Approaching Viral Vector Manufacturing With an Emphasis on Quality and Design

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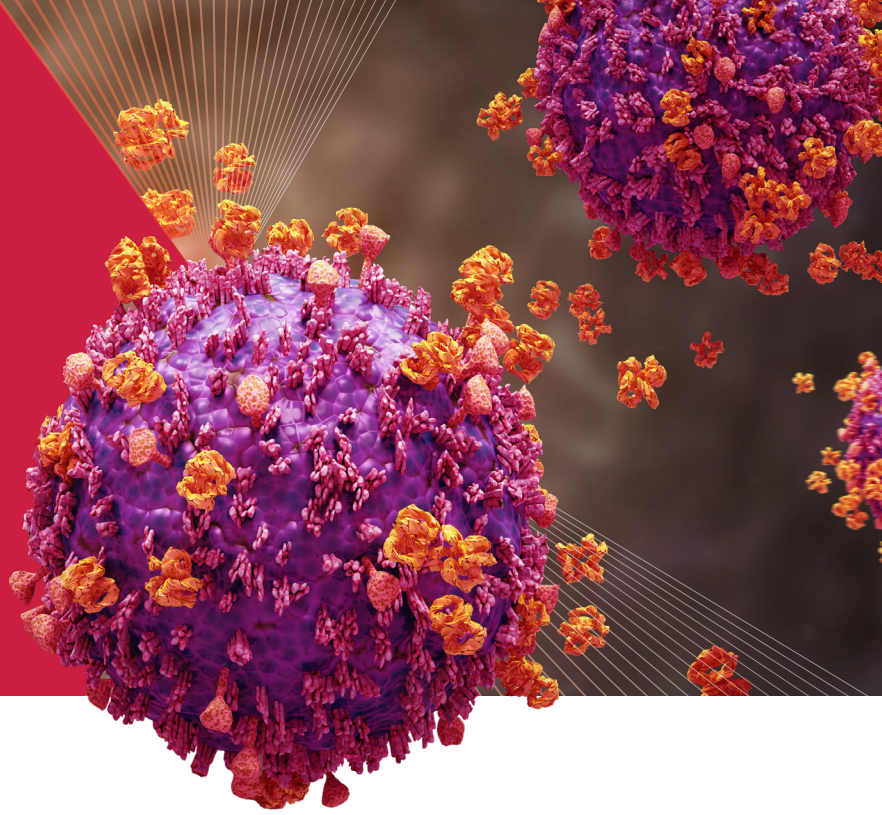

Process development and manufacturing for viral vectors intended for cell and gene therapies present unique quality and safety challenges requiring rigorous quality culture and systems and relevant experience and expertise. Building on its long quality and compliance track record and a team of gene therapy process development and manufacturing experts, Avid Bioservices is building a purpose-built viral vector manufacturing facility that will extend Avid's unparalleled dedication to quality into the cell and gene therapy sector.

Still Early Days for Viral Vector Manufacturing

Cell and gene therapy manufacturing remains in the early stages. Only a handful of products have received approval in the United States and less than a dozen worldwide. That translates into limited commercial manufacturing experience. With hundreds if not thousands of candidates progressing from preclinical to early and late-phase clinical testing globally, however, there is potential for strong growth and an increasing need for high quality viral vector manufacturing capacity.

While some cell and gene therapy developers elect to build in-house capabilities, the majority of these companies are start-ups, emerging firms, academic groups, or patient advocacy organizations who rely on contract development and manufacturing organizations (CDMOs) like Avid Bioservices to provide the resources they lack in terms of quality infrastructure and regulatory support from CMC data development to development of regulatory filing strategies.

In the viral vector space, a mix of CDMOs are now offering services, from very large players to newer academic entries that are hoping to gain a foothold. Some small and medium-sized CDMOs have also sought to develop viral vector manufacturing capabilities to take advantage of the anticipated growth to come.

Viral vectors present unique process development and manufacturing challenges that only a team with experience in the field can overcome to ensure on-time delivery of gene therapies to patients with the highest levels of quality and patient safety.

A Purpose-Built Approach Brings Real Benefits

Converting existing facilities into viral vector production sites carries many risks. One of the greatest is the potential for cross-contamination. Viral vectors are not like traditional proteins and antibodies, and must be handled accordingly. A ground-up design philosophy allows for a facility with the proper engineering controls to ensure that material, people, and air flows do not increase the risk of contamination events.

Overall, building a facility designed specifically for viral vectors allows CDMOs to address expected concerns from future clients and regulatory authorities, including the performance of risk assessments

to identify potential sources of failure and the implementation of engineering controls and, when necessary, procedural controls to mitigate those risks.

Performing Risk Assessments is Critical

Risk assessments looking at each failure mode, which consists of not only sources of contamination but of many other aspects of production, are critical to the start-up of a successful viral vector manufacturing operation. Some CDMOs overestimate their capacity and accept more projects than the facility and personnel can effectively manage without performing a capacity analysis with respect to equipment, analytical resources, and the supply chain. Emerging biotech clients that have strong technical expertise but limited manufacturing experience may begin working with these CDMOs and then find themselves presented with unanticipated challenges and issues related to lack of capacity and quality.

These problems can be avoided if CDMOs perform the proper risk assessments and capacity analyses to understand the current state of operations and the availability of equipment, people, consumables, quality control capabilities, and so on to support additional projects before accepting new work. Drug developers looking for viral vector CDMO partners should therefore request a risk assessment report that contains evidence to support a CDMO's claims that it is in a position to take on new programs and safely and compliantly manufacture their products.

Ensuring that appropriate risk assessments are performed, that manufacturing operations are not overburdened, and that process development and clinical- and commercial-scale production occur efficiently and cost-effectively requires a leadership team with experience in viral vector manufacturing.

Risk assessments should be performed collaboratively, with process development, quality control, quality assurance, procurement, and supply chain departments working together to review current capacity utilization and challenges to identify how much capacity exists before introducing any new programs and the types of programs that would fit.

Gaps in capacity understanding and communication may lead to overbooking, with some CDMOs attempting to complete too many projects simultaneously. Inevitably, that results in decreased quality and an increase in batch failure risks, directly linking capacity questions to quality and ultimately to batch success. A CDMO that truly cares about quality will not overwhelm its facility, equipment, supply chain, or production and quality personnel.

Employee frustration and burnout are other potential consequences of poor capacity management. Given the current shortage of available talent with appropriate viral vector expertise, skilled and experienced people often have multiple opportunities to find work elsewhere and will take advantage of them. Maintaining a low turnover rate to ensure that institutional knowledge and norms are maintained with the business is paramount to a successful CDMO business.

Ensuring that appropriate risk assessments are performed, that manufacturing operations are not overburdened, and that process development and clinical- and commercial-scale production occur efficiently and cost-effectively requires a leadership team with experience in viral vector manufacturing. More specifically, members of the leadership team should have hands-on experience in process development, production, and quality operations and should have performed failure mode and effects analysis (FMEA) assessments. They should be intimately aware of potential safety and quality risks and the systems developed to mitigate them.

A Strong Quality System is Essential

Quality and a patient-first mindset cannot be stressed enough. A strong quality record is a critical criterion in evaluating CDMOs offering viral vector manufacturing services for both clinical- and commercial-stage products. Speed to market is recognizably crucial, but it cannot be achieved at the expense of product quality and safety.

Avid's existing organizational structure and established internal processes for tech transfer, project management, facility management, process design and layout, etc. will be equally useful and applicable to viral vectors projects, since these products are also manufactured via mammalian cell culture.

A strong quality management system is a big differentiator, particularly if it enables seamless transfer from one development stage to another. CDMOs like Avid that offer end-to-end services, effective and sufficiently robust quality systems, a wealth of clinical and commercial manufacturing expertise, and an ingrained mindset that places quality and patient safety first can accelerate the movement of projects from process development to clinical production and, ultimately, commercial manufacturing.

Quality systems must be comprehensive; containment, segregation, changeover, and line clearance play significant roles in gene therapy manufacturing operations. A CDMO must ensure that raw materials of the right composition and purity are selected, that proper engineering controls between the viral negative and viral positive space are appropriately implemented, and that the facility is purposely designed to avoid quality issues for both raw materials and the products manufactured at the site.

Leveraging Existing Expertise at Avid

Avid has been involved in commercial biologics manufacturing since 2005 and has over 20 years of successful regulatory inspection history. An expansion into viral vector manufacturing was a good fit for the company, because Avid can leverage its experience and expertise in bioprocess development, scale-up, and clinical/commercial manufacturing to support this sector.

Three criteria should be met before a CDMO can be considered qualified to provide viral vector manufacturing services: a clear and demonstrated regulatory and quality track record of performance; a leadership team experienced in viral vector process development and manufacturing; and a facility with the proper quality systems in place for this kind of manufacturing. Simply expanding on existing infrastructure and applying equipment and processes used for recombinant protein and antibody production is not sufficient.

Avid is taking a two-pronged approach to meet industry demand. On the one hand, we are bringing in external experts in viral vector process development and manufacturing. On the other, we are transferring our highly successful quality management system to the new facility, following a thorough risk assessment on an SOP-by-SOP basis that will lead to the creation of quality systems specific to viral vector manufacturing. With this strategy, Avid is leveraging our strong regulatory history and ability to manufacture commercial products with specialized technical knowhow and the purpose-built facility.

Having originally evolved from an innovator company, the Avid team has experienced drug development from the other side. We know how important each molecule is to our customers and how much trust is placed in Avid as a CDMO partner. The work we do for each client is always the most important work we can be doing, and every client is a high priority. This client-centric philosophy and desire to establish long-term partnerships with our customers are more attractive to many gene therapy developers, which contrasts with the transactional approach to business offered by many larger CDMOs.

One of the first steps Avid took after deciding to enter this space was to establish a highly experienced management team, including quality, process development, and manufacturing experts, to ensure that our quality systems and risk management principles are ingrained in the facility from the outset. For example, Elie Hanania, Avid's head of viral vector process development, brings over 30 years of gene therapy experience to the organization, while other members of the leadership team have experience in both contract manufacturing and clinical and commercial production at leading biopharma companies.

Avid's Fit-for-Purpose Viral Vector Manufacturing Facility

From the start, we decided to separate the viral vector business unit from the existing biologics business, allowing us to take our core expertise and implement it in a new way within a facility built with its purpose in mind.

Starting from the ground up has made it possible for Avid to design a world-class viral vector manufacturing facility with systems in place that would not be possible when adapting an existing facility. We are leveraging past experiences in our existing biologics plant where appropriate. For instance, not only does the facility have optimized material, personnel, and air flows, it includes viewing windows for client visits and cameras that enable remote monitoring, providing a flexible person-in-plant experience for our clients.

The backbone of the facility leverages systems from Avid's current biologics operations, but with features and controls for safely handling viruses incorporated into the design and other modifications that take into account efficient management of processes, equipment, materials, and waste. As with all other aspects of the facility, the perspective was always one of safety: ensuring that operators remain safe and products meet all critical quality attributes while remaining free of defects so that patient safety is assured.

A key element of the design process was the performance of an FMEA risk assessment that considered every potential failure mode and what facility, engineering, and process controls should be implemented to minimize the number of potential manufacturing issues. As a result, we will be able to answer client questions about changeover controls, cleaning protocols, HVAC inspection schedules for the viral positive program, our biowaste plan, and so on early in client discussions versus learning about failure modes during an actual manufacturing campaign. Some of these considerations may sound simple or obvious, but they are all very important failure of only one of these controls can lead to batch failure and/or rejection.

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With Avid's approach, future gene therapy clients can have confidence that we have anticipated these types of issues and concerns and taken steps to implement measures that minimize operational risks during the construction of the facility. A summary of specific quality-driven actions taken prior to build out of the viral vector facility are depicted in Figure 1.

Risk Management–Based Quality System

We are pursuing a hybrid approach to quality system implementation. Key systems for document control, change management, discrepancy management, and training will be transferred directly from the existing quality system, but each core SOP has been subjected to a risk assessment to determine if it can be applied to viral vector manufacturing. High-risk SOPs, such as for the procedure for drug product filling, will

Figure 1: Quality-Driven Activities Performed Before Construction of Avid's Purpose-Built World Class Viral Vector

- Performing capacity and quality risk assessment before accepting and introducing a new program to the GMP facility.
- Dedicated air-handling units per suite and single-pass HVAC airflow (100% non-circulated) for viral-positive suites.
- Physical segregation for viral +/- areas. Robust badge access and procedural controls for dedicated manufacturing associates for viral +/- operations.
- Unidirectional GMP flows for personnel, materials, and waste for viral + processing suites.
- Validated cleaning method (VHP fumigation) of the room and equipment for changeovers.
- Utilizing a validated disinfectant for inactivating viral-positive biowaste, double bagged, and secondary container in each room prior to removal from the suite to a dedicated biowaste disposal area outside of the facility.
- Process dedicated equipment and tools for each suite (welders, filter integrity testers, mixers, tube sealers EM equipment, cleaning equipment, maintenance tools, etc.)
- Robust and comprehensive training curriculum for all viral vector personnel (manufacturing, QA, QC, maintenance, engineering, vendors) before getting badge access and manufacturing products.
- Performing and presenting a comprehensive contamination control strategy and FMECA (cross-contamination failure modes effects and criticality analysis).

ABOUT THE AUTHOR

Atef Khezri
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Atef Khezri has more than 16 years of CGMP manufacturing leadership experience working at global life sciences companies. Most recently he worked for Catalent at their Cell & Gene Therapy clinical and commercial manufacturing sites as an associate director of operations. Atef is well versed in the latest FDA guidelines and best industry practices and implementing engineering, procedural, facility and process controls around multi-product viral vector CDMO organizations. Atef earned his Bachelor of Science degree in pharmaceutical sciences from the University of Toledo, Ohio.

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Chris Berger
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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 19 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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be redrafted completely to be optimized for viral vectors.

The quality team for the viral vector site will also be dedicated to the site, including a separate quality assurance team performing lot-release activities for viral vectors independent of the biologics business, while a few functions will not be duplicated, such as QA compliance and internal auditing. In these cases, the existing capabilities will be expanded to support both businesses.

Already Planning for the Future

As a CDMO, it is essential to build flexibility into any manufacturing facility. Some clients may be conservative; others are less risk-averse. Predicting capacity demands is challenging, as is anticipating further innovations in constantly evolving technologies. As such, Avid's new facility must be sufficiently flexible in terms of both manufacturing and QC space and capabilities to handle not only current industry expectations but possible future requirements.

Our philosophy is to be at the cutting edge so that we can support clients today and tomorrow. We welcome innovation and are interested in implementing new technologies broached by customers, provided that they can integrate with our quality system. In addition, the viral vector facility is designed to be as flexible as possible with respect to accommodating a growing scale and volume of work, taking into consideration the associated risks and engineering controls needed to mitigate them. Avid also has an adjacent warehouse space, which provides room to expand when needed within the same general building footprint. Avid's clients can be confident that we will get their products into the clinic and on the market without any regulatory concerns.

Not a Bolt-On Capability

Adding viral vector manufacturing capability involves much more than simply investing in new capacity. In the end, the right quality system, the right people with a quality mindset, and the right facilities, equipment, and processes are what ensures high-quality viral vector products to the benefit of patients requiring these advanced therapies. Avid meets all of these criteria and is looking forward to starting operations at our fit-for-purpose viral vector facility with process development capability in the summer of 2022 and full GMP manufacturing operations in the spring of 2023.