WHITE PAPER

The benefits of 5,000L single-use bioreactors for biologics manufacturing

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Executive Summary

The entry of the 5,000L single-use bioreactor (SUB) into biologics manufacturing is providing an important bridge between small-scale and large-scale production. This new choice offers biotech and pharma companies, as well as CDMOs, more flexibility than ever before to respond to fluctuations in demand quickly and efficiently.

As the market for complex biologics continues to grow, effective capacity planning becomes more important—and more challenging.

This report offers a guide for biopharmaceutical innovators on evaluating capacity needs and the advantages of using SUBs at each stage of development. Topics include:

- Features and benefits of 5,000L SUBs
- How improvements to turndown ratio, oxygen transfer rate, and more with SUBs provide a more efficient and flexible biologics development ecosystem and help accelerate scale-up and time to market
- Efficiency and sustainability advantages that SUBs offer over stainless-steel bioreactors, helping to accelerate time to market for biologics manufacturing and lowering carbon footprint
- What to look for in a CDMO partner for manufacturing with SUBs to ensure reliability, flexibility and collaboration

Introduction: Understanding the importance of capacity

The market for complex biologics including monoclonal antibodies, bispecific antibodies and fusion molecules is growing at a rapid pace. Recent estimates suggest the global market for monoclonal antibodies will grow 11% annually to reach nearly $500 billion in 2030.[1] The global market for fusion proteins is expected to grow 4% a year to $33 billion in 2030,[2] and the market for bispecific antibodies is projected to expand at a rapid 43% per year to $110 billion in that time period.[3]

This unprecedented growth is increasing the pressure on biopharma developers and their partners to improve efficiencies at every stage of the manufacturing process. Ensuring that the correct manufacturing capacity is in place for a new biologic is an essential part of that process.

Capacity planning, however, is challenging. Predicting future demand for a novel therapy that's still in clinical development requires significant guesswork, as well as contingency planning in case projections are either too high or too low. Supply and demand for marketed biologics can fluctuate, requiring that therapeutics manufacturers and CDMOs have the capacity to scale production up or down flexibly and efficiently.

The ability to quickly scale up capacity based on demand significantly impacts cost efficiency, potentially lowering costs per unit. What's more, effective capacity planning can shorten the time to market for new biologic drugs. That gives developers a competitive advantage as they aim to speed patient access to new biologics.

Single-use bioreactors (SUBs) offer biologics manufacturers the flexibility to respond to rapid changes in demand for new therapeutics. Until recently, manufacturers typically started with 2,000L SUBs for biologics in clinical development, then jumped up to 10,000L or larger SUB or stainless steel bioreactors for commercialization. But this limited their flexibility to respond to fluctuations in demand, and many traditional large-scale SUBs have suboptimal qualities, such as oxygen transfer rates that are not suitable for some cellular processes.

The recent introduction of 5,000L SUBs fills a significant gap in the industry. These new SUBs enhance scale-up and scale-down flexibility, as they can be used alone, at sub-5,000L volumes or in pairs at full capacity when more output is needed. Coupled with enhanced capabilities in single-use technology, this new choice in capacity improves efficiencies and in turn helps accelerate biologics drug development and speed to market.

Thermo Fisher Scientific works with developers to project their capacity needs early in clinical development, and to put in place a flexible and scalable manufacturing process using SUBs. With its depth of biomanufacturing expertise and multiple sites around the world, Thermo Fisher can help ensure that realistic timelines are established and met, and that developers have a reliable supply at each stage of development.

Evaluating capacity needs and single-use bioreactors

To build the most efficient manufacturing ecosystem, manufacturers can partner with CDMOs to start capacity planning before a new therapeutic enters Phase I clinical trials. They can work together to forecast the quantity of drug needed at each stage of development based on the number of planned clinical trials, as well as the potential commercial requirements based on the target patient population.

Working with a CDMO allows biotech and pharma manufacturers to leverage the most advanced and up-to-date single-use platforms across a wide range of cell lines and processes. In situations where future demand may be hard to predict, the new generation of SUB technology offers the flexibility to scale up or down quickly. Thermo Fisher's DynaDrive 5,000L SUBs, for example, have agitator shafts that extend the full length of the bag. This results in a turndown ratio of 20:1, offering more flexibility to adjust volumes than previous generations of SUBs, most of which have turndown ratios of 10:1.

Additionally, DynaDrive SUBs offer an optimal oxygen transfer rate (OTR) for advanced processes. An efficient drive train, coupled with multiple impellers, allows for lower RPM, and by extension less shear stress on cells. A combination of uniform mixing and a high oxygen transfer rate helps improve cell growth.

Other recent advances in SUBs are expanding their utility in biologics manufacturing. New features include improved container design optimized for advanced processes such as perfusion cell culture. Consumables are made with improved materials that are more pliable and durable than they were in the past, and that minimize leachables and extractables. And advanced sensor technology allows manufacturers to monitor the environment inside each SUB, so they can ensure they are maintaining optimal conditions for cell growth.

Another valuable attribute of SUBs is that they help manufacturers advance their sustainability goals, while significantly reducing the cost associated with stainless steel bioreactors. Many biopharma developers are increasingly focused on reducing their carbon footprint, and as a result may be reluctant to deploy SUBs because of emissions concerns and the fact that the bioreactors generate waste from consumables such as bags, tubes, and filters. However, avoiding cleaning and sterilization procedures that are necessary with stainless steel bioreactors significantly reduces emissions. Deploying SUBs also drives down the use of water and expensive chemicals , thereby lowering the amount of wastewater and chemical waste. As a result, SUBs reduce the overall size of the required manufacturing footprint. And biopharma companies can partner with third parties to recycle plastic consumables.

Benefits of 5,000L single-use bioreactors

By providing an alternative capacity option above 2,000L, the 5,000L SUB facilitates the logarithmic and efficient scale-up of a new biotherapeutic. Drug developers can work with CDMO partners to establish a roadmap for deploying SUBs that will be both flexible and cost efficient.

The ability to easily scale production up or down within a 5,000L SUB helps to increase efficiency and lower costs. For example, the DynaDrive 5,000L SUB can handle volumes starting as low as 250L, making it easy to deploy in early-stage clinical trials. As demand grows, volumes can be increased gradually. If demand surpasses the capability of the 5,000L, a second 5,000L SUB can be quickly deployed. Multiplexing with 5,000L SUBs is nimbler and more cost effective than scaling up with stainless steel bioreactors. In fact, the up-front investment required to deploy SUBs is significantly less than that of stainless steel.

Another advantage of SUBs is that they reduce the risk of cross-contamination from other biologic products that are being manufactured in the same facility and from improper handling techniques. The DynaDrive 5,000L SUB's high turndown ratio allows developers to consolidate several steps of the scale-up process in one bioreactor. The bioreactor also has semi-automated loading systems and fewer connections inside, lowering contamination risks by reducing the amount of manual labor needed.

Deploying 5,000L SUBs from clinical trials through early commercialization eases the regulatory process for full commercial production, as well. That's because the manufacturing process, equipment, and materials will have already been validated in clinical trials.

SUBs offer cost and efficiency benefits over stainless steel bioreactors. While the consumables costs are typically higher than they are for stainless steel bioreactors, resulting in higher costs per run, savings come later in the process. SUBs eliminate turnaround and cleaning costs, which can be substantially more per batch with stainless steel. The net result is lower operational costs across the board, including reduced spending on cleaning chemicals, water, energy, and labor.

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Choosing a CDMO with a robust and flexible manufacturing offering

When selecting a potential CDMO partner, there are several considerations to keep in mind. First, the CDMO should have extensive experience in the drug modality that's being developed. That will ensure the partner has regulatory expertise and a track record of setting and meeting realistic timelines for customers.

Choosing a CDMO with multiple sites around the globe is also important, because it offers several advantages, including the opportunity to scale up quickly when demand is higher than expected. Thermo Fisher has four facilities in four countries that are equipped to manufacture complex biologics with SUBs. Thermo Fisher's facility in Lengnau, Switzerland, was built to enable flex capacity, with multiple open manufacturing bays. This allows customers to quickly multiplex 5,000L SUBs—staggering harvesting and purifying steps—to efficiently fulfill growing demand. All facilities are equipped with similar, often identical, technology, making the tech-transfer process seamless.

Thermo Fisher also has expertise in developing predefined and qualified scale-down models for development with SUBs.

Additionally, Thermo Fisher offers end-to-end services, from cell-line development through fill-finish capabilities. This improves efficiency and minimizes interruptions in the manufacturing timeline, with robust platforms that aim to provide reliable, on-time delivery from early development through commercialization.

Conclusion

As the market for monoclonal antibodies, bispecific antibodies, fusion molecules, and other advanced biologics grows rapidly, so does the demand for manufacturing processes that are flexible, efficient, and environmentally sustainable.

SUBs with a capacity of 5,000L offer biopharmaceutical developers a cost-effective way to quickly scale up manufacturing in response to demand, from clinical development through commercial manufacturing. Thermo Fisher's DynaDrive 5,000L SUBs have a turndown ratio of 20:1, a favorable oxygen transfer rate, and other features that improve the flexibility of scale-up and scale-down processes.

Thermo Fisher collaborates with drug developers to select, design, and implement an effective manufacturing strategy using SUBs. With its multiple, complementary sites around the world and end-to-end services, Thermo Fisher can help accelerate the path to market using flexible 5,000L SUBs.

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