Single-use technologies

Spin it first

Finding an optimal harvest solution by considering both cost and sustainability

Keywords
Single-use centrifuge, DynaSpin, depth filtration, harvest solution

Introduction

Driven by the need to support the production of high-intensity cell cultures of higher volumetric scales, the demand for performance efficiency at each step of bioproduction has grown in tandem. When a manufacturer decides on what technology to use, multiple methods can be applied to help facilitate the harvest step of bioprocessing. The purpose of harvest is to separate the product of interest from the remaining cell debris and particulates left in the bioreactor medium following the upstream process. The drug substance is then run through a series of downstream clarification steps to remove any unwanted aggregate or particulate that may be left over from earlier upstream processes.

Historically, many facilities used stainless steel centrifuges, which require cleaning via SIP and validation of such cleaning from batch to batch to assure regulatory compliance and sterility. In contrast, depth filtration is more scalable using a series of filtration steps to remove waste from wet biomass. Many modern processes bring unique challenges requiring a more flexible harvest solution. This allows for further facility optimization of cleanroom space and other efficiencies. The ratios of consumable to hardware costs vary between these two most common harvesting methods.

Purpose of Evaluation

This paper evaluated two technologies for direct comparison. The two harvest methods assessed were depth filtration—the most common technique utilized in the harvest market, and single-use centrifugation—a technology that has been leveraged primarily at the small to mid-volume range. Alternatively, stainless steel centrifugation has been used at large volumes, but this technology is different from single-use in that it requires steam-in-place (SIP) clean-in-place (CIP) systems and is always accompanied by extensive validation work. As a point of differentiation, stainless steel centrifugation is fundamentally less flexible and requires more upfront investment via capital expenditure (Cap-Ex) due to regulations regarding the cleaning and operation of these systems. Single-use centrifugation, much like any other single-use technology (SUT), is far more flexible because batch turnover is as simple as replacing the consumable and line sets. Single-use offerings are less Cap-Ex intensive due to their consumable-based nature and, therefore, incur more recurring operating expenditure (Op-Ex) costs when the drug is produced commercially.

It is important to note that any form of centrifugation requires a secondary filtration step which typically follows the depth filtration method. A pure depth filtration harvest approach also has two filtration steps, where the product is passed through a specific-sized filter, then passed through a second that is sized even smaller to achieve proper separation. Figures 1a and 1b illustrate the concept behind the primary and secondary filtration steps needed for both depth filtration and centrifugation.

We are proud to lead the charge in expanding the viability of single-use centrifugation with our launch of the Thermo Scientific™ DynaSpin™ Single-use Centrifuge. The comparisons made in this paper will focus on the implications of harvesting from production single-use bioreactor (SUB) between the sizes of 1,000 L and 5,000 L. While the product is viable outside of this range, this analysis focuses on comparing the results in a GMP clinical phase scenario where large amounts of product are required.

Key features:

- Significant consumable reduction at all volumes resulting in ~70% less depth filters and 78% liquid requirements (buffer, WFI, NaOH)
- Extensive automation that meets 21CFR part 11 compliance and allows for recipe planning, data tracking, audit traceability, user access, and real-time process monitoring
- Efficient separation which results in reduced burden on the filtration step allowing higher filter capacity, measured in Liters per meter squared (LPM2)
- Poka-Yoke design that minimizes setup and takedown time and helps reduces the chance of user error
- Push buttons walk away automation enabling more efficient operation including automation of priming, steady state operation, and shutdown & drain

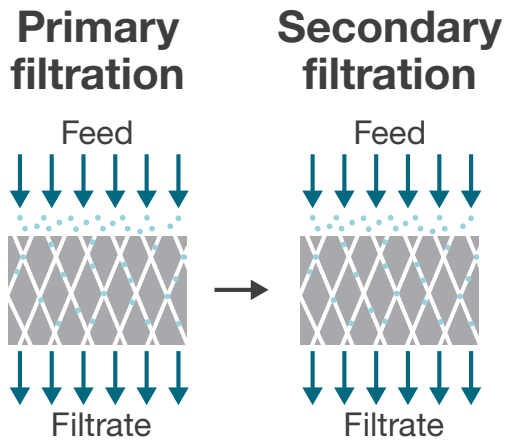

Figure 1a. Depth filtration process.

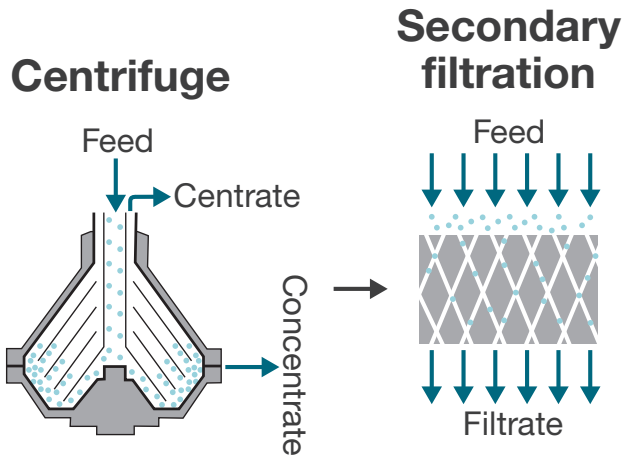

Figure 1b. Centrifugation process.

Methodology

The theoretical modeling discussed in this paper was carried out with the BioSolve Process software developed by BioPharma Services Limited. This software has been used in multiple industry papers to evaluate the financial and operational implications of a given process and is also used by many drug manufacturers to model their processes in-house. The following information details the key inputs that were varied in the model and how that was subsequently used to generate key comparisons.

Both depth filtration and centrifugation have a myriad of variables that could impact the performance of the harvest. Variables such as titer, peak cell density (PCD), packed cell volume (PCV), and viability can impact product performance and yield. In this model, all three are held constant to show how both technologies would compare under similar circumstances. Because this modeling focuses exclusively on the harvest step, upstream and downstream portions of the model are held constant between processes so as not to adversely affect the harvest step. For example, the 2,000 L scale assumes that both depth filtration and single-use centrifugation pull from the same type of bioreactor with identical seed trains. This also means that labor, material, and consumable costs are held constant. To avoid facility costs from skewing the data the cost of the facility itself (including suite buildout) was excluded from the model, though this would have an impact should one technology allow a manufacturer to produce a much smaller suite.

Additional assumptions were made around the quantity of personnel needed for process setup and takedown, the time required to set up/takedown a process, and filter/centrifuge performance. Table 1 highlights the key assumptions made that had an impact on the outcome of the model.

Upon building the harvest models in BioSolve Process and identifying a range in potential product performance, the sensitivity of said performance was tested by iterating on the expected range. This meant running the model with different filter capacities as called out in Table 1. In all, the modeling performed included ~50 iterations. The data produced from these iterations were then leveraged to produce the comparisons highlighted in this paper.

Table 1. List of base assumptions used in the BioSolve harvest cost modeling.

	Depth filtration	DynaSpin Single-use centrifugation
Setup time	1.5 hours per filter housing rack for material movement, documentation, installation, hydraulic compression and inspection, and tubing management	.5 hours per single-use rotor, per filter
Takedown time	20 minutes per filter housing rack for tubing teardown and cleanup, and 10 minutes per filter for teardown and disposal	.5 hours per single-use rotor, per filter
Minimum personnel requirement	2 personnel	2 personnel
Primary filtration performance range	Depth filter: filter capacity of 70-120 LPM^2	Centrifuge: flow rate of 180-660 L per hour
Secondary filtration performance range	Depth filter: filter capacity of 140-240 LPM^2	Depth filter: filter capacity of 150-300 LPM^2
Additional assumptions	**Labor Costs:** Calculations assume some pre-staging has taken place for both technologies. This means the filter housing racks or the DynaSpin unit are already staged in the harvest suite, but the consumables have not yet been placed in the equipment. **Capital Cost:** Capital costs only account for equipment, the cost of building out the suite is not included. Equipment required includes pumps, filter housings, centrifuge housings, hold tanks, and break tanks.	

"…between the 2,000–5,000 L range, DynaSpin is on average 25% less expensive than a pure depth filtration solution."

Spin it first: cost considerations

Delivering an efficient and cost-effective harvest within a reasonable period of time is extremely important to any manufacturer. When comparing depth filtration to single-use centrifugation a big driver is the number of consumables needed to complete a full harvest. As the consumable count increases customers must spend more per batch on both filters as well as a buffer (manufacturers must use a buffer to flush each filter), raising operational costs. Additionally, increasing the filter count can result in more labor needed to set up and take down the full harvest of each batch. Finally, as more filters are needed for a given harvest more filter housing racks must be purchased which can raise capital expenditures.

The high-level cost differences are highlighted in Figure 2. In it, projected harvest costs are shown on the Y axis and production volume on the X axis. The colored lines (with DynaSpin in blue and depth filtration in gray) show the excepted average cost at each volume with colored bands that show a cost sensitivity. The cost sensitivity is tied to changes in product performance, or filter capacity, as explained in the methodology section. It's important to note that the costs shown in Figure 2, and subsequent images, are projected and therefore, likely to change depending on factors such as location, regulatory landscape, and local market dynamics. However, the relative cost differences discussed would remain the same in the majority of situations.

The primary takeaway from this modeling is that DynaSpin is not only competitive with depth filtration at all the key single-use production volumes but that above the 1,000 L production level it is a more cost-effective option. In fact, between the 2,000—5,000 L range, DynaSpin is on average 25% less expensive than a pure depth filtration solution. Additionally, it's worth noting that as the volume increases DynaSpin captures additional economies of scale. This means that the savings of leveraging the technology increase with volume, resulting in the widening gap between the lines when moving leftward. Finally, one will likely notice how the gray depth filter band is much thicker than the blue DynaSpin band. This is because the technology is more sensitive to changes in product performance than single-use centrifugation. For example, if a specific culture tends to force low filter capacity with depth filtration, it's almost guaranteed to also have the same effect on centrifugation. However, as is shown by the width of the bands, the impact of poor performance from a cost perspective is more significant on depth filtration than it is on DynaSpin.

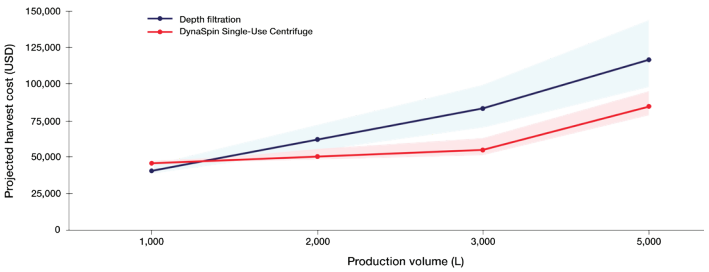

Figure 2. Depth filtration vs. DynaSpin: harvest cost sensitivity analysis.

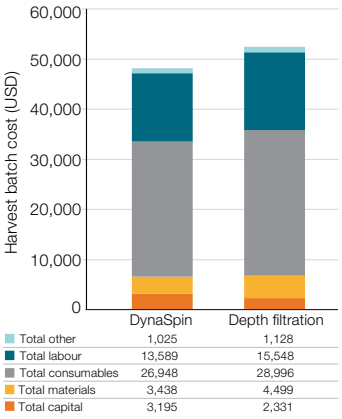

Figure 3a.
1,000 L comparison

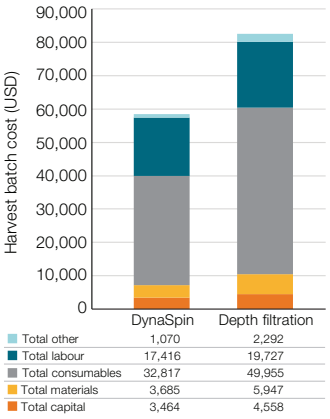

Figure 3b.
2,000 L comparison

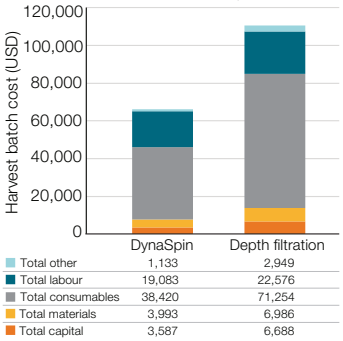

Figure 3c.
3,000 L comparison

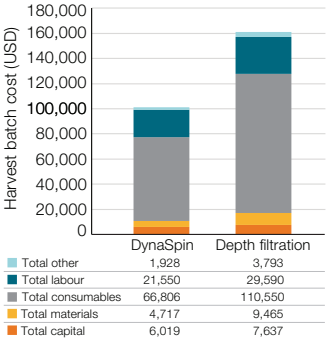

Figure 3d.
5,000 L comparison

The cost implications are clear from a high level, but it's worth exploring the specifics to better understand just why DynaSpin can be a more cost-effective option. These specific cost areas worth highlighting can be broken up into capital, consumables, buffer, and labor; as shown in Figures 3a, b, c, and d. Examining these cost areas helps to better understand DynaSpin's economies of scale effect from Figure 2. The more filters the centrifuge replaces, the more financially advantageous the technology. Given that depth filter requirement scales linearly with volumetric production, and DynaSpin does not, the cost savings become more significant as the bioreactor size increases. The following discusses each cost area in more detail.

Capital

Capital investment tends to be low with SUT because it is inherently a more OpEx-heavy technology. For depth filtration, these capital costs come from the following equipment:

- Hold tanks to hold processed material prior to chromatography steps
- Pumps needed to push process material from the bioreactor into depth filters
- Filter housings to hold depth filters

On the other hand, a single-use centrifugation process via DynaSpin incurs capital costs from the following:

- Hold tanks to hold processed material prior to chromatography steps
- Rotor housings to hold, run, and automate the rotor
- Filter housings to hold depth filters.

The difference in amortized capital is highlighted in Figures 3a, b, c, and d. In said images capital costs are higher when using depth filtration for all volumes except Figure 3a at the 1,000 L scale. This difference in capital costs speaks somewhat to the economies of scale associated with using DynaSpin. From a cost lens, the capital cost needed to use single-use centrifugation is most opportune when it replaces a significant amount of filter housing units. At a 1,000 L scale it replaces a relatively small quantity of units and thus results in a higher capital cost. Regardless, in this instance the increase in capital cost also enables significant amounts of process automation (ie. rotor housings are designed to automatically solve problems like clogs and run a process of start to finish once being started) something a filter housing unit is not capable of doing.

Consumable

As has already been emphasized in this paper, a majority of the cost savings are driven by the reduced consumable filter burden. In fact, Figures 3a, b, c, and d show a reduction in consumable costs for all volumes except the 1,000 L scale. As is the case with capital, for a reduction in cost to take place the rotor must replace a high dollar amount of filters than its own price point. This is highlighted well at the 3,000 L production volume where leveraging DynaSpin results in a ~37% reduction of consumable costs.

Buffer

The quantity of buffer usage in harvest is directly tied to filter count and therefore shows an identical pattern in terms of cost reduction. Single-use centrifugation via DynaSpin does not require any buffers to operate. Depth filtration, however, does. In a typical depth filtration process three different buffers are used to flush filters. They are water for injection (WFI), phosphate-buffered saline (PBS), and sodium hydroxide (NaOH). Because every filter must be flushed the cost of buffer per batch is directly correlated with the number of filters needed. Figures 3a, b, c, and d all show that buffer costs are less with DynaSpin at all volumes. Using the 3,000 L example again, using DynaSpin results in a ~33% cost reduction. It is also worth noting that reducing water usage can also save on energy costs from purifying large quantities per batch, and reduced need for warehouse space to store filters may also result in smaller operating footprints and CO_2 emissions.

Labor

Substantial filter requirements result in long setup and teardown time which subsequently impacts total labor costs. Depth filtration is by nature very labor intensive because setup alone requires time for material movement, filter housing installation, documentation, hydraulic compression and inspection, and tubing management. Teardown takes less time but still requires operators or remove the tubing, clean up each housing, and individually remove bag filters. The setup and teardown of a DynaSpin unit can happen faster due to the optimized design. Figures 3a, b, c, and d all show that labor is reduced across all volumes.

While the clear theme in each of these closeup looks is that filter reduction breeds cost savings, the most significant impacts are seen in both consumable and labor costs. A drug manufacturer can also expect these savings to scale proportionally with volumetric demand.

Spin it first: key sustainability considerations

Sustainability is rapidly, and rightfully, becoming a top priority for the biopharmaceutical industry. Before choosing single-use, a manufacturer must first decide between stainless steel solutions and single-use. Despite the irony of the name, it is well proven that single-use is the superior option in that it requires far less water, energy, and hazardous chemicals for cleaning and sterilizing. Myriad studies have shown this time and time again [1, 2].

For manufacturers that have already decided to leverage single-use technology in their workflow, there is still a need to improve, and waste reduction is naturally a major focus area. Technologies that require fewer consumables, therefore, become an exceptional option in achieving this. DynaSpin can be an ideal option because it achieves a more sustainable harvest by reducing solid waste, liquid waste, and space requirements.

Solid waste reduction

The physical waste generated by depth filtration is a challenge for facilities attempting to reach ambitious sustainability goals. Subsequently, the amount of plastic sent to landfills is always top of mind for drug manufacturers.

Depth filters act as a key contributor to this solid waste number. For example, a 2,000 L harvest that leverages 2-stage depth filtration contributes an average of 700 kg of solid waste from filters alone while DynaSpin contributes only 200 kg on average for the same volume. A facility performing 100 batches a year would reduce its annual solid waste contribution by 25 tons upon DynaSpin adoption.

For a broader look, Figure 4 shows the total filter reduction between the two types of harvest technologies across the already discussed volumes. On average, filter reduction is ~70% across all volumes when utilizing a DynaSpin harvest. The savings discussed at a 2,000 L level, therefore, translate proportionally across all other key single-use volumes shown. Put differently, manufacturers generate more than two and a half times the necessary solid waste by electing not to use a single-use centrifugation harvest.

Liquid waste reduction

The usage and disposal of liquid waste is yet another concerning factor in a manufacturing process. Flushing and equilibrating depth filters account for most of the water used for the entire batch biopharmaceutical production process. On average, over 9,000 L of water is needed for a 2,000 L harvest that leverages 2-stage depth filtration. The same harvest with DynaSpin averages only 2,600 L.

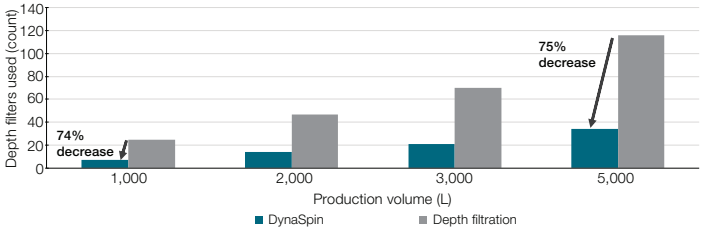

Figure 4. Total filters usage comparison: DynaSpin vs. depth filtration.

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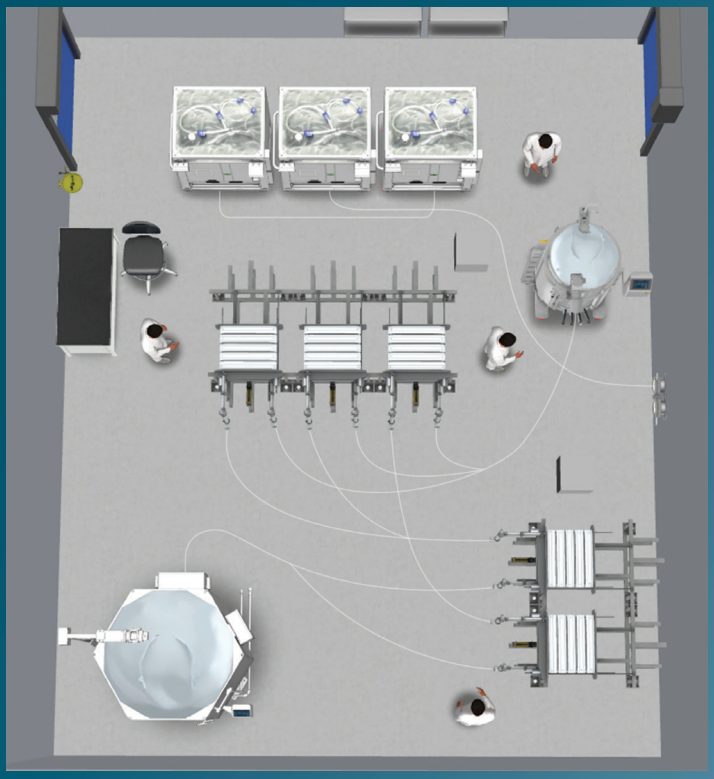

Figure 6a. Harvest suite layout for a 5,000 L bioreactor using depth filtration.

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

While water is the liquid most used, waste is also generated from the buffer, and sodium hydroxide is also used in the depth filter flushing process. Figure 5 looks at a 2,000 L example for all three liquids discussed. These reductions remain constant as harvest volumes increase from 2,000 L. When grouped together, total liquid waste is reduced by 78% on average.

Space and CO_2 reduction

If a harvest needs less equipment, consumables, and buffer, then it also needs less space to operate. The harvest burden for cleanroom HVAC is significant and must meet International Organization for Standardization (ISO) standards. Clean room infrastructure accounts for the largest electricity consumption in a process, and therefore is the biggest contributor to CO_2 emissions (depending on type of electricity production that is tied to a given facility, ie., coal, nuclear power) [3] . Reductions in cleanroom footprint are correlated with CO_2 reductions.

Figures 6a and b show a hypothetical scenario that helps illustrate this point. In them, two different harvest suites are shown. One on the left, where 2-stage depth filtration is used, and another on the right, where DynaSpin and filtration are leveraged. In both scenarios, 5,000 L of product are and the required equipment such as mixers, holding tanks, filter housings, and DynaSpin units are placed in the suite. The scenario on the right illustrates a harvest workflow with a significantly reduced footprint requirement compared to traditional workflow setups. Alternatively, the same size suite could process even more material.

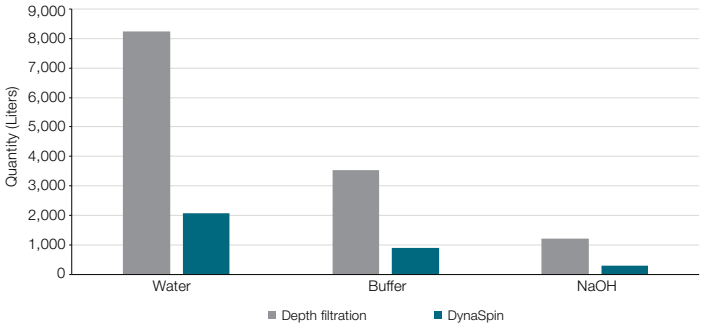

Figure 5. Harvest comparison: water, buffer, and NaOH reduction.

Conclusion

Two-stage depth filtration has long dominated the market as one of the primary harvest methods of choice for drug manufacturers. However, as single-use technology continues to advance into the larger-scale centrifugation realm, biomanufacturers would be wise to question their current and future harvest solutions. Thermo Fisher Scientific's DynaSpin single-use centrifuge emerges as an exceptional technology by creating cost savings while also being a more sustainable solution. Biopharmaceutical companies that manufacture their own drugs do so at less cost, with reduced waste, all while simplifying operations through automation. Contract development and manufacturing organizations (CDMOs) can benefit uniquely from leveraging DynaSpin because they capture the discussed improvements while also gaining ever-needed flexibility. For CDMOs, being able to do more with the same suite space is vital to optimizing profits. When assessing the cost and sustainability of the harvest step for the production lifecycle of a drug, single-use centrifugation is an optimal harvest option.

References

1. https://cdn.cytivalifesciences.com/api/public/content/digi-16801-original
2. https://bioprocessintl.com/manufacturing/supply-chain/environmental-impact-of-single-use-and-reusable-bioprocess-systems-183572/
3. Budzinski, Kristi, et al. "Streamlined life cycle assessment of single use technologies in biopharmaceutical manufacture." *New biotechnology 68* (2022): 28-36.

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