TERUMO BLOOD AND CELL TECHNOLOGIES

Unlocking Potential

White Paper

Matters of Scale: Centralized vs. Decentralized Manufacturing of Advanced Therapies

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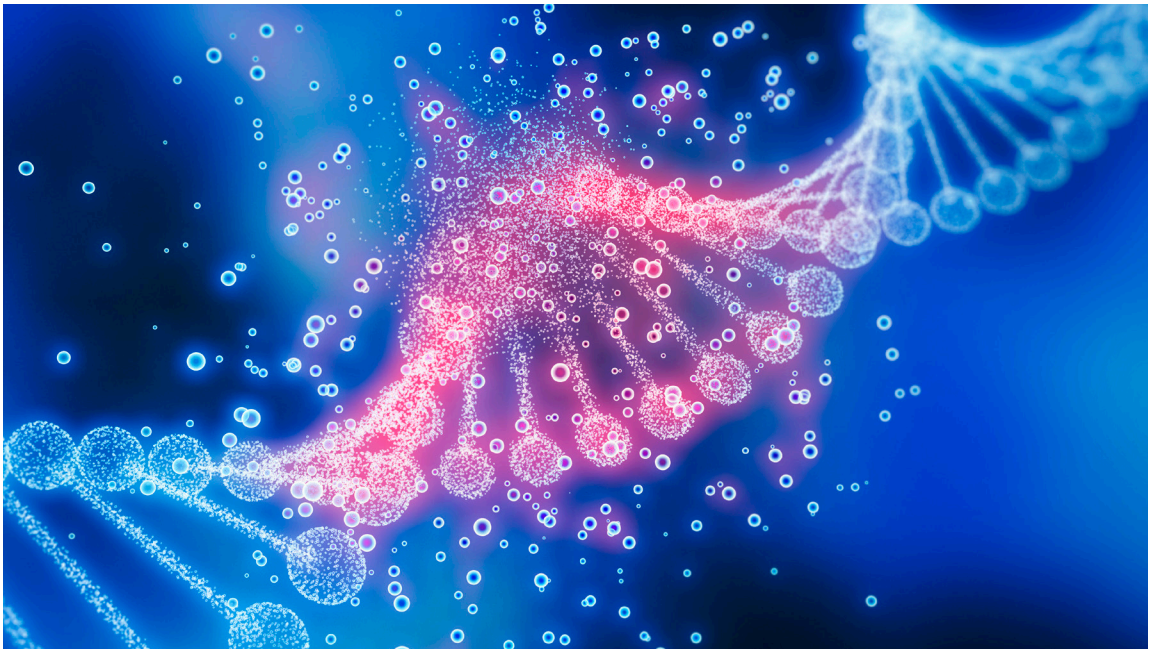

The cell and gene therapy space has continued to grow over the last decade, with new manufacturing facilities coming online at a rapid pace to accommodate new development. This capacity can come in different forms depending on the target modality or patient population, and optimizing a manufacturing paradigm based on its level of centralization requires an examination of the technologies that support scaling of the desired operations.

For cell and gene therapies, centralized manufacturing is structured around manufacturing the cell therapy product at a central hub, where therapy manufacturing processes, namely cell isolation, modification, and expansion to fill/finish, occur. For an autologous therapy, that means a patient's cells are collected and sent to this hub, transformed into a completed therapeutic, and then returned to a medical facility for administration. In contrast, decentralized manufacturing for these therapies tends to occur in the same location — typically, the cell collection, manufacturing and modification, and infusion as a final therapeutic product take place within the medical facility itself.

Each manufacturing approach has its challenges and opportunities, often centered around five primary variables — logistics, manufacturing, regulation, quality, and labor. To address the major hurdles that accompany each consideration, organizations must prioritize technologies that can automate as much of a process as possible. The value that automated, modular, interconnected technology platforms can provide to both centralized and decentralized models of commercial manufacturing is ultimately tied to the process controls, efficiency, and level of "hands on" interaction required of operators. Reducing human intervention and manual processes in advanced therapy manufacturing is critical to improving an overarching manufacturing paradigm, safeguarding quality, simplifying processes, and improving efficacy through better data and superior consistency.

Centralized and Decentralized Manufacturing: Challenges and Opportunities

The logistical considerations that accompany an advanced therapy manufacturing paradigm tend to be greater for centralized manufacturing, as shipment to and from the facility requires additional cryopreservation steps. This alone creates new levels of complexity, requiring precise coordination between the manufacturing site and medical facility to ensure that an infusion product is not jeopardized by added manufacturing steps and cryopreserved material logistics. This is eliminated in a decentralized paradigm, wherein every phase of manufacturing occurs within the same facility. As a consequence, autologous therapies may potentially be better served by decentralized manufacturing if the right skills and tools are available at a single site, whereas allogeneic therapies may be more suited to a centralized paradigm.

Yet the greater the scale, the more valuable a centralized manufacturing process, particularly as it relates to regulatory compliance. A centralized site comes with specialized labor, which can prove invaluable both for allogeneic therapies as they scale up and for autologous therapies as they scale out. The larger the patient population for a given therapy, the higher the burden for a manufacturer; scale can prove especially challenging for decentralized manufacturing models, which often rely on medical staff to undertake these processes with the aid of specialized equipment. Attempting to keep pace with scale forces decentralized sites to expand their clean rooms, diversify their personnel's skill set, and incorporate new quality controls to deal with additional complexity.

Because these therapies follow the Biologics License Application (BLA) pathway, the regulatory considerations for both centralized and decentralized manufacturing models must adhere strictly to the expectations set forth for biologics. When evaluating the appropriate in-process controls, release assays, necessary labor skill sets, and other variables that can impact regulatory success, the type of manufacturing model can impact the relative complexity of each of these considerations. These variables, taken alongside the logistical constraints of a centralized model, all serve to influence the time it takes to produce a therapy. In a decentralized paradigm, the bulk of the streamlining that can be achieved in production is often through eliminating those added logistical considerations; for centralized models, streamlining often occurs in a compounding way as production scales.

While decentralized manufacturing models can afford operators a faster, more simplified turnaround, they can also introduce complexity as operators work to achieve scale. If an organization wishes to manufacture across five separate sites, for example, it must work much harder to achieve standardization in the face of different teams, varying equipment, and differing perspectives. Aligning a single process, such as a potency assay, across multiple sites can represent a heavy lift; achieving the same consistency across every facet of a manufacturing paradigm is likewise a challenge that often requires a pronounced focus on automation.

Achieving Automation Through Modular, Next-Gen Technologies

While automation can help both centralized and decentralized manufacturing models achieve greater reproducibility and standardization, perhaps the most straightforward way of accomplishing optimal decentralization is to begin with a centralized site. Starting by automating the processes at a single site, with a focus on achieving GMP compliance, can help establish a "control center" around which subsequent sites are modeled. The complexity of advanced therapeutics almost necessitates this approach, and having a designated site where all data is aggregated can afford operators optimal interoperability and insight.

To address the major hurdles that accompany each consideration, organizations must prioritize technologies that can automate as much of a process as possible.

Arriving at an optimal level of integration also requires organizations to consider whether to pursue manufacturing technologies that are fully integrated or to opt for more modular approaches. While integration may seem the more straightforward route, modularity can afford operators a number of distinct advantages. If, for example, an organization has instituted automated modular processes for manufacturing, with each person or team managing two or three processes, organizations can see very high utilization of that automation and those skilled resources. Although this is also true of integrated technologies, challenges arise if something goes wrong with that integrated system — a breakdown may require a high level of expertise be available to address it and can take a significant amount of time to remedy. This opens a manufacturing process up to significant amounts of downtime, whereas a modular operation can accommodate more opportunities for backups to circumvent downtime.

Modular operation can allow operators, through the incorporation of quality checks, to flag any issues with a unit operation in time to shift to a contingency unit. This approach also allows operators to specialize in two or three unit operations, rather than relying on deep expertise to manage a single integrated technology. Operators may also be trained on one or two secondary unit operations, allowing for flexibility in staffing that might not otherwise be achievable in an integrated paradigm.

How Quantum Flex Can Help You Scale

The Quantum Flex Cell Expansion System, a functionally closed bioreactor system capable of automated operation, can support cell and gene therapy manufacturing from bench to commercial scale for both centralized and decentralized manufacturing paradigms. With its small and standard size bioreactor options, the Quantum Flex can be integrated at the very start of a development process, enabling seamless scaling with greater sterility and fewer processing steps. Quantum Flex affords operators the modularity necessary to achieving true flexibility, as well as adaptable cross-functionality; Quantum Flex can be applied across a range of culture systems, from suspension to adherent to viral vector and exosome production.

The Quantum Flex system is likewise supported by Terumo Blood and Cell Technologies' Cell Processing Application (CPA), which can manage multiple devices from a central server, supporting cGMP compliance with user authentication, electronic batch reporting, and workflow configuration.

Terumo Blood and Cell Technologies is a medical technology company. Our products, software, and services enable customers to collect and prepare blood and cells to help treat challenging diseases and conditions. Our employees believe in the potential of blood and cells to do more for patients than they do today.

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