Introducing the Enhanced and DynaDrive™ S.U.B.s: Meeting the Demands of Intensifying Upstream in Single-Use

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Bioprocessing

ABSTRACT

S.U.B.s have emerged as a tool-of-choice in many PD and Pilot spaces and are now transitioning into certain commercial manufacturing spaces. Simultaneously, upstream bioprocesses have intensified to considerable benefit in increased titer and decreasing production-vessel size. As upstream cultures continue to intensify, these processes are beginning to strain the performance envelope of single-use bioreactors designed for less demanding cultures of yesteryear. We describe simple yet effective enhancements that enable Thermo Scientific HyPerforma™ S.U.B.s to meet the mass-transfer and mixing needs of intensifying processes at 50-500 L scale, while leveraging the hardware of existing systems. We also introduce a next generation of single-use bioreactor – DynaDrive S.U.B. – that exceeds upstream process needs in a novel framework that was developed with a keen eye toward robust operations, exceptional ease-of-use, future flexibility, and unprecedented mass transfer and mixing scale-up predictability up to 5,000 L working volumes.
performance

CONTINUAL SINGLE–USE INNOVATION

Since 2006 Thermo Scientific has provided best-in-class innovations to single-use bioproduction:

- 2006 – First S.U.B., 50 and 250 L
- 2010 – First 2000 L S.U.B.
- 2014 – Precision Laser Drilled Hole Sparge (DHS)
- 2016/2017 – 5:1 HyPerforma S.U.B., increased turn-down ratio

In this tradition, we introduce:

- Enhanced S.U.B. for Fed–batch (50–500 L)
- Enhanced S.U.B. for Perfusion (50–500 L)
- DynaDrive S.U.B. for intensified cultures (50–5,000 L)

All systems include improved mixing and gassing.

- Enhanced S.U.B.s include upsized impeller (Fig. 4)
- DynaDrive includes flexible drive-train with multiple impellers (Fig. 4)
- All include Enhanced DHS (decreased pore size, increased pore quantity)

ENHANCED S.U.B. FOR FED–BATCH

Building upon the base of the HyPerforma S.U.B. hardware, the Enhanced S.U.B. for Fed-Batch focuses on increasing mass-transfer and power input while maintaining a 4:1 turn-down for seed-train efficiency.[1] By changing a few bolt-on hardware items and bioprocess container (BPC) design, these benefits can be realized:

- Substantial k_La Enhancement (>3x Legacy)
- High Power per volume (up to 100 W/m^3)
- Optimal CO_2:O_2 Mass-transfers (Fig. 2)
- Similar BPC changes as Enhanced S.U.B. for Perfusion
  - Upsized Impeller
  - Enhanced DHS (laser-precision Drilled-Hole Sparge)

The increased impeller dimensions enable high power while lowering tip-speed at a given power input (Fig. 1). In parallel, the Enhanced DHS with smaller pore diameter and increased pore count enables increased mass transfer while maintaining low gas-entrance velocities, enabling support of high density fed-batch cultures.

Figure 1. PIV versus tip speed for legacy HyPerforma, Enhanced, and DynaDrive S.U.B.s. Note that the tip speed of the Enhance and DynaDrive S.U.B.s are substantially lower for a given power input at a given volume.

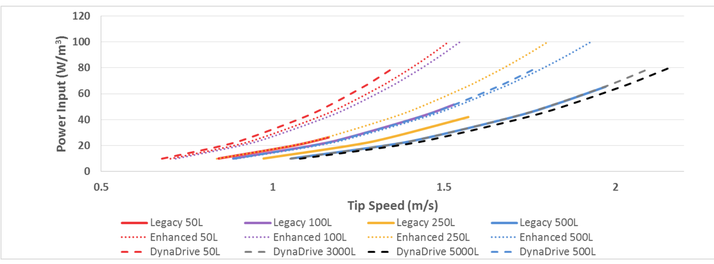


Figure 2. O_2 and CO_2 mass transfer results for Enhanced S.U.B.s for fed-batch. Mass transfer studies performed in 1 g/L poloxamer 188, 3.5 g/L HEPES at 37ºC and analyzed using standard dynamic method (n_P = 2.1, PIV 5:1=20 W/m^3, Enhanced=100 W/m^3).[2]

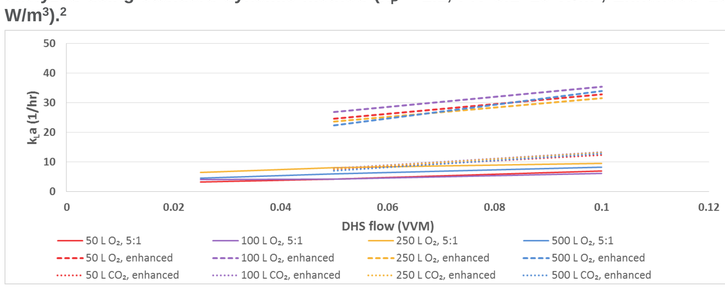
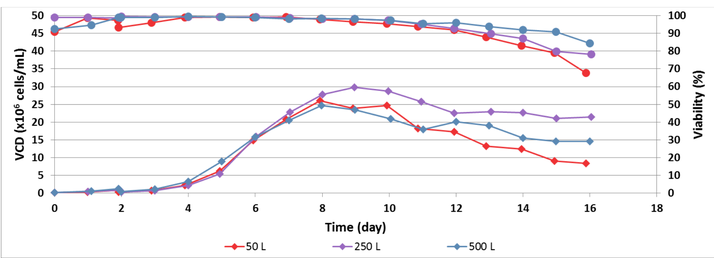


Figure 3. CHO-S cells grown in Gibco™ Dynamis™ medium supplemented with EfficientFeed™ C+ feed. Gassing with DHS only (O_2, N_2, CO_2 cascade) to maintain pH and DO setpoints. Mixing at 20 W/m^3. Culture conditions maintained using HyPerforma G3Pro controller.



ENHANCED S.U.B. FOR PERFUSION

The Enhanced S.U.B. for Perfusion again builds on the HyPerforma S.U.B. hardware and focuses on maximizing performance at terminal volume to support the specialty demands of perfusion processes.[3]

- Substantial k_La Enhancement (up to 4x Legacy)
- High density cell culture (>260x10^6 cells/mL)
- Large ports for cell-retention connections (e.g. ATF, TFF)
- Automated foam control by foam-probe
- Similar BPC changes as Enhanced S.U.B. for Fed-Batch
  - Upsized impeller
  - Enhanced DHS (laser-precision Drilled-Hole Sparge)

The elevated impeller location in the Enhanced S.U.B. for Perfusion helps to ensure the power is well distributed in the volume and results in good mixing, which can be a challenge at extreme cell densities with resulting high viscosities (e.g. >80x10^6 cells/mL). Automated foam control reduces foam-out risks while generally reducing total antifoam usage, alleviating antifoam's impact on downstream processing.

Figure 4. Cross section of each generation of HyPerforma S.U.B.

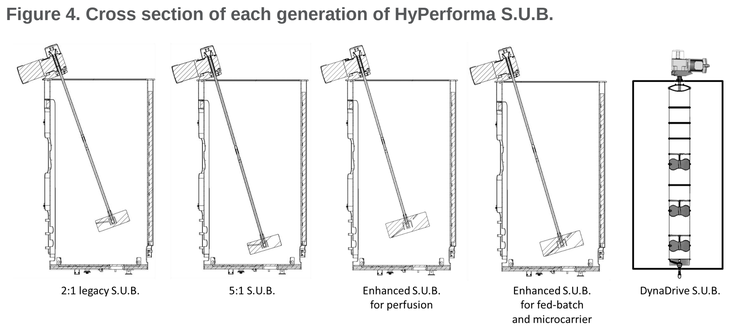


Figure 5. O_2 and CO_2 mass transfer results for Enhanced S.U.B.s for Perfusion. Mass transfer studies performed in 1 g/L poloxamer 188, 3.5 g/L HEPES at 37ºC and analyzed using standard dynamic method (n_P = 2.1, PIV 5:1 = 20 W/m^3, Enhanced S.U.B for Perfusion = 100 W/m^3).[2]

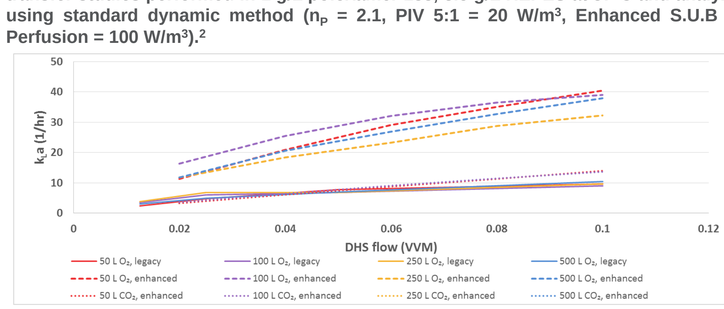
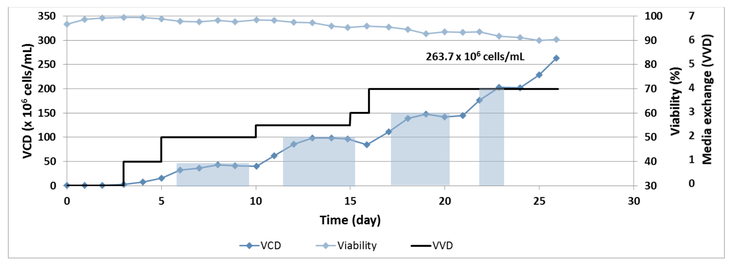


Figure 6. CHO–DP12 cells grown in Gibco™ OptiCHO™ medium. Gassing with DHS only (O_2, N_2, CO_2 cascade) to maintain pH and DO setpoints. Mixing up to 100 W/m^3. Perfusion performed with Repligen XCell™ ATF6. Culture conditions maintained using HyPerforma G3Pro controller.



DYNADRIVE S.U.B.

As the demand for single-use technologies increases in terms of performance, efficiency, and ease-of-use, Thermo Scientific is bringing a truly next generation of bioreactor to the Biopharma industry: DynaDrive S.U.B. Building on our extensive experience and nearly two decades of end-user feedback, The DynaDrive S.U.B. employs a new agitator drive technology with carefully engineered hardware that enables exceptional performance:

- higher turn-down ratios (up to 20:1)
- reliable power input (up to 80 W/m^3)
- maximum working volume (up to 5000 L)

Such high turn-down opens a new paradigm of what is possible with seed-trains, potentially eliminating multiple vessels, reducing logistical and operating costs dramatically, while increasing the efficiency of the train through reduced connections and transfer losses.

Figure 7. Turn-Down Cultures and Scaled-Geometry of the DynaDrive S.U.B.

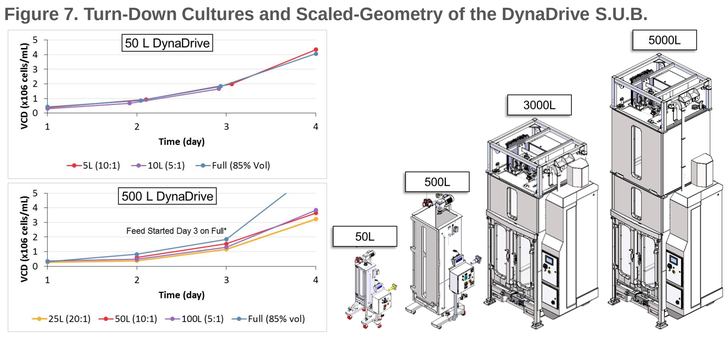
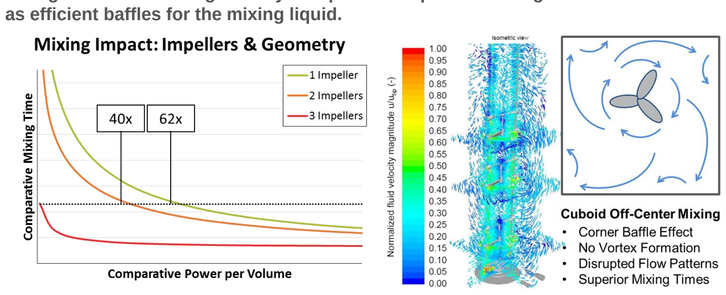


Table 1. Highlighted Performance comparisons between the HyPerforma, Enhanced HyPerforma, and DynaDrive S.U.B. systems. Mass-transfer coefficient (k_La) presented is using DHS-only at~20 W/m^3 for system efficiency comparison.

S.U.B.	HyPerforma		Enhanced HyPerforma		DynaDrive
Generation	2:1	5:1	Enhanced Fed-Batch	Enhanced Perfusion	DynaDrive
Volumes	50 to 2000 L		50 to 500 L		50 to 5000 L
Sparge	Frit & DHS		Enhanced DHS		
Turn-Down	2:1	5:1	4:1	2:1	**≥10:1**
Max P/V	500 L → 65 W/m^3 2000 L → 40 W/m^3		**100 W/m^3**		**80 W/m^3**
k_La (hr^{-1})	50 L 10.1 500 L → 10.5 2000 L 15.0		50 L 500 L → **17.2** **15.2**	50 L 500 L → **17.6** **20.3**	50 L 500 L → **≥20** 5k L

Figure 8. Geometry, impeller design, and impeller location can have a dramatic impact on mixing performance. A simple impeller in a standard position (e.g. 1-$d_{impeller}$) above the floor took in this example 62x more power than a 3-impeller design with optimal configuration. Cuboid geometry can provide improved mixing with the corners acting as efficient baffles for the mixing liquid.



CONCLUSIONS

To address the trend toward specialization in bioproduction, Thermo Scientific has upgraded the HyPerforma S.U.B. product platform to feature application-specific enhancements for high-demand fed-batch and perfusion cell cultures. Additionally, Thermo Scientific is launching a newly-designed DynaDrive S.U.B. to improve on best-in-class performance and provide customers a meaningful, lasting solution to upcoming process intensification needs.

For more information, please visit us at:
thermofisher.com/sub or thermofisher.com/dynadrive

REFERENCES

1. Madsen, B. S.U.B. Enhancements for High-Density Fed-Batch Cultures. Thermo Fisher Scientific. 2019.
2. Doran, P.M. Mass Transfer. In Bioprocess Engineering Principles 416-425 (Elsevier, 2013).
3. Madsen, B. Cobia, J. Jones, N. S.U.B. Enhancements for High-Density Perfusion Cultures. Thermo Fisher Scientific. 2018.

TRADEMARKS/LICENSING