A VIRAL VECTOR CDMO VISION THAT RESONATES

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Leveraging its longstanding quality and compliance track record and a team of viral vector process development and manufacturing experts, Avid Bioservices has completed construction on a fit-for-purpose manufacturing facility to support viral vector programs. In this Q&A, a group of professionals from Avid discusses how starting from the ground up has enabled the company to design a world-class viral vector manufacturing facility, in conversation with *Pharma's Almanac* Editor in Chief David Alvaro, Ph.D.

David Alvaro (DA): We discussed the initial plans for the viral vector facility back in May 2022. Have there been any significant changes to the original plan for the new biologics facility since they were established approximately two years ago?

Drew Brennan (DB): We had a vision of a purpose-built viral vector facility, one that would utilize the latest technologies and be sufficiently flexible to allow us as a CDMO to accommodate the largest variety of viral projects possible and to have good throughput through the facility. In addition, we wanted to optimize the customer experience in every way. Avid adhered to that vision and delivered on that initial blueprint.

One change that is worth noting is the upgrade from what was initially planned to be a fill-finish solution for early-phase projects only comprising semi-automated filling within a biosafety cabinet to one that involves semi-automated filling and capping within an isolator. The latter is a much more robust solution and affords Avid the ability to comprehensively support clients with viral vector manufacturing from phase I through commercial production.

DA: How did Avid's patient-first mindset and commitment to making quality paramount shape the company's approach to the facility with respect to the design and engineering decisions?

Chris Berger (CB): Our focus has been to ensure that the facility design considers the people, processes, and materials involved. To that end, time was taken to conduct different design reviews, engage with custom-

ers and consultants across the industry, and make appropriate changes based on their feedback.

Some of the most important questions that were constantly addressed throughout the project revolved around emphasizing quality and avoiding cross-contamination issues, maintaining minimal setup and changeover times, and keeping run times as short as possible while still ensuring that we exclusively produce products at the highest standards of quality. By asking these questions, it was possible to put our guiding vision into practice with respect to project execution and delivery of the facility.

DB: I would emphasize the iterative nature of Avid's design process, with consideration of quality risk principles at each stage to ensure the design was meeting our ultimate needs – delivering high-quality product to our clients. That included looking at the latest technologies to minimize cross-contamination, controls built into each suite, and the overall development of the facility's operations and capabilities.

DA: What are the unique aspects of viral vector manufacturing that made the construction of a purpose-built facility a far better approach than, for example, upgrading an existing large molecule facility?

Elie Hanania (EH): The facility includes suites for virus production and purification. The starting process is based on culturing mammalian or insect cells in dedicated non-viral suites before they are transferred to different suites to generate the safety-modified viral vectors. Each has unique attributes with respect to access, pressure requirements, and so on. It would be extremely challenging to establish this range of suites by retrofitting an existing site, and it would likely not even be possible for some existing facilities. By starting from the ground up, Avid has ensured that our facility has the exact design and features we set out to achieve.

DB: To elaborate on that, mammalian cell culture most significantly differs from viral vector manufacturing because the latter requires the additional containment level to protect workers and products from exposure during viral vector production, which does not exist for traditional biologics. Significant thought and effort must therefore go into the planning and design of access and security controls and other facility features. In a pre-existing site, it may not be possible to implement the full range of features needed.

CB: Exactly. A biosafety level 2 (BSL-2) viral manufacturing facility must focus on both containment and microbial contamination, whereas for an antibody facility, the concern is focused primarily on the latter.

DA: Were you able to apply any lessons learned from your own experience or from that of Avid as a whole in designing and operating mammalian facilities to the new plant?

Rami Barghout (RB): One of the tendencies in biopharma facility design is to underestimate how much space is needed within a facility. Looking at a design on paper, it is often difficult to grasp how large an actual facility will be. As a result, spatial capacities within suites, hallways and corridors, and other areas almost always end up being too small, which creates operational bottlenecks in the process.

These bottlenecks generally arise when there is a lack of experience or when project managers are not fully engaged in operational mode. Avid has extensive experience in biomanufacturing, and that experience was leveraged to prevent those bottlenecks. Thoughtful planning and consideration of the potential maximum throughput in terms of scale and the movement of large volumes of materials through corridors and suites has made it possible to ensure the design of a facility with sufficient space for our people, products, and materials.

DB: To add to Rami's point, you cannot underestimate the amount of storage required for in-process material. If you are running a 3,000-liter bioreactor, the upstream volume of media and the downstream buffer volumes are tremendous. In fact, for a 2,000-liter batch in Avid's mammalian protein production plant, approximately 40,000 liters of liquid are used in one campaign. Where you store and stage different operations must be taken into consideration from the outset. Building all that upfront makes operations a lot easier, which leads to higher-quality operations and fewer deviations down the road.

EH: The viral vector team members at Avid have decades of experience in viral vector production and manufacturing in biopharmaceutical and CDMO settings, and they all brought their knowledge to the table. In addition, having extensive knowledge of real-world operations made it possible to design the facility to streamline the process, including the number of suites, the flow of people, and the other activities already mentioned.

I would also stress the importance of having process development closely tied with manufacturing and QC in terms of both equipment and location. Having these groups in close proximity, with open communication and interaction, ensures technical support and streamlined process transfer when generating clinical and commercial product in the CGMP manufacturing suites.

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Starting with spatial consideration, the laboratories and manufacturing suites are all designed for expected future growth. The quality control space, for instance, is sized for future expansion needs. There were also numerous engineering decisions with respect to process equipment, with a lot of focus on equipment capable of performing multiple tasks to adapt to different unit operations without cluttering the facility.

DA: What do you view as the key differentiators for the new Avid facility compared with facilities you have worked at or visited in the past?

RB: To optimize the customer experience, we incorporated a 360-degree controllable camera in each of the suites that allows visitors to view what is going on in those suites and communicate with the operators from the conference room. Our clients have more confidence when they can observe the process and have some level of constant contact with the team internally. At the same time, this remote access makes things more comfortable for our operators because they do not have a lot of extra people in the suite.

Dave Ingamells (DI): The incorporation of ionized hydrogen peroxide (IHP) sterilization in the production suites is also very positive. It uses a lower concentration of hydrogen peroxide, which makes it safer for our staff and the equipment. Additionally, it has been integrated into the facility and it is fully automated, which is a big differentiator. This type of system is a great achievement and speaks volumes to the level of effort that has gone into bringing this capability online.

DA: From an engineering perspective, what would you identify as some of the notable challenges you had to overcome to successfully execute your vision and plan for the new facility?

RB: I often say, "The perfect project never gets built." Most of the issues related to the fact that Avid used an existing building within which to construct the purpose-built facility — a brownfield design–build project. The challenges we faced largely involved getting existing, somewhat antiquated systems brought up to code. To do so, it was necessary to apply advanced engineering principles and Avid's best judgment on how to accommodate while simultaneously maintaining budgets, schedules, and so forth.

DA: Were there any engineering decisions or choices you want to highlight about the flexibility built into the facility to ensure it will accommodate future customer needs?

RB: Starting with spatial consideration, the laboratories and manufacturing suites are all designed for expected future growth. The quality control space, for instance, is sized (approximately 6,000 ft^2) for future expansion needs. There were also numerous engineering decisions with respect to process equipment, with a lot of focus on equipment capable of performing multiple tasks to adapt to different unit operations without cluttering the facility.

Again, the principles we kept in mind from day one around the infrastructure of the facility, especially around the IHP, IT, and automation architectures, were directed at ensuring sufficient capacity, redundancies, and data protection.

DA: Can you describe your team's approach to process development, what makes it unique in the industry, and how it influenced the design of the process development area?

EH: The focus of process development (PD) is to ensure that the optimized process is CGMP-ready, which means it is scalable, robust, and provides batch-to-batch consistency. That end goal is kept in mind whenever we approach any project, whether we are tech transferring it in from a client or developing it from the ground up.

Next, it is necessary to ensure a seamless transfer of developed processes to manufacturing. That is achieved by employing equipment in the PD lab and pilot plant that is identical to the equipment used for clinical and commercial production, but at smaller scale. In this manner, we can ensure that processes that work well in PD will work well in manufacturing without further issues.

Flexibility is another key attribute of Avid's PD approach. We pursue data-driven approaches and work closely with clients to implement solutions that result in a robust process that can be scaled to meet their needs. Through early interaction with clients, we identify process-related gaps and develop a plan to fix them. That includes creating design-of-experiment studies, generating comprehensive data, and making tailored recommendations for a strong and reliable production process.

DA: With regard to flexibility, do you anticipate any major, transformative innovations that may change your PD strategy?

EH: In this field, it is critical to stay up to date. Technologies are constantly changing, new solutions are brought to the market on a reg-

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ular basis, and existing technologies are constantly updated and improved. It is important to be aware of these changes and what new options are available so they can be evaluated for potential applications, including new raw materials, processes, or equipment. The key is to make sure any new solution will make a measurable difference and not simply consider them for their novelty.

DA: What can you tell me about Avid's philosophy regarding CGMP operations and how that influenced engineering and design decisions?

DI: The main strategy is to always have the entire manufacturing group, including managers, on the floor, at least initially, to ensure that everyone has hands-on involvement and experience. Once the team has been fully trained, some personnel may temporarily step into other roles. In addition, as Elie expressed earlier, co-locating CGMP operations with PD enables constant interaction and a much more efficient exchange of information. The focus on facility design is also readily apparent, with everything laid out to allow for efficient flow of personnel and materials.

RB: Our vision was to establish a multi-product facility with the ability to run multiple campaigns. To that end, multiple upstream suites feed into a single downstream suite, which in turn feeds into the semi-automated fill-finish area – a design based on process duration and timing considerations, as well as input from clients and the market.

Indeed, considerable care was taken to ensure that we do not have to travel in circles from one end of the facility to the other. There is a natural flow that aligns with the reality of operations: material comes from the warehouse and through the production suites, and product traverses a straight path back out to the warehouse.

DA: Avid is known for a strong quality system. How does that align with your viral vector business?

CB: Avid has a single quality system undergirded with a set of principles that are the same regardless of the modality being produced. The proven quality system allows Avid to support clients with products in early-phase clinical manufacturing through commercial approval. However, that does not mean production of a lower quality of goods, but it does involve applying a risk-management principles to identify opportunities to reduce timelines but also to meet CMC and other regulatory requirements to ensure that high-quality products are being manufactured. We are also taking a close look at our quality tools to make sure we are managing risks appropriately and that clients are comfortable with any risk being taken to get them to market with the necessary speed.

Another important goal is to offer the right portfolio of solutions and support that make it very attractive for clients to stay with Avid throughout their product life cycles. That means any decisions made during early-phase development must be acceptable all the way through to BLA filing and commercial production.

DA: Much of the work on the new facility took place during the COVID-19 pandemic. Were there things you had to do differently than you would have during more normal times?

DB: From a recruitment standpoint, there were many more Zoom interviews than ever done before. Even so, Avid worked hard to meet all new hires in person, especially those at the managerial level.

RB: In the early phases of design, we faced challenges owing to the higher level of uncertainty resulting from changing policies regarding how many people could be in a room at one time and so forth. As the situation improved, however, that became less of an issue, and people became more comfortable coming onsite. This was of course crucial to design and construction, just like manufacturing, because you have to be onsite to take measurements, cut materials, and create the structure.

DB: The other change we saw with COVID-19 and still see today involved client interactions. Many of Avid's clients come to the site, but a few will never do so. They prefer virtual tours and 3D walkthroughs. Implementing those technologies to showcase the facility remotely, which was largely driven by the pandemic, has been a big change that has yielded benefits in attracting clients that are unable to travel to our site.

DA: We've mostly focused on the facility, but what can you tell me about building the teams?

DB: Around a year a half ago, the biggest risk we had was bringing in the necessary talent. Since then, we have been extremely fortunate in that regard and have been able to attract top-level talent with very strong experience from across the cell and gene therapy space – from both other viral vector CDMOs and innovator companies – to form our process development; manufacturing, science, and technology; and manufacturing teams. That adds tremendous value for both Avid and our customers. To build on that success, Avid has also established several intern programs at different universities.

DA: Looking at the bigger picture, how important do you see the viral vector business becoming to Avid Bioservices in the near term?

DI: It is an extremely important part of the business, as can be seen by the size of the investment Avid has committed to viral vector manufacturing. We still anticipate very significant growth in our traditional mammalian protein business, but in terms of what the next 5–10 years will bring to Avid, there is no question that our move here into the cell and gene therapy space is significant. The company is absolutely counting on the future growth of this market, and we are very confident that our offering will provide significant value to our cell and gene therapy customers.

DA: As you think about the future of viral vectors and Avid's role in the AAV space, are there any further innovations you see on the horizon for the facility?

EH: There is the facility, and then there is the technology.

From the point of view of the facility, as the field is advancing, the need for larger production scales is growing, especially for some *in vivo* applications. Hence, Avid has started with 50-liter and 500-liter bioreactors, for which we are already seeing demand. Some customers are even asking for larger-scale runs, and we have factored in the space and capability to go up to 3,000 liters.

From the point of view of technology, evolution and innovation are innate aspects. There have been some beneficial improvements in some bioreactor designs, and Avid has made a point of installing state-of-the-art equipment to enable better production. We are staying abreast of other relevant technologies that can lead to increased yield and productivity as well. Furthermore, Avid has acquired testing equipment with wide range, high accuracy, and precision to enable the characterization of produced viral vectors.

DA: How do you see Avid's position as a viral vector CDMO compared with competitors of a similar size?

DB: Avid offers the perfect combination of mature quality systems and commercial manufacturing experience that few CDMOs have, which is extremely valuable to customers, while being a very flexible, adaptable CDMO. We are a medium-sized public company not owned by a large multinational corporation. As a result, we can maintain that smaller company feel, which is more in line with the size of our customers. At the same time, we have a very strong quality system and commercial manufacturing background.

EH: On top of those attributes, Avid has the subject matter experts, knowhow, and experience in every department. While we are very small and lean, we have a very strong foundation, which is something clients value. They know we are here to help and support them and do so based on that foundation of profound knowledge.

DA: When considering the new finished facility, is there anything that you think stands out as the cornerstone of what the company has built and achieved?

RB: From its inception to where we are today, it has been a tremendous effort – and a tremendous achievement – for Avid and everyone involved with the project, from our project engineers up to our CEO. It took the whole team's commitment, aspirations, and pervasive entrepreneurial spirit to build this facility. Given all the macro challenges that we did not and still do not have control over – the uncertainty and volatility created by the COVID-19 pandemic, supply chain issues, getting people to come to the site to work – getting to where we are today is monumental.

CB: I am most proud of the team that we are building here. Even though Avid is a company very well known on the mammalian side and the protein side, we can be classified as a startup in the cell and gene therapy space. We do feel that our vision is resonating. We have been able to attract a great team because they believe in the vision. They believe in what Avid is going to be bringing to the marketplace.

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