Single-use bioprocessing

Next-generation single-use harvest solutions

Efficiency for today and sustainability for tomorrow

Keywords
DynaSpin Single-Use Centrifuge, DynaDrive S.U.B., filter reduction

Introduction

The use of single-use technologies (SUTs) and systems in bioprocessing enables many benefits, such as rapid product changeover, reduction or elimination of caustic waste from cleaning, and facility flexibility for activities like multi-product operations. Facility updates to match processes with new and emerging technologies are more straightforward with SUTs, allowing facilities to be deployed more quickly and modularly than traditional steel buildouts.

As bioprocesses intensify through larger volumes, culture processes, and cell line development, SUT facilities are increasingly becoming economically competitive with large steel buildouts. This is particularly the case with enabling technologies like the Thermo Scientific™ DynaDrive™ Single-Use Bioreactors (S.U.B.s), which have unique high-performance capabilities to support high-intensity cultures and scale-up from 50 L to 5,000 L in working volume.

Increasing bioprocess intensity and SUT volume has increased demand for performance across the bioprocess workflow. This demand for performance is perhaps most acutely felt with traditional single-use harvest and clarification solutions, i.e., single-use depth filtration. The required depth filter area is proportional to the volume filtered and contaminants to be filtered away. Using depth filtration as a stand-alone solution thus becomes less desirable as cell densities and volumes increase in single-use processes.

To address the growing challenges of single-use harvesting, Thermo Fisher Scientific has created the Thermo Scientific™ DynaSpin™ Single-Use Centrifuge. This fully continuous and automated single-use centrifuge serves as the primary tool for the cell removal step and functionally replaces the coarse filter in a traditional two-stage depth filtration unit as shown in Figure 1. The resulting filtration area is considerably smaller, the implications of which are discussed below.

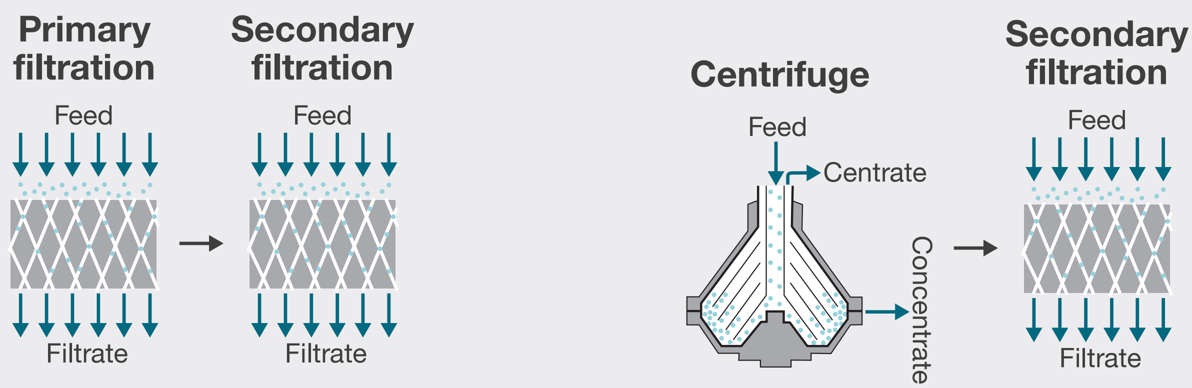

Figure 1. A schematic representation of harvesting methods.

Filter area reduction

One advantage of the DynaSpin centrifuge is that it is not limited by volumetric throughput. As the user scales in volume or process intensity, the cost of consumables for the single-use centrifuge remains fixed, whereas an increasing number of coarse depth filters are required for standard two-stage depth filtration. To demonstrate this, several representative fed-batch cell cultures were harvested using both a traditional two-stage depth filtration method and the DynaSpin centrifuge followed by secondary depth filtration. We then compared the total depth filter surface area required to achieve clarification. A total of five different 14-day fed-batch cultures were processed with a range of peak viable cell densities and final viabilities. A summary of fed-batch cell culture performance is shown in Table 1.

Table 1. Cell culture performance characteristics at harvest.

	Viable cell density (x 10^6 cells/mL)	Viability (%)	Packed cell volume (%)	Cell type
Culture 1	12	87	6.0	Gibco™ ExpiCHO-S™ cells
Culture 2	20	81	6.0	ExpiCHO-S cells
Culture 3	29	70	5.0	Gibco™ CHO-K1 cells
Culture 4	37	90	6.0	CHO-K1
Culture 5	32	75	5.0	CHO-K1

While culture characteristics can significantly affect filter capacity, centrifugation feed flow rates impact downstream clarification efficiency. For this study, feed flow rates were chosen in a way that allowed a 2,000 L bioreactor to be harvested in less than 4 hours. As shown in Figure 2, the filter area required when using a traditional two-stage depth filtration strategy was approximately 3–5 times that needed when using the DynaSpin centrifuge prior to depth filtration. Projecting for a 2,000 L harvest of such cell cultures, traditional two-stage filtration would require a filter area of 60–70 m^2, two thirds of which would be for the primary depth filter and one third for the secondary filter. In contrast, only 11–24 m^2 of filter area would be required for DynaSpin processes using a single filter type. Assuming 1.1 m^2 of filter area per filter capsule, this translates to total filter counts of 56–65 and 11–21 for depth filtration and DynaSpin processes, respectively. A 63–83% reduction in the total number of filters required to perform a 2,000 L cell culture harvest can be expected if implementing the DynaSpin centrifuge for primary clarification (Figure 3).

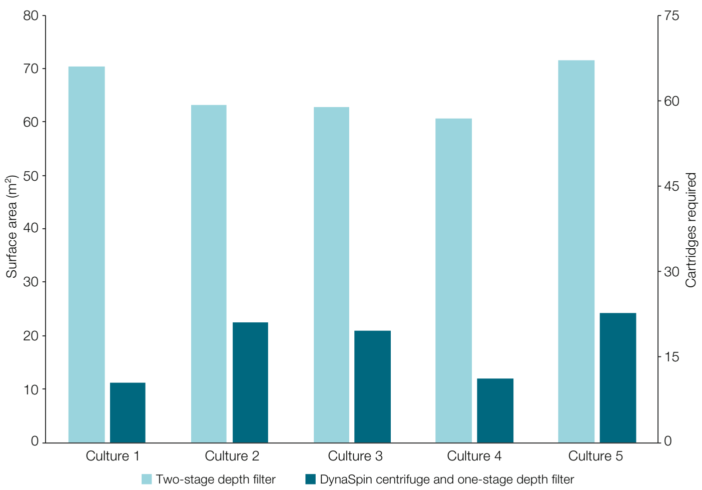

Figure 2. Depth filter (DF) surface area required for a 2,000 L harvest.

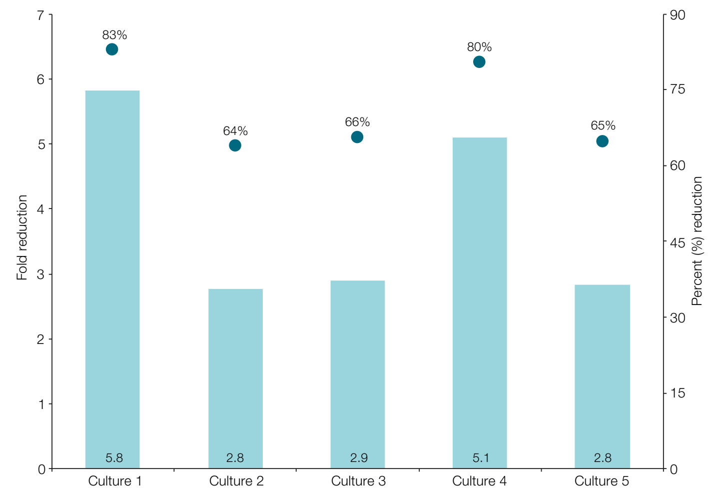

Figure 3. Filter quantity reduction when implementing the DynaSpin centrifuge for primary clarification.

Operational efficiency

Adding equipment to a process can add complexity and may require additional processing time. We examined the impact of the filter area reduction provided by the DynaSpin centrifuge and found a reduction in the overall operation time. This was mainly driven by a dramatic reduction in setup and teardown time, including the time needed for buffer preparation. An example breakdown of harvest duration is shown in Figure 4.

The substantial filter area required for traditional depth filtration makes setup take longer than the combined setup, process, and teardown time required for the DynaSpin process. In addition to long setup times, used filters often need to be decontaminated, individually bagged, and transported to a waste accumulation area. This involves a large amount of tedious manual labor. The DynaSpin process is more efficient, so facilities can execute harvest in a single shift. The combination of these benefits can eliminate over 11 hours of suite time.

As a result of reducing the depth filter area required for harvest, fewer filter housings or racks will be needed in the manufacturing suite, which will reduce the process footprint. Traditional depth filtration for tested cultures at the 2,000 L scale would require an average footprint of 111 sq. ft. With the DynaSpin centrifuge, these processes would require an average footprint of 85 sq. ft. This footprint includes a single-use mixer for product collection, a single-use mixer for water for injection (WFI), depth filter racks, DynaSpin units, 1,000 L totes for chase buffer, and pumps. Efficient use of the additional cleanroom suite area gained by using the DynaSpin centrifuge enables users to increase scale and culture challenge without running into facility limitations, improving the versatility of existing suites.

Savings in facility footprint do not stop at the suite. Limited GMP warehouse space is a challenge for sites expanding their production capabilities. Use of consumables like depth filters in large quantities leads to inefficiencies in the supply chain in terms of inventory, motion, and transportation. Reducing the number of consumables in your process relieves stress on procurement and shipping through fewer orders and shipments, reduced physical inventory, and less material transfer into manufacturing suites. The reduction in filter area from one 2,000 L harvest equates to nearly two full pallets, or 25 ft^2 of warehouse space. A summary of the operational efficiency gains at the 2,000 L scale is shown in Table 2.

Facilities pursuing lean manufacturing will find a multitude of benefits by adopting the DynaSpin centrifuge for harvest. Reducing filter area cuts waste out of every stage of the overall workflow—from alleviating stresses on supply chain to freeing up facility space to vastly reducing worker motion.

For a more comprehensive economic analysis of the impacts of implementing the DynaSpin process at the 2,000 L or 5,000 L scale, please refer to “Spin it first: Finding an optimal harvest solution by considering both cost and sustainability” [1].

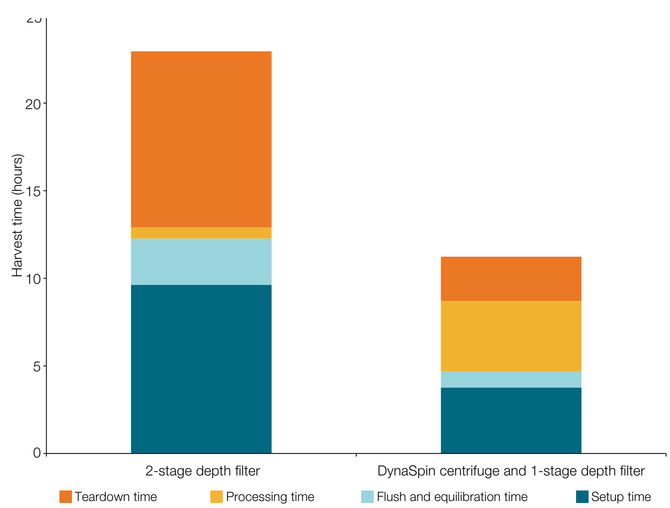

Figure 4. Total time comparison for 2,000 L harvest unit operation: two-stage depth filtration (DF) vs. the DynaSpin centrifuge plus DF.

Table 2. Operational efficiency of harvest approaches at 2,000 L.

	Suite footprint (ft^2)	Warehouse footprint (ft^2)	Total harvest time (hours)
Traditional depth filtration	111	25	22.9
DynaSpin process	85	5	11.25
DynaSpin reduction (%)	24	80	51

Implications for >2,000 L bioprocess harvest

While the bulk of the analysis was performed for a 2,000 L use case, the benefits of utilizing the DynaSpin centrifuge are compounded at larger scales. At the 5,000 L scale, using one of the exemplary cell cultures tested as an example, six filter holders would be required for harvest using traditional two-stage depth filtration, while the DynaSpin centrifuge brings this number down to a single individual filter holder. Figures 5 and 6 show visual comparison of the harvest methods.

Eliminating five filter holders from the harvest suite creates ample space for a second DynaSpin unit, allowing facilities to maintain a single-shift harvest at the 5,000 L scale. The benefits of the DynaSpin process compared to a two-stage filtration are amplified at larger scales, expanding the differential of footprint and total process time between the two methodologies. A summary of these improvements is shown in Table 3.

Table 3. Operational efficiency of the DynaSpin centrifuge at 5,000 L scale.

	Suite footprint	Warehouse footprint	Total harvest time
Traditional depth filtration	192 sq. ft.	62 sq. ft.	55 hrs
DynaSpin process	129 sq. ft.	15.7 sq. ft.	20 hrs
Reduction using DynaSpin process	33 %	75 %	64 %

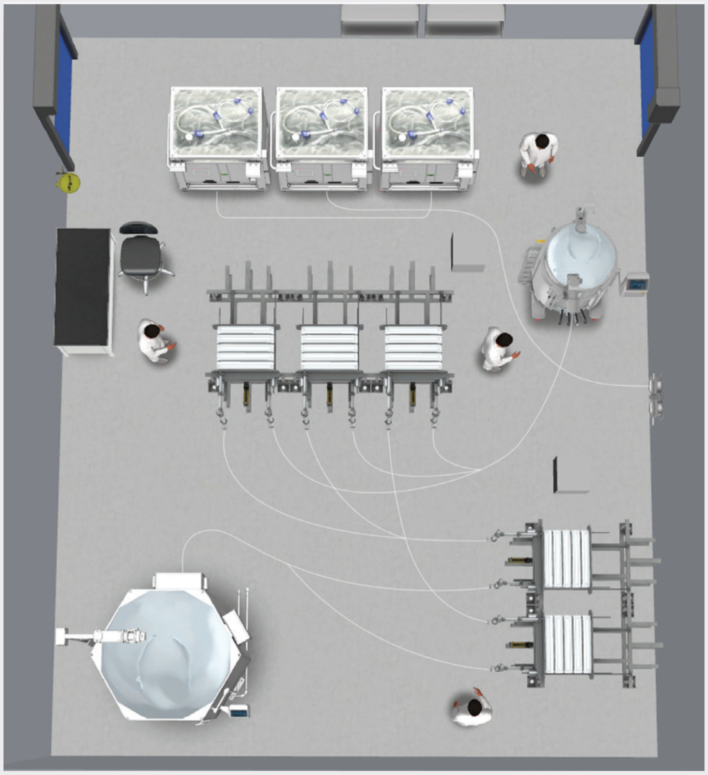

Figure 5. Harvest suite layout for a 5,000 L bioreactor using depth filtration.

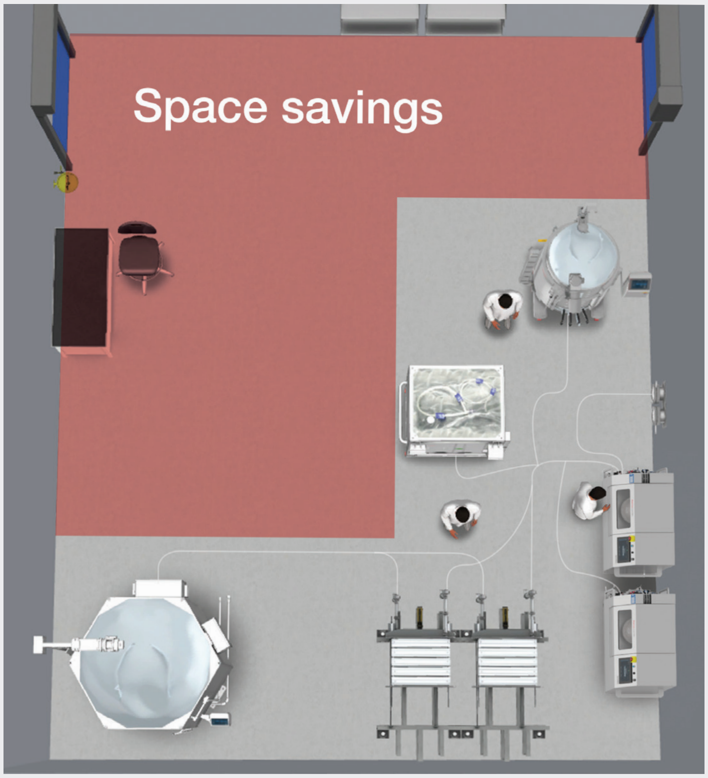

Figure 6. Harvest suite layout for a 5,000 L bioreactor using the DynaSpin centrifuge with depth filtration.

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Conclusions

As processes continue to intensify and the desire to take advantage of the benefits of single-use technology remain, implementation of the DynaSpin Single-Use Centrifuge for cell culture clarification is a perfect fit. One can expect to reduce their use of depth filters by 60–80% while increasing their operational efficiency by >50%. These benefits can be realized not only at the 2,000 L scale but even more so at larger scales. The robust performance of the DynaSpin centrifuge across multiple different cultures gives confidence that it will be able to handle more challenging cultures that arise with process intensification. For companies looking to remain in the single-use paradigm while scaling their processes beyond the clinical supply phase, or looking to intensify their process to improve yields, the DynaSpin centrifuge paired with depth filtration offers a more efficient harvest solution than traditional two-stage depth filtration and should be considered for implementation.

Authors

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Reference

1. Levi M. Larsen, Economic Analyst, Thermo Fisher Scientific; Jon Kruger, Engineer II, Systems Design, Thermo Fisher Scientific; Kayla J. Spivey, Content Specialist III, Thermo Fisher Scientific (2023) Spin it first: Finding an optimal harvest solution by considering both cost and sustainability.

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