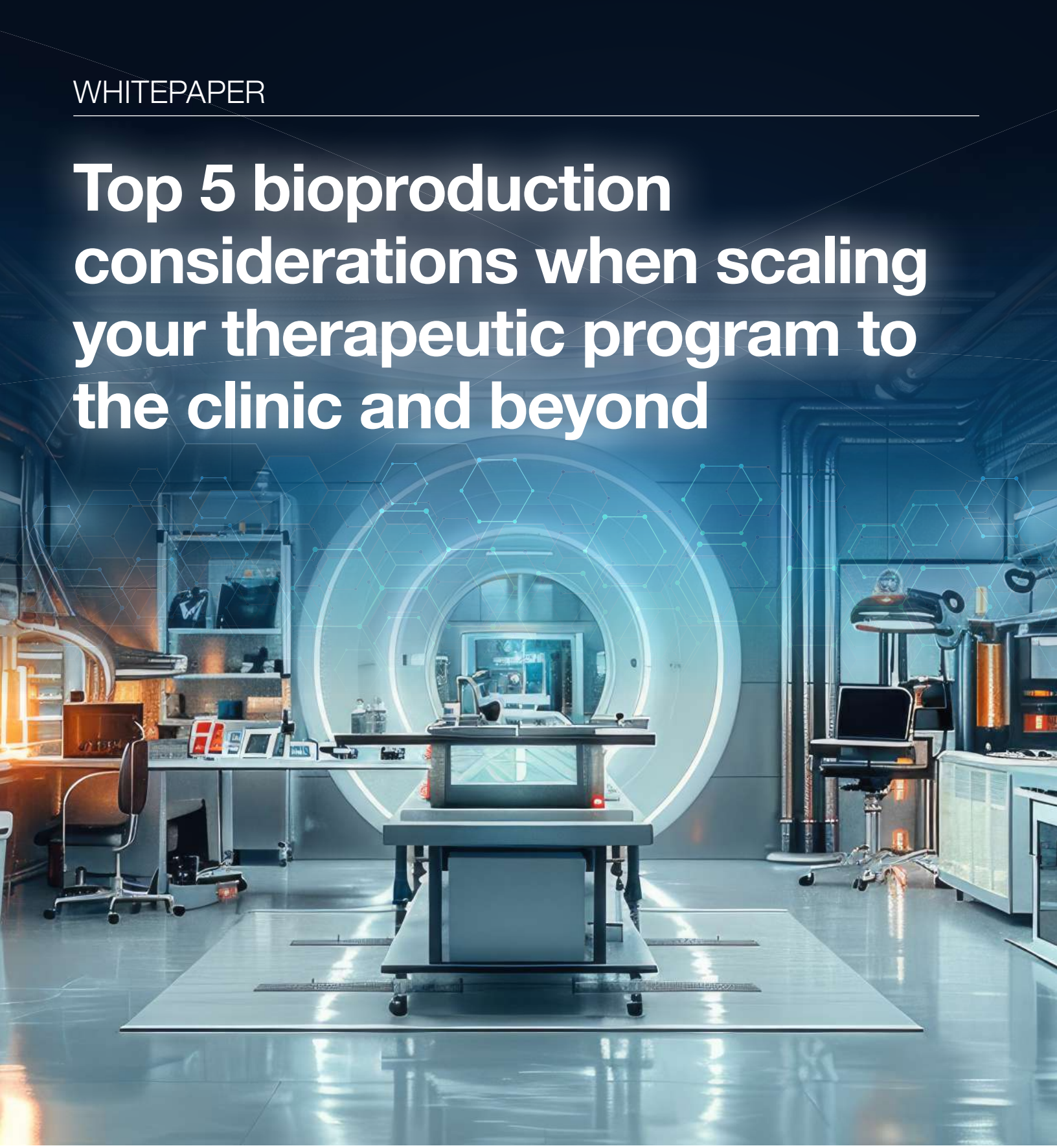
WHITEPAPER

Top 5 bioproduction considerations when scaling your therapeutic program to the clinic and beyond



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Executive summary

Scaling up new biotherapeutics from development to commercial production is becoming more and more complex with the growing pipeline of advanced biotherapeutics such as cell and gene therapies, RNA therapeutics, and monoclonal antibody variants.

To facilitate a successful scale-up of an advanced biotherapeutic from the clinic to commercialization, manufacturers should prioritize five key considerations:

- Optimize the manufacturing process for efficient and scalable production
- Ensure regulatory compliance within relevant guidelines
- Plan clinical trial design to include representative patient populations
- Develop a sound commercialization strategy
- Establish a reliable and sustainable supply chain to meet increasing demand

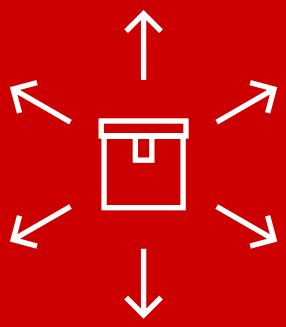
This report describes essential processes biologics developers should implement to enable effective scale-up of new therapies. It includes examples of emerging technologies and workflows to improve key steps including cell culturing, equipment validation and qualification, and chemistry, manufacturing, and controls strategies. Furthermore it explains how developers and suppliers can work together to proactively address each consideration, avoiding delays and speeding new therapies to market.

Introduction

Today there are more than 1,100 antibody therapeutics[1] and 4,000 gene, cell, and RNA therapies in the biopharmaceutical pipeline.[2] The complexities involved in developing these advanced biotherapeutics are requiring the biopharmaceutical industry to consider everything from how they strengthen their supply chains to how they navigate rapidly changing regulatory requirements.

Working with suppliers that have depth and breadth of experience across all these modalities will allow small and emerging therapy developers and manufacturers to design and implement an optimal scale-up process to meet the unique requirements of their new product.

There are five key considerations in bioproduction that manufacturers should address when planning the scale-up of a new therapeutic from pre-clinical, to clinical trials to commercialization. Thermo Fisher Scientific can provide the technical experience and services to help you work through these considerations quickly and effectively.



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Consideration 1: Optimize the manufacturing process for efficient and scalable production

The complexity of advanced biotherapeutics presents many challenges in complying with Good Manufacturing Practice (GMP) standards during the scale-up process. Strategies for optimizing the manufacturing process will differ depending on the modality.

For *in vivo* gene therapy, for example, an important part of developing a scale-up strategy that's suitable for GMP manufacturing is selecting and evaluating optimal formulations for cell lines. Adeno-associated virus (AAV) vectors are the most used delivery vehicles for gene therapies, and they are typically produced using mammalian HEK293 cells.

Technology advances are enabling the miniaturization of cell screening, which makes it possible to efficiently screen large populations of alternative cell lines. Gene therapy developers can work with Thermo Fisher to conduct process development projects investigating how the use of different cell lines, transfection reagents, culture media, and other variables will impact productivity. Thorough examination of the entire process with a specialist team can help narrow down optimal conditions.

Novel purification strategies that can streamline chromatography can also be employed. Customized chromatography resins can be tailored to requirements for both affinity ligands and non-affinity chemistries.

For example, Thermo Fisher's team worked closely with a CDMO producing AAV vectors on their purification strategy using POROS™ Capture Select™ AAVX affinity resin+. The CDMO team needed a pan-affinity tool to capture multiple serotypes. In a study, the resin captured AAV1 to AAV9 serotypes, as well as synthetic and recombinant serotypes. With just a few adjustments, the customer standardized the purification platform for several of the AAV serotypes, with low levels of captured impurities. A reduction in residence times and high loading volumes lowered costs, resulting in an easily scalable, GMP-compliant AAV manufacturing platform.

The manufacturing process can be further optimized with single-use bioreactors. Legacy single-use bioreactors were widely adopted in bioprocessing to reduce contamination risk and cleaning needs, and to enable quick equipment changeovers between batches, but they often were not well-suited to advanced cell culture processes.

Newer systems such as the Thermo Scientific™ Single-Use Bioreactors (SUB) offer enhanced options that facilitate high turndown ratios and optimized mixing and gassing. For example, the 50-liter Thermo Scientific™ DynaDrive™ Single-Use Bioreactor (SUB) allows for cell cultures as low as 5 liters to be grown and scaled up at an early stage. This eliminates the need for rockers, and it offers the ability to seed the 5,000-liter DynaDrive directly from the 50-liter bioreactor.

As Senior Director R&D Collaborations Adam Goldstein puts it, "Our family of HyPerforma™ and DynaDrive SUBs are designed to be scalable from laboratory to production scales, allowing for quick and easy transfer from development to commercial operations. The SUBs are increasingly being utilized in flexible manufacturing ballrooms, allowing for rapid changeovers between product runs."

Additionally, extractables and leachable often becomes a concern for small and emerging biotech companies as they expand. "With continued innovations and the advancement of Single-Use Technology (SUT) polymers – good industry standards (such as the BioPhorum Operations Group (BPOG) model family solvent testing) have been employed allowing for robust characterization and acceptance for many SUT polymers in the bioprocessing space – most of the SUT materials pass this rigor via COA and have no compatibility issues with bioprocessing conditions or products any more," said Adam Goldstein.

Finally, the personnel and training element of process transfer done correctly is critical. "Adopting single-use technology can require specialized training for staff who may have been trained on steel systems. Primarily handling and gaining expertise on pressure management and integrity testing are key to the successful implementation of SUT technology," states Goldstein.

Consideration 2: Ensure regulatory compliance within relevant guidelines

Regulatory requirements for ensuring quality and data integrity in the manufacturing process are rapidly evolving as biotherapeutics become more complex. Drug developers are responding by distributing key steps of the process to multiple suppliers, which are often spread across the globe.

With the increasing globalization of drug manufacturing, it's essential to develop qualification and validation strategies early in production to avoid delays. Qualification involves verifying that manufacturing equipment has been installed correctly and is operating in a way that helps ensure the quality of the final product. The U.S. Food and Drug Administration (FDA) requires installation, operational, and performance qualification, all of which must be documented according to strict requirements.[4] All computer and software systems must be aligned with regulatory requirements.

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> Senior Director R&D Collaborations

Regulatory agencies also have strict rules for data verification. Over the past decade, the FDA and UK Medicines and Healthcare products Regulatory Agency (MHRA) have released regulations aimed at improving quality drug-making by laying out processes for ensuring data integrity along the entire production process.[5,6]

Properly implementing and maintaining audit trails is essential for compliance with data-integrity requirements. Audit trails are reviewed as part of data verification, but it is not always easy to make sense of the data collected by auditing systems. Thermo Fisher offers a wide range of solutions and experience in bioproduction to support compliance with regulatory requirements and supports customers as they aim for the highest standards of quality and data integrity.

As stated by Mike Brewer, Product Management Leader in BioProduction at Thermo Fisher, "Globalization of manufacturing has increased the level of effort and diligence required for monitoring updates and changes in regulatory and pharmacopeial guidance across all jurisdictions. Working with a global supplier like Thermo Fisher can help reduce some of this burden as we design our solutions to enable our customers to comply with the most rigorous guidance globally."

Working with a supplier that can help check that your bioprocessing sites are globally aligned and equipped to produce the documentation required by regulatory agencies is useful. Thermo Fisher can also assists with design and implement training programs for commercial and field application specialist teams that are centered around regulatory compliance.

A molecular biology, immunology, and cell engineering services provider collaborated with Thermo Fisher to build a plasmid production facility. Transitioning from a research environment to a GMP environment presented numerous challenges. Assistance was required with cGMP regulation, staff training, building design, and comprehensive documentation. Implementing equipment in a highly regulated GMP environment necessitated extensive documentation to support equipment specifications and performance, and considerable time was needed to validate quality control methods.[13]

For sterile dose manufacturing, developing and implementing corrective and protective actions (CAPAs) to remedy quality shortfalls is an important element of facilitating regulatory compliance. The FDA has a 10-point

checklist of CAPA compliance requirements, which requires drug-makers to routinely analyze quality problems and develop corrective actions. They must also track CAPA implementation and document analysis showing the CAPAs will fend off future problems.[7] The European Union recently issued new guidelines requiring CAPAs for sterile medicines, as well.[8]

Consideration 3: Plan clinical trial design to include representative patient populations

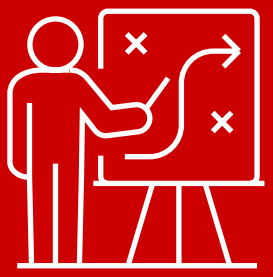
In June 2024, the FDA issued a draft guidance requiring biopharmaceutical companies to develop "diversity action plans" for each new clinical trial.[9] The guidance stemmed from the 2022 Food and Drug Omnibus Reform Act, which focused on boosting participation from underrepresented groups in clinical trials for new drugs and medical devices. This effort was fueled by growing concerns that clinical trial participation often does not adequately reflect the diversity of the target patient populations for new therapies, with notable shortfalls in the participation by women, older adults, and Black, Latino, Asian and Indigenous people.

For example, an analysis of data collected by the FDA between 2015 and 2019 found that participation in clinical trials by Black patients was at or above the U.S. census level for that demographic group, but participation was below the U.S. census level for other ethnic or racial minorities.[10] An analysis of data collected by the National Cancer Institute between 2005 and 2020 found significant under-representation of older adults, women, Hispanics, American Indian or Alaska natives, and Asian or Pacific Islanders in cancer trials.

The FDA's guidance stipulates that for each new clinical trial, drug makers develop a plan for recruiting and retaining clinical trial participants who reflect the affected patient population in age, race, ethnicity, and gender. They must also develop a strategy for monitoring enrollment goals and retaining participants for the duration of each trial.

In anticipation of the guidance, the National Academies of Sciences, Engineering, and Medicine published comprehensive guidelines in 2022 for improving representation in clinical trials. Key strategies include:

- Anticipate and remove barriers to study participation by offering participants multiple options and tailoring recruitment strategies to individual cultural groups. Options include using digital tools to allow for remote enrollment, implementing flexible scheduling to accommodate patients who are only available after-hours, and employing trial investigators who can travel to participants' homes to collect data.
- Foster communities that reflect the diversity of the target patient populations for clinical trials. This can be done by establishing relationships with community leaders, including those associated with faith-based institutions, who can aid



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in the recruitment of diverse patient populations. Investigator teams should also be optimized to reflect the target demographic groups of each study.

- Establish a plan for monitoring progress in recruiting and retaining participants who reflect the demographic characteristics of the target patient population for the therapy under investigation. This plan should include a process for remediation if diversity goals are not being met.

Consideration 4: Develop a sound commercialization strategy

As a candidate therapy moves into late-stage clinical testing, it's important for developers to establish a comprehensive commercialization strategy that includes a full market assessment, as well as pricing and reimbursement plans. Getting an early start will not only help ensure there's enough inventory for pivotal clinical trials and the commercial launch, but it will also help keep all the players in the process on track.

A successful commercialization plan starts with a solid Chemistry, Manufacturing, and Controls (CMC) strategy. Because the CMC is part of the licensing process, it's important to coordinate closely with regulators in developing and implementing the strategy.

Process optimization is a key component of a good CMC strategy. But due to the challenge of forecasting demand, it can be difficult to determine the scale at which to produce a new therapeutic. In the past, for example in monoclonal antibody-based development, manufacturers typically planned for new products by building new facilities or retrofitting existing plants, and by jumping straight from low-volume bioreactors to 15,000-liter bioreactors to accommodate the most optimistic demand scenarios.

A more effective strategy is to adopt a flexible, gradual scale-out approach. Using 5,000-liter bioreactors provides a flexible scale-up approach that allows for more manageable adjustments to meet demand compared to larger 15,000-liter vessels.

It's important to ensure the plan for production is robust and the manufacturing process well-characterized before embarking on the Process Performance Qualification (PPQ). Rushing into PPQ can uncover inconsis-

tencies that affect product quality, such as hold times that differ from one facility to another. Resolving quality issues before PPQ is essential for avoiding delays that could derail the launch timeline.

A growing selection of digital tools can be invaluable in developing and maintaining a strong commercialization strategy. These systems analyze data from every step of the process and create audit trails, providing real-time visibility that allows manufacturing and commercialization teams to ensure everything is running as planned. Cloud-based interfaces provide data visibility to team members across the globe.

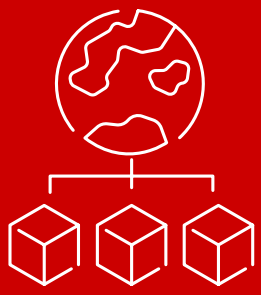
Outsourcing the development and implementation of all or part of a commercialization strategy can streamline this process. Working with a supplier with broad experience across a range of therapeutics can help manufacturers fill gaps in their capabilities and keep a commercialization plan on track. Thermo Fisher can provide a CMC lead, who can coordinate the selection and implementation of digital tools, help ensure the program is on schedule and meeting its targets, and advise on anticipating and managing risks.

Consideration 5: Establish a reliable and sustainable supply chain to meet increasing demand

The COVID-19 pandemic exposed weaknesses in the global supply chain, including a shortage of raw materials that disrupted manufacturing timelines. In response, Thermo Fisher and other suppliers have expanded their operational sites globally. As Senior Manager of Business Operations, Cole Clifton, explains, "The expansion of operational sites around the world has helped Thermo Fisher create a network affect that better enables us to serve our customers. Within the Production Chemicals and Services business, there is a focus on increasing its global footprint to be near customer locations, ensuring >99.5% On-Time-In-Full (OTIF) with our Assurance of Supply service. Thermo Fisher is not only expanding and leveraging operational sites but adding further capabilities to better serve our customers.'

The expansion of operational sites by Thermo Fisher and other suppliers has addressed weaknesses in the global supply chain, such as raw material shortages that disrupted manufacturing timelines. By building redundancy and diversification into their operational sites, these suppliers have helped to mitigate future risks to their customers' supply chains. This strategic approach has made it easier for drug developers to source materials from suppliers in different locations worldwide, reducing the risk of shortages. Moreover, adopting a global approach to sourcing raw materials simplifies transportation challenges and streamlines the complexities of import and export procedures, ultimately shortening supply timelines.

Drug developers can work with Thermo Fisher to implement integrated demand planning. This process connects the manufacturer's commercial, sales, operations, and production teams with key suppliers to manage the continuity of materials



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supply. Working closely with suppliers enables more effective manufacturing requirements planning, which in turn help ensures that production will align with patient demand.

Manufacturers can build even more resiliency into their supply chains by taking a proactive approach to identifying and managing risks. Developing two- to three-year timelines will help ensure supply continuity. Manufacturing plans should include a variety scenario-based alternatives that provide the flexibility to manage any disaster. Importantly, these plans should be re-evaluated on a regular basis to see that they align with demand predictions, emerging risks, and the needs of customers and suppliers.

Case study: Aligning supply with demand to improve OTIF

A contract development manufacturing organization (CDMO) came to Thermo Fisher with a problem: To support the growth of its customers' portfolios, it needed to expand its raw material warehouse – at a high capital expense – so it could hold enough inventory to provide On Time in Full (OTIF) performance.

After assessing the CDMO's needs, Thermo Fisher discovered that its existing suppliers couldn't provide reliable OTIF on vital raw materials. That forced the CDMO to hold excessive amounts of safety inventory to overcome long supplier lead times. As a result, the CDMO experienced frequent manufacturing interruptions and often needed to expedite shipping to its customers to make up for supply delays.

Thermo Fisher formed a stocking agreement with the CDMO for its critical and routine chemicals, which included Assurance of Supply Services. Thermo Fisher analyzed OTIF performance and aligned the CDMO's forecasted demand with its material lead times. Safety stock was optimized to help ensure a one-day lead time and just in time delivery.

As Cole Clifton explains, "This was accomplished by working with our customer and providing the subject matter experience to utilize our Assurance of Supply service (AOS). We take the customer's demand forecast, bill of materials (BOM), and specific requirements to create a stocking model that is unique to the customer to help ensure they are getting the best service possible. We also gather data from the various suppliers that make up the BOM for other pertinent information such as minimum order quantity, units per pallet, expiration date, and lead time. Using all the information gathered we create a dynamic model so that the customer will always have material to pull from plus adequate safety stock levels in case of supply chain disruptions or increases in customer demand. We have a dedicated inventory analyst supporting our customers by constantly checking lead times, updating the model, and leveraging AI to facilitate constant supply. of materials that enable our customers to make the world healthier, cleaner, and safer."

The customer did not have to build out its own warehouse, and as a result saved $2.5 million in capital expenses. OTIF exceeded 99.5% – a 17% improvement. The CDMO also saved $359,000 a year in warehouse expenses and $120,000 annually in inventory carrying costs. And by eliminating expedited shipping fees, they saved $120,000 a year.

Conclusion

The rapid growth of advanced biotherapeutics has increased the pressure on developers to improve how they plan and implement the scale-up of emerging therapeutics for commercialization. Successfully scaling up a new biotherapeutic for commercialization requires optimizing manufacturing and commercialization processes, while maintaining regulatory compliance.

Key considerations include selecting and implementing optimal cell lines, purification processes, and bioreactors for manufacturing, carrying out an effective CMC strategy, improving global supply chains – all while complying with rapidly evolving regulatory requirements.

Thermo Fisher offers advanced experience across all these areas and can work together with developers to select and implement tailored solutions.

References

1. Crescioli, S, Kaplon, H, Chenoweth, A, Wang, L, Visweswaraiah, J, Reichert, J. (2024). Antibodies to watch in 2024, MABS, 16:1, 2297450, DOI: 10.1080/19420862.2023.2297450.
2. American Society of Gene + Cell Therapy, Citeline. 2024. Gene, Cell, + RNA Therapy Landscape Report, Q1 2024 Quarterly Data Report. https://www.asgct.org/global/documents/asgct-citeline-q1-2024-report.aspx.
3. Ravault, V., Laroudie, N. (2022). Platform optimization for efficient AAV purification: insights from a CDMO. Cell & Gene Therapy Insights 2022; 8(1), 1–14 DOI: 10.18609/cgti.2022.001.
4. The FDA Group LLC. 2024. A Basic Guide to IQ, OQ, PQ in FDA-Regulated Industries. https://www.thefdagroup.com/blog/a-basic-guide-to-iq-oq-pq-in-fda-regulated-industries.
5. U.S. Food & Drug Administration. 2018. Data Integrity and Compliance With Drug CGMP: Questions and Answers. https://www.fda.gov/regulatory-information/search-fda-guidance-documents/data-integrity-and-compliance-drug-cgmp-questions-and-answers.
6. Medicines and Healthcare products Regulatory Agency. 2018. Guidance on GxP data integrity. https://www.gov.uk/government/publications/guidance-on-gxp-data-integrity.
7. FDA. 2023. Corrective and Preventive Actions (CAPA). https://www.fda.gov/inspections-compliance-enforcement-and-criminal-investigations/inspection-guides/corrective-and-preventive-actions-capa.
8. European Commission. 2023. "Annex 1: Manufacture of Sterile Products." https://health.ec.europa.eu/sytem/files/2020-20/2020_anex1ps_sterile_medicinal_products_en_0.pdf.
9. FDA. 2024. FDA Guidance Provides New Details on Diversity Action Plans Required for Certain Clinical Studies. https://www.fda.gov/news-events/press-announcements/fda-guidance-provides-new-details-diversity-action-plans-required-certain-clinical-studies.
10. Lolic M, Araojo R, Okeke M, Woodcock J. Racial and Ethnic Representation in US Clinical Trials of New Drugs and Biologics, 2015-2019. JAMA. 2021;326(21):2201–2203. doi:10.1001/jama.2021.16680.
11. Nirmal Choradia, Fatima Karzai, Ryan Nipp, Abdul Rafeh Naqash, James L Gulley, Charalampos S Floudas, Increasing diversity in clinical trials: demographic trends at the National Cancer Institute, 2005-2020, JNCI: Journal of the National Cancer Institute, 2024;, djae018, https://doi.org/10.1093/jnci/djae018.
12. National Academies of Sciences, Engineering, Medicine. 2022. Improving Representation in Clinical Trials and Research.
13. ON24. (n.d.). Scaling your therapeutic program to the clinic and beyond. Retrieved from https://event.on24.com/wcc/r/3928553/27BDAF6DAEBEA0CE7A912478AA389577?partnerref=scalingwebinar

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