client team) and eliminates undesirable lag times that can occur if these two development groups are located at different sites, whether within one company or at different outsourcing partners.

Many Benefits of Co-Development and Manufacturing

The ideal solution for a biopharmaceutical company developing viral vector–based therapies or vaccines is to form a strategic partnership with a CDMO that can provide an integrated approach to analytical method development, process development, manufacturing, and QC. In this scenario, the analytical and process development teams can work closely together, facilitating both process and method development. Rough assays can be established to facilitate early process development, which can lead to generation of test samples that can be used to refine the initial assays, further supporting the development of more optimized processes. This rapid and iterative information sharing leads to truly robust processes backed by truly robust methods.

That speed is lost if process and/or analytical development is outsourced, and it also may be lost if the analytical lab is offsite. Turnaround times for samples can be weeks, and that longer feedback loop extends the development timeline. These issues are compounded when the QC lab is also located elsewhere. Tech transfer will take longer, and the potential for problems as outlined above is much greater.

Having the same instruments, the same principles guiding what a test method should look like, and the same data integrity principles on what to document and when – combined with an analytical development team that introduces those principles early in assay development and well before transfer to QC – helps to avoid the majority of common problems encountered in viral vector development. Close interaction between analytical development and not only process development but also QC helps to ensure that the QC team has sufficient training on specific methods and that methods can be managed throughout their entire life cycle after tech transfer.

Partnership Between Analytical Development and QC

One of the keys to Avid's unique analytical method development solution is the close partnership that has been established between the analytical development and QC groups. In many companies, these groups operate in a traditionally adversarial and antagonistic manner toward one another, with each group preferring its own approach to working.

At Avid, that "throw it over the wall" attitude has been dismantled and eliminated. Experts within the analytical method development group understand the attributes of robust QC methods and work within those constraints from the start. No time is wasted on the development of methods that will be impossible to implement in a QC environment because the protocols are too complex or because the techniques are not accepted by regulatory agencies, are cumbersome, or do not scale well.

There is an added benefit to this partnership between the analytical development and QC groups: information is constantly shared about new technologies, techniques, and instruments being explored in R&D. When sufficient data have been generated to support the use of a novel solution in QC, comparability studies are performed first by the analytical development group and then in QC.

In addition, the pursuit of beta testing projects with vendors is facilitated by the partnership between the analytical development and QC groups. Avid actively seeks opportunities to get involved in the very early development of novel instruments and materials for viral vector analytics, working closely with vendors and customers. These efforts can lead to introduction of innovative and differentiating analytical solutions in advance of other CDMOs, which benefits both Avid's clients and Avid itself.

Challenges to Tech Transfer of Analytical Methods Offsite

Many problems can arise when transferring an analytical method from R&D to QC if the two groups are located at different sites. The problems generally increase when transferring methods to a third-party testing lab, but issues may still arise when methods are transferred from one company location to another.

If there is significant distance between the method development and QC labs, it is costly from a time and dollar perspective to train technicians in the QC lab in person, which can be crucial for ensuring correct implementation and the avoidance of problems. Indeed, watching someone run an assay is typically the best approach to troubleshooting a technique issue and identifying less-than-obvious factors or nuances that might influence outcomes. Close proximity to the method development team and method subject matter experts also helps to resolve issues that develop during the life cycle of a method.

Outside of method execution issues, additional problems can arise with the reagents and equipment used by labs in different physical locations. Qualifying reagents, introducing certificates of analysis, and transferring those reagents into the GMP space is always challenging and generally assay and reagent dependent. Differences in the age of equipment can be problematic. Slight differences in equipment accessories, such as a binary

versus a quaternary pump for feeding chromatography gradients, can impact separations and ultimately method performance.

Finally, having the right people on the tech transfer team is necessary to avoid these fundamental problems. Clearly, representatives from the analytical development and QC groups must be included. Someone from supply chain should also participate to ensure that all materials are in place and released by quality assurance so that they can be used in the QC environment. A regulatory expert should be involved to ensure that the method is compliant and that all required documentation has been generated correctly.

A QC Mindset Is Essential from the Start

Along with a close relationship with the process development group, it is equally valuable for analytical method development efforts to consider the needs of QC from the outset. Methods run in the QC environment must be easy to implement, rapid, and highly robust. In QC, method protocols must be followed exactly, and there is no opportunity for adjustment. Protocols must therefore be written in a manner that is executable, and specifications must not be so tight that the system suitability fails. There is a balance that must be maintained between system suitability failures that are due to control limits that are set too tight and the ability for the system suitability to properly detect an assay that did not perform correctly. This should be addressed during development activities, with consultation from the QC department.

All factors with the potential to influence results must be evaluated during analytical method development. That includes, for example, evaluating different lots of reagents and supplies, including chromatography columns and polymerase chain reaction (PCR) reagents and/or supplies, to ensure that the method performs as designed regardless of any lot-to-lot variability in raw materials. Taking this approach to method development requires more upfront investment in time and resources but ensures that the resulting methods are truly robust and unlikely to face issues upon transfer to QC where the method will ultimately be performed for the duration of the asset life cycle.

Heading Toward Platform Assays

With the field still in a nascent stage, analytical assays for viral vectors have (for the most part) yet to be platformized. A few standard assays for residual impurities and other analytes common across different types of viral vectors and between serotypes have the greatest potential to be platformized and used across multiple programs.

For product quality assays, however, a high level of standardization — such as that achieved for monoclonal antibody (mAb) assays — cannot be expected across different vector types. There are too many significant differences between adeno-associated viruses (AAVs), lentiviruses (LVs), oncolytic viruses, and the many other viruses leveraged as nucleic acid delivery vehicles. Some platformization may be possible within a class of viral vectors, but each vector type will require its own set of platform assays. Given that as many as 10–20 assays may be required for each product, the number of platform assays can grow exponentially.

Contract development and manufacturing organizations must achieve a balance between the level of assay readiness and the ability to rapidly tailor assays to each client's specific viral vector. For certain quality attributes — most notably the gene of interest packaged in a vector — custom assays or at least assay optimization will be required. Similarly, each AAV serotype has a different charge value (isoelectric point), which determines the appropriate gradient needed for anion exchange chromatography and the isoelectric focusing profile.

There are some standard assays offered by instrument makers and contract research organizations (CROs) for AAV vectors, which are widely used. For oncolytic viruses, however, there is very little in the literature that would serve as the basis for platform method development. Often, the assays — quantitative PCR (qPCR) or digital droplet PCR (dd-PCR), for example — have been developed for nonclinical viral vector applications, and thus extensive screening must be performed to determine whether those assays can be adapted for viral vector analysis in a practical manner.

Fortunately, innovation is currently proceeding at an unprecedented pace in the biopharmaceutical industry. As a result, if regulatory guidance for assay requirements is clarified within the next few years, then platform assays will likely be available at least for AAVs. For these viral vectors, it is partially possible to modify and adapt some of the assays used for mAbs to make them fit-for-purpose (e.g., size-based purity and aggregation by size-exclusion chromatography). Due to size and other factors, that might not generally be the case for other vector types, and therefore these platform assays must be developed from scratch.

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Emphasis on Data Integrity Required

Start-ups with viral vector–based products seeking a CDMO partner should be sure to find one that has established experience working in a QC environment with instruments that have a long track record of Title 21 CFR part 11 compliance and a very strong company-wide data integrity program (e.g., full audit trails, password protection, clear user access rules and controls, in-depth training program, regular gap assessments).

Ideally, the same instrument models will be used by the analytical development and QC groups and will be very well locked down and audit-ready with respect to Title 21 CFR part 11 requirements. In addition, the same computer system validation team should be responsible for preparing the instruments and associated electronic documentation for data-tracing exercises.

Purpose-Built Facility

Another differentiator for Avid is the new site for viral vector production, which was purpose-built for this application (i.e., developing and manufacturing viral vector products) and is at the forefront of manufacturing technology in the field. All the analytical method development and QC equipment was purchased in a span of months, so there is no difference in the ages of the instruments used by the two groups and hence no issues with regard to life cycle differences for the instruments.

In addition, the equipment installed in the analytical development lab is the same as the equipment used by the QC group, so there are also no issues with tech transfer from an instrument perspective. The same is true for the software systems – the control systems, platforms, report methods, custom calculations, and so on; all are the same for R&D and QC. The only differences in the equipment and software used by the two groups relate to permissions and data integrity, not technical capabilities.

As a result, every assay tech-transferred into QC is ready for immediate qualification or validation depending on the stage of the program; no further development work is required. Furthermore, if assistance is needed during the transfer process, the analytical development scientist that developed the method can work directly with QC personnel to answer questions and provide clarification.

It is also worth noting that the systems that Avid has in place ensure that all the data are maintained within the company. A few years down the road, when issues with assays inevitably arise due to changes in available technicians or reagents, columns, and other materials, the data from the original method development work will be accessible and used to troubleshoot those problems.

Avid Reduces Analytical Pain

Facilitating process development and tech transfer of methods from R&D to QC and having the analytical development, process development, and QC group under one roof reduces the challenges that CDMO clients face from both technical and project management perspectives. Analytical method development is always a critical path activity for viral vector development. Streamlining analytical-related workflows and providing transparency and open communication ensures that clients are able to make informed decisions as their projects progress.

Avid addresses client concerns relating to analytical methods from the start of any new project. Differences in instruments and assays used at the client compared with those at Avid are identified and addressed as a first step. As their projects progress, the same methods are performed on the same instruments, data is always generated in the same formats, reports are all consistent, and so on. This consistency between the analytical development and QC departments reduces painful rework that may occur immediately after tech transfer to the GMP environment.

A validation team, whether within the analytical development group or a separate manufacturing, science, and technology (MSAT) group, manages the interface between analytical development and QC, assisting with validation or qualification of each method depending on the point in the program's life cycle. Consequently, qualified assays are available when it is time to perform GMP batch production. Overall, the move from R&D to QC can be seamless, which eases the stress that typically accompanies time-constrained viral vector development programs. At Avid, the analytical development team has the ultimate accountability to ensure that all methods transferred to QC can be qualified and validated.

This approach is supplemented by a very robust quality system, the high performance of which is reflected in Avid's outstanding track record when it comes to clinical and commercial GMP material release. Avid has been manufacturing commercial biologics since 2005 and has released over 200 commercial batches to the market. The strong quality framework, infrastructure, and mindset deployed in Avid's biologics facility has been transferred to the new viral vector operations, providing a strong foundation going forward. The robust quality program is in turn fortified by quality staff with extensive experience in the field covering all type of viral vectors, including those that require biosafety level 2 containment.

Commercial Mindset with Built-in Flexibility

For viral vector development and manufacturing, Avid offers its commercial mindset and capability for GMP manufacturing and final batch release combined with the flexibility needed for early-phase clinical material production. Avid has the knowledge necessary to be successful at commercial manufacturing and considerable experience supporting clients with early-phase clinical programs. Avid can support clients at any development stage and support those projects all the way to commercialization and on to postlaunch production. Avid's facility, experts, and systems can effectively and efficiently take clients with AAVs; LVs; oncolytic viruses, such as adenovirus and herpes simplex virus or more exotic viruses; and other vectors and vector-related products, such as exosomes, from where they are today to the market.

ABOUT THE AUTHORS

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Chris Berger joined Avid Bioservices in 2015 and is responsible for Quality Assurance for all cell and gene therapy products produced at Avid. Mr. Berger brings over 20 years of experience in various aspects of Quality Control and Quality Assurance to the Avid team. In addition to a strong quality background, Mr. Berger has extensive experience in the development, validation, and transfer of analytical methods used to support manufacturing.

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Kilian Witzel joined Avid Bioservices in the beginning of 2022 and is responsible for the Assay Development for all cell and gene therapy products produced at Avid. He has over 10 years of experience in analytical development for biologics. Furthermore, Mr. Witzel has extensive experience in method validation as well as in in-process, release, and quality control testing of biomolecules.

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