



**MADE
WITH**
HEART & SCIENCE

WHITEPAPER

5,000L single-use bioreactors: The next generation in biologics manufacturing

Preeti Phanse, Mark Smith PhD, Jordan Cobia, Hailey Mauro, Jeff Hou PhD, Matt Zustiak PhD

• API

• **BIOLOGICS**

• VIRAL VECTOR
SERVICES

• EARLY & LATE
PHASE DEVELOPMENT

• CLINICAL TRIAL
SOLUTIONS

• LOGISTICS
SERVICES

• COMMERCIAL
MANUFACTURING

patheon



Abstract

The Thermo Fisher Scientific HyPerforma™ DynaDrive™ Single-Use Bioreactor line is suited for volumes ranging from 50L to 5,000L. Optimized for modern cell culture processes in a scalable, ergonomic design, the platform allows intensified, flexible manufacturing, enhanced by high-power input per volume, and better volumetric mass transfer performance.

This whitepaper highlights features and benefits of the DynaDrive™ SUB platform and explains how any new or existing facility can leverage the platform to achieve expected development and manufacturing objectives. From pre-clinical trials through commercialization, manufacturers and companies looking to outsource their biologics can use the DynaDrive™ SUB to gain maximum efficiency and flexibility across a wide range of processes, cell lines, and molecules.

Introduction

As scientific advancement in biopharmaceuticals continues to rise, so will the market. By 2030, total biologics revenues are expected to be worth \$450 billion—up from the \$285 billion biologics revenues seen in 2020. This rapid and continual growth has created a demand for therapeutics, expanding indications for biologics, and the growing portfolios of biosimilars. While these projections are good news for patients and for makers of therapies, growth always comes with new challenges. In this case, the industry must learn how to deploy efficient, flexible manufacturing technologies that can respond to many variables. These variables include the proliferation of new biologics, rapid shifts in annual volumetric requirements, and improvements in cell culture strategies.

A new generation of single-use bioreactors (SUBs), built to deliver high-volume performance, addresses many of these issues. This innovation outperforms existing 2,000L SUBs that were once the only cost-effective alternative to stainless steel bioreactors.



HyPerforma™ DynaDrive™ Single-Use Bioreactor

Redesigned for higher kLa through better mixing performance

Most SUBs with legacy designs have a single agitator attached to the top or bottom of the bag. Neither design mixes to a high degree of homogeneity, which can lead to product gradients and quality issues. The DynaDrive™ SUB, however, has a redesigned agitator shaft that spans the entire length of the bag—this new design contributes significantly to the technology's reliable turndown ratio of up to 20:1.

Prior to the introduction of DynaDrive™ SUB, most turndown ratios on SUBs ranged from 2:1 to 5:1. Fast forward to today's needs, many modern processes use higher producing cell lines and greater sophistication in process design. The need for greater oxygen transfer and mixing has become even more critical in process development.

One way to improve the oxygen transfer rate (OTR) is to increase agitation, thereby distributing gases more efficiently in a bioreactor. Many traditional SUBs, particularly at larger scales, are excessively challenged in terms of OTR for intensified processes and higher viable cell densities, making scale-up unfeasible.

The DynaDrive™ SUB helps overcome such limitations and improves processes in several ways. The increased efficiency of the drive train allows lower RPM setpoints while maintaining P/V ratio. The lower RPM correlates with lower mechanical shear stress experienced by the cells. Multiple impellers provide significantly more power in high-demand applications.

Bags are securely fastened at the top and bottom of the bioreactor and multiple impellers are distributed throughout the bag to achieve optimal mixing with lower gas consumption. The enhanced laser-drilled hole sparger in the DynaDrive™ SUB minimizes gas entrance velocity, reduces foam formation, and is scalable from small-to large-scale bioreactors for a wide variety of processes.

The state-of-the-art design offers best-in-class performance with mixing power of greater than 80 W/m³ and a mass transfer rate of up to 40 hr⁻¹. Biomanufacturers gain freedom to manage processes without losing productivity or product quality as they migrate from bench-scale bioreactors into large-scale manufacturing.

The state-of-the-art design offers best-in-class performance with mixing power of greater than 80 W/m³ and a mass transfer rate of up to 40 hr⁻¹.



Smarter ergonomics and greater operating efficiency

The DynaDrive™ SUB has flexible drive trains that allow smaller packaging, simpler material airlock transfers, and quicker set up in the suite. A fully open door allows operators access to the internal bioreactor space for easier set up and take down.

The 3,000L and 5,000L DynaDrive™ SUBs have semi-automated loading systems that give operators the ability to load and unload bioprocess containers quickly with less risk of damage to the container. Installation can be completed in less than 45 minutes for the 5000L vessel, which is 25% faster than 2000L bioreactors. Fewer connections inside the bioreactor reduce labor costs and lower the risk of contamination at each connection.

Enabling intensified seed-train strategy

In a traditional scale-up, cells expand from their initial vials through a variety of intermediate vessels to generate a cell mass that's sufficient for a production run. Scaling up this way typically requires different vessels at each n-stage operation.

Each switch from one vessel to another adds time and expense to set up and fill a new shake flask, rocker bag, or stirred tank reactor. And each transfer and manipulation of the cells adds the risk of contamination or improper handling, which can affect optimal cell behavior.

With a higher turndown ratio than ever before, the DynaDrive™ SUB allows users to consolidate multiple scale-up steps in a single vessel.

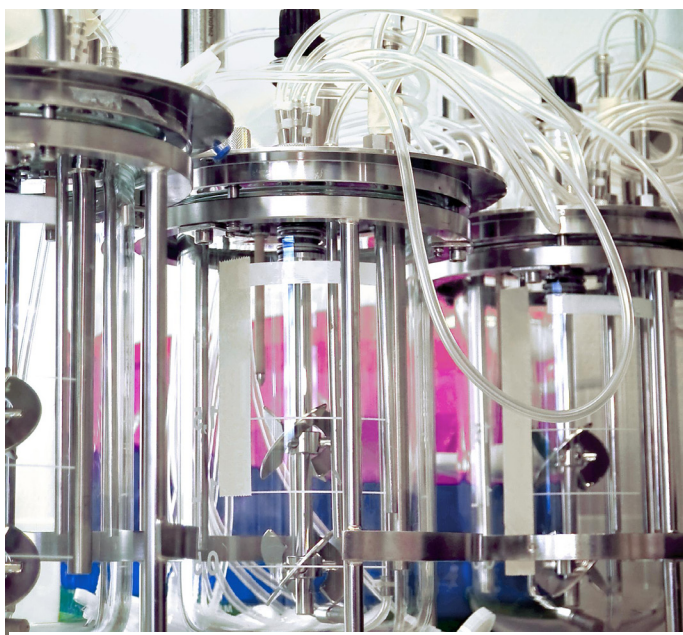
The DynaDrive™ SUB, with a maximum vessel volume of 50L, can be operated at a 10:1 turndown ratio and scale up can be accomplished in the same vessel—starting at 5L and ending at 50L. With a turndown ratio of up to 20:1 in the 500L and 5,000L SUBs, there can be starting volumes of 25L and 250L for each reactor respectively.

Staying in one bioreactor vessel and increasing volume as cells grow offers the following benefits:

- Reduces overall labor associated with cell-culture.
- Lowers consumable costs.
- Trims time in suite, enabling greater suite throughput and faster cycle time.

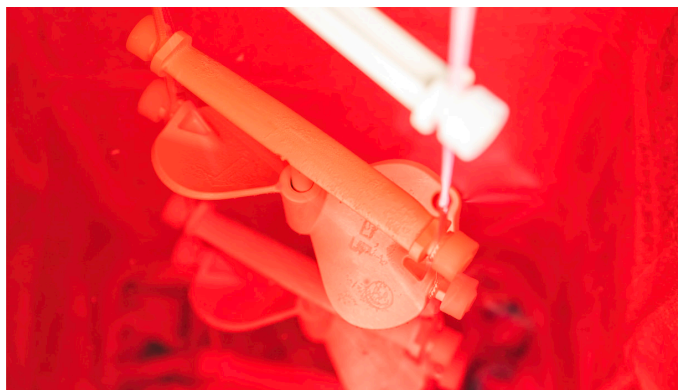
Higher batch volumes, lower operating cost, and reduced capital investment

DynaDrive™ SUB technology (5,000L) delivers mid-range economies of scale with less upfront capital and lower long-term operational costs. When a product's success in the market is unproven, choosing mid-range 5,000L SUBs help biologics manufacturers avoid scaling up by moving processes to larger facilities, where they will be subject to transfer and validation activities. Manufacturers retain greater flexibility for processing multiple products in the same space—they can also process low-demand products that don't meet minimum volumes requirements imposed by stainless-steel CMOs.



Material requirements typically increase as products progress from pre-clinical trials through Phases I, II, and III, and up to commercial manufacturing.

When considering a bioreactor for scaling and production, phase-appropriate demand of kilograms product should be tied to phase-appropriate volumes and batch count as described in Figure 1. For most Phase I activity, 50L SUBs (~0.75 kg required at P-I) provide sufficient batch-count to allow for continued CMC development exercises.



The enhanced laser-drilled hole sparger in the DynaDrive™ SUB minimizes gas entrance velocity, reduces foam formation, and is scalable from small- to large-scale bioreactors for a wide variety of processes.

Similarly, 500L SUBs are well sized for Phase II (~ 3-4 kg at P-II). While enough for Phase III (~30 kg at P-III), 2000L reactors are limited in commercial scale-out possibilities. Comparatively, 5000L reactors meet demand at Phase 3 and can readily scale out to even the largest commercial manufacturing demands. The high turndown ratio of the DynaDrive™ SUBs further helps to reduce capital investment.

DynaDrive™ SUBs gives new sites and retrofitted facilities a wider range of volume alternatives with better operating efficiency and less time in suite, while retaining the benefits of SUB technology. One 5,000L DynaDrive™ SUB, for example, reduces the cost of consumables and labor by 50% and produces two and a half times the volume of a 2,000L bioreactor in the same time and footprint.

Existing sites with ceiling height restrictions can replace 2,000L vessels with DynaDrive™ SUB 3,000L and leave controllers in place, improving efficiency by 50% without investing additional capital in new facilities. New facilities can build higher ceilings and achieve two and a half times the output of traditional 2,000L SUBs when they choose 5,000L DynaDrive™ SUB technology.

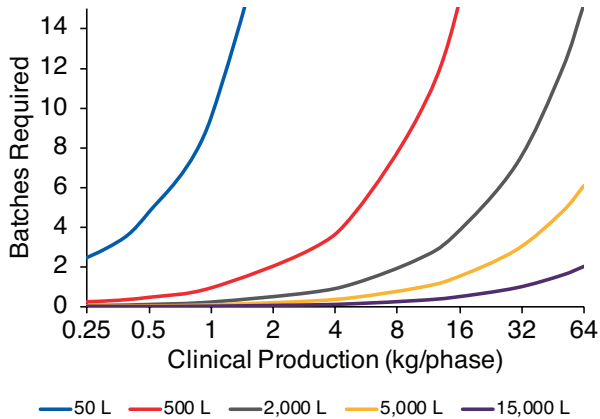


Figure 1

Benefits for facility or upstream suite construction

The 5,000L DynaDrive™ SUB also provides biomanufacturers with several operational efficiencies when compared to 2,000L SUBs or stainless-steel bioreactors:

- Eliminating clean-up and validation costs when switching from one product to another in a stainless-steel system.
- Meeting high-titer product demands and pipelines in a more versatile mid- to small-capacity facility.
- Avoiding long periods of low use and low efficiency when product pipelines aren't large or broad enough to support stainless-steel economies of scale.
- Responding to changing production volumes due to shifts in the clinical pipeline, such as targeted drugs for orphan diseases and precision medicine with lower volumetric requirements vs. blockbuster biologics.

Conclusion

With strong application data, showing cell growth and viabilities across all scales and cell densities, the DynaDrive™ SUB platform is a trusted solution that brings flexible manufacturing to modern cell culture processes.

Learn more about how to leverage DynaDrive™ S.U.B.s for better Cost of Goods Sold and Net Present Cost results in our special report, **Updating the Economics of Biologics Manufacturing with 5,000L Single-Use Bioreactors.**

For more information, visit:

[Thermofisher.com/dynadrive](https://thermofisher.com/dynadrive)

[Thermofisher.com/sut](https://thermofisher.com/sut)

[Thermofisher.com/flexiblecontainment](https://thermofisher.com/flexiblecontainment)

About us

Thermo Fisher Scientific provides industry-leading pharma services solutions for drug development, clinical trial logistics and commercial manufacturing to customers through our Patheon brand. With more than 55 locations around the world, we provide integrated, end-to-end capabilities across all phases of development, including API, biologics, viral vectors, cGMP plasmids, formulation, clinical trials solutions, logistics services and commercial manufacturing and packaging. We give pharma and biotech companies of all sizes instant access to a global

network of facilities and technical experts across the Americas, Europe, Asia, and Australia. Our global leadership is built on a reputation for scientific and technical excellence. We offer integrated drug development and clinical services tailored to fit your drug development journey through our Quick to Care™ program. As a leading pharma services provider, we deliver unrivaled quality, reliability, and compliance. Together with our customers, we're rapidly turning pharmaceutical possibilities into realities.