White Paper

The commercial sweet spot for complex biologics

Demand for 5,000 L single-use bioreactors is on the rise among biopharma manufacturers. Here's why.

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Contract development and manufacturing organizations (CDMOs) are increasing their global capacity to accommodate growing demand for biologics and biosimilars. As they break ground on new facilities and expand existing sites, one common piece of equipment is notably less common: large, stainless steel 10,000- to 20,000 L bioreactors. In its place: 5,000 L single-use bioreactors (S.U.B.s).

As biopharma companies better understand potential market demand for a molecule in development, they face a critical decision: scale up or scale out manufacturing processes. When scale up requires capacity that exceeds 2,000 L production vessels, they traditionally move from S.U.B.s to traditional stainless steel systems.

Complex biologic therapies demand efficient manufacturing processes and swift progression from lab to clinical production. Advances in upstream processes, such as AI-powered vector design, have accelerated the path to IND; however, fluctuating market demands necessitate pivots downstream.

Stainless steel systems simply don't have the flexibility to accommodate rapid changeovers, new technologies or variations in scale and product demand without significant time, cost and facility modifications. With the arrival of 5,000 L S.U.B.s, biopharma companies get the best of both: large-scale capacity of stainless and the flexibility, efficiency and scalability of single-use systems.

Thermo Scientific™ DynaDrive™ 5,000 L S.U.B. serves as an ideal middle ground between 2,000 L S.U.B.s and 10,000 L stainless steel. This capacity is where biopharma companies can reap significant rewards.

When biopharma companies source too little capacity, they risk falling short of market demand. Source too much, and they could end up with product that sits unused or goes to obsolescence. That means lost revenue, lost market share and possibly loss in confidence by investors and shareholders.

"Biopharma companies shouldn't have to pay for capacity they don't need," said Paul Jorjorian, Vice President, Development and Scientific Solutions within the Pharma Services Group at Thermo Fisher Scientific. "If they end up with more available product than needed, that's capital that could have been deployed somewhere else."

The 5,000 L S.U.B. is built for moderate- and large-scale manufacturing, rapid process development and turnaround times, and high variability. Users can scale up or down, adjust process strategies and respond to changing demand—something stainless steel systems simply can't do once a scale is set.

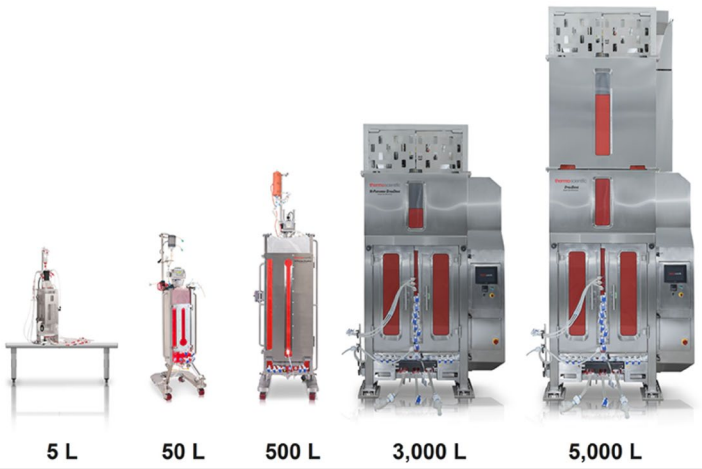
Our analyses indicate that the 5,000 L S.U.B. often delivers higher effective capacity and more favorable economics than lower-volume S.U.B.s and stainless steel systems at comparable demand ranges.

To elaborate, we take an in-depth look at how the 5,000 L S.U.B. compares to other options in flexibility, performance and speed. Through case studies and expert commentary, we explore:

- Why the volatile biopharma market demands flexible, efficient manufacturing
- How 5,000 L S.U.B.s unlock new value by bridging the gap between 2,000 L disposables and oversized stainless steel assets
- How S.U.B. performance and scalability compare across 50 L to 5,000 L
- Why the future of biologic development is single use

An expanding, fluctuating market

The biopharma industry is growing and diversifying. Rising prevalence of chronic disease combined with a demand for personalized treatment has led to increased biologic development, while technological advances have led to novel life-changing therapies.[1]



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Combined with an industry push to operate faster, leaner and more sustainably, biopharma companies must balance competing priorities when determining scale. They demand high performance and quality, but they also need to move fast.

Single-use manufacturing aligns well with these priorities. The inherent versatility of single-use technology allows clients to transition from clinical to commercial production without re-engineering processes or sacrificing timelines. In a race where the difference between first and second to market could mean billions in revenue, biopharma companies simply cannot afford inflexible capacity.

How to bring flexibility to large-scale manufacturing

The annual commercial demand for most specialized biologics is about 100 kg or less, with only about 10% exceeding the 750 kg/year range.[2] The combination of lower volume, compressed timelines and the need for capacity flexibility has significantly increased the demand for single-use technologies (S.U.T.) in both clinical and commercial settings.

Historically, biopharma companies were pushed into one of two directions: 10,000 L – 15,000 L stainless steel bioreactors or 2,000 L S.U.B.s. Stainless offers high-volume potential but commits companies to fixed batch sizes and rigid process architectures that have the potential to waste capacity. An analysis from consulting firm BDO found only about 20% of commercial biologics would require a bioreactor of >10,000 L.[3]

Smaller S.U.B.s come with lower capital costs, flexibility and lower risk of contamination compared to stainless steel. However, commercial production would require either scale up to stainless steel or scale out across multiple vessels. Both options introduce facility complexity, contamination risk, and higher operating costs.

The operational and cost advantages of single-use over stainless steel are well known: faster turnaround times and reduced spending on cleaning materials, water, energy and labor equate to lower operational costs. The 5,000 L S.U.B. unlocks new value by bridging the gap between 2,000 L disposables and oversized stainless steel assets. Its more distinguishing attributes include:

Enhanced scale-up and scale-down flexibility: The DynaDrive 5,000 L S.U.B. supports starting volumes as low as 250 L, making it suitable for both early- and late-stage clinical trials. As demand increases, batch sizes can expand incrementally. When higher output is needed, multiplexing 5,000 L S.U.B.s offers an agile, cost-effective path without the capacity commitment required by stainless.

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Regulatory continuity: Deploying 5,000 L S.U.B.s from Phase I through early commercialization simplifies comparability and validation. Process equipment, materials and operating parameters are already clinically qualified, reducing regulatory burden and eliminating scale-transition surprises.

Faster installation and changeover: The DynaDrive 5,000 L S.U.B. incorporates a semi-automated bag-loading assist that reduces setup time and handling steps. It can be installed in less than 45 minutes, a process that is 25% faster than for 2,000 L bioreactors.[4]

Because of their fixed scale, stainless steel systems have tangible financial and operational consequences. They limit the ability to respond to fluctuating market demand and come with high cleaning and turnaround overhead. Given their flexibility and capacity, 5,000 L S.U.B.s provide economic advantage.

Thermo Fisher's economic analysis found a 5,000 L S.U.B. in a CMO is an ideal solution for products expected to be in the 30–250 kg/yr demand range.5 In early clinical phases, cost of goods are competitive with 2,000 L bioreactors, even at low production throughputs typically associated with preclinical and early clinical phase demands.

When early-phase production moves directly to a 5,000 L S.U.B., volume demands can be met smoothly and cost-effectively for 30–250 kg/yr, without the need for additional technology trans-

Scalable performance of the DynaDrive S.U.B. from 50–5,000 L

What we did:
We evaluated the scalability and performance of the Thermo Scientific™ DynaDrive™ Single-Use Bioreactor across 50 L, 500 L and 5,000 L working volumes using two widely adopted CHO-S platforms—ExpiCHO-S and Freedom CHO-S—each run in a standard 14-day fed-batch process.

How we did it:
Using previously developed fed-batch processes for each cell line, cultures were run at full working volume at each scale under consistent scale-up criteria, including matched power-to-volume ratios and aeration strategies. Process performance was supported by the DynaDrive's enhanced drilled-hole sparger (DHS) and multi-impeller drive-train design. Daily measurements included viable cell density (VCD), viability, pH, key metabolites (glucose, lactate, ammonium), dissolved gases, and titer.

What we achieved:
Performance was consistent across scales for both cell lines, with several highlights:

- **ExpiCHO-S:** Peak viable cell densities ranged from about 17 × 10^6 to 21 × 10^6 cells/mL across vessels, with comparable growth and viability profiles maintained from 50 L through 5,000 L. Volumetric productivity at harvest fell within a narrow range of approximately 2.7–3.1 g/L, demonstrating reproducible performance at manufacturing scale.
- **Freedom CHO-S:** Peak cell densities ranged from approximately 22 × 10^6 to 29 × 10^6 cells/mL, with harvest viabilities spanning ~64–81% across scales. Day-14 titers were consistently reproduced across vessels, ranging from approximately 0.6–1.0 g/L, with similar metabolite and gas-control trends observed at each scale.
- **Product quality:** For both CHO-S platforms, critical quality attributes—including charge variants, aggregates, and fragments—remained tightly aligned between pilot- and manufacturing-scale vessels, with differences generally <2% between the 200 L and 5,000 L bioreactors.

Across both studies, the DynaDrive S.U.B. maintained dissolved oxygen and pCO_2 within acceptable operating ranges, confirming robust mass-transfer capability without reliance on shear-inducing microsparging and enabling efficient CO_2 stripping at scale.

Conclusion:
These results demonstrate that the DynaDrive S.U.B. platform supports predictable, scalable performance from 50 L to 5,000 L for both ExpiCHO-S and Freedom CHO-S cell lines. Linear scale-up was achieved while preserving cell growth, viability, titer, and product quality—reinforcing the suitability of 5,000 L single-use bioreactors for late-stage clinical and commercial manufacturing.[6]

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fer and associated costs and risks. Above 250 kg/yr, production can feasibly remain at 5,000 L volumes because of costs and timeliness associated with technology transfer to a stainless steel bioreactor.[5]

Scale up or down with the 5,000 L DynaDrive S.U.B.

The DynaDrive 5,000 L S.U.B. represents the latest in single-use technology. Designed for complex biologics, including monoclonal antibodies and bispecific antibodies, the 5,000 L S.U.B. combines the flexibility and efficiency of single-use technology with the mixing and mass transfer performance that demanding cell lines require.

For example, Thermo Fisher designed the 5,000 L DynaDrive's agitator shaft for maximum versatility. Its 20:1 turndown ratio gives it the ability to adjust to a wider range of volumes than previous S.U.B.s.

"At 20:1, we can go to much lower volume than what we have had in the industry otherwise," said Erica Byerley, Global Senior Tech Transfer Engineer at Thermo Fisher Scientific. " Biopharma companies should be able to use existing SUBs in their single-use facility to inoculate the 5,000 L as N-1 with a reduced working volume leveraging the higher turndown ratio. Subsequently the same 5,000 L S.U.B. can then be used as the production vessel."

An efficient drive train and multiple impellers allow for lower RPM, which puts less shear stress on cells. Its combination of optimal oxygen transfer rate and uniform mixing help improve cell growth.

"The probe belt is designed at very low level, which allows us to run at very low volumes in a very tall vessel," said Qingwei Luo, Manager of Process Development at Thermo Fisher Scientific. "At volumes as low as 250 liters, it still can efficiently control all the parameters."

The future of biologics is flexible, agile and single use

With titers increasing, single-use technologies improving and biopharma companies developing therapies for smaller markets, the value promise of stainless steel only holds true for a small number of products.9 The flexibility, efficiency and speed that come with single-use technology provide economic and scientific advantages unmatched by reusable equipment. And when the time comes for commercial scale-up, biopharma no longer must choose between

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ERICA BYERLEY
Global Senior Tech Transfer Engineer
Thermo Fisher Scientific.

2,000 L single-use and 10,000 L stainless steel options. The middle ground—5,000 L—has become an in-demand option for early clinical trials through to commercial release.

For biopharma companies that outsource manufacturing, single-use CDMOs generally operate on considerably lower capital and operating expenses than facilities with reusable stainless steel—savings they can potentially pass on to customers.9 When that CDMO has multiple sites around the globe, the advantages multiply. Clients can scale up quickly to meet increased demand. End-to-end services, from cell line development through to fill/finish, further improve efficiency and minimize interruptions in the manufacturing timeline.

"We can run as many smaller batches as needed to supply clinical trials and then go into PPQ / commercial manufacturing when a product gets approved," said Byerley, referring to Patheon's network. "Because all our sites use a standardized catalog of single-use materials, we have an interconnected system that helps derisk and expedite timelines, so our clients get the product they need on time."

The emergence of 5,000 L single-use bioreactors combined with the rise of single-use CDMOs give biopharma companies a new path to commercial release. That path combines right-sized capacity with speed, flexibility and global reach. For complex biologics with moderate and uncertain demand, that combination can mean the difference between simply having a process on paper and having an efficient, scalable manufacturing strategy.

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Demonstrating robust scale-up to 5,000 L across two client molecules

What we did:
Having completed the production of more than 5 different molecule types in the 5,000 L S.U.B., we evaluated the scalability of the DynaDrive S.U.B. platform for two client programs—one monoclonal antibody (Case 1) and one fusion protein (Case 2)—by running their existing fed-batch processes at 50 L, 500 L and 5,000 L. The goal was to confirm that processes originally developed at 2,000 L could be transferred reliably to the new 5,000 L scale.

How we did it:
For each molecule, we scaled up or down from 2,000 L parameters to 50 L, 500 L and 5,000 L parameters. We tracked viable cell density and viability, product titer (IgG for Case 1, total protein for Case 2), pCO_2, and key metabolites (ammonia and lactate), along with gas flows measured via the mass flow controller. One 5,000 L run for the monoclonal antibody was terminated early due to a bioreactor bag issue (prototype bag), but the available data still allowed direct comparison of growth and productivity trends across scales.

What we achieved:
For both the monoclonal antibody and the fusion protein, cell growth, viability and titer profiles at 50 L, 500 L and 5,000 L followed the same overall trends, indicating that the processes scaled cleanly across all volumes. pCO_2 and metabolite profiles remained within expected ranges at each scale, and gas-flow data confirmed that the 5,000 L DynaDrive could support the oxygen transfer requirements of these higher-demand cultures without compromising performance.

Despite the early stop on one 5,000 L run, the clients judged the data sufficient to proceed with 5,000 L implementation, reinforcing confidence that their existing 2,000 L processes could be reliably translated to commercial-scale single-use manufacturing.[8]

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