Single-use technologies

Top 5 considerations when making decisions for a more robust harvest

Sustainability, time, cost, space, and scale

Source: Thermo Fisher Scientific

Once a drug developer has identified a viable molecule, one of the more complex decisions that must be made is defining the process used to produce, harvest, and purify said molecule. There is a need for innovative single-use technology to support the monoclonal antibody (mAb), recombinant protein, bioengineered vaccine, gene therapy, and cell therapeutic segments, accommodating the market growth forecast in the coming years. With a growing need for optimization of processes requiring high cell densities and more efficient workflow steps to alleviate bioproduction bottlenecks, customers are seeking robust innovations in the harvest step to address unmet needs they are facing. More specifically, those needs often revolve around finding ways to drive down operational costs while still managing to develop a process that is sustainable.

For secreted biologics produced in a batch process, the harvest process requires the full bioreactor volume until all the drug products have passed through the harvest equipment and are ready for the downstream purification step. Historically, many facilities used stainless steel centrifuges, which require steam-in-place (SIP) systems to be run between batches to assure regulatory compliance and sterility. In contrast, depth filtration is a much more flexible technology in relation to scalability and uses a series of filtration steps to remove waste from wet biomass. Many modern harvest steps have become more abbreviated and result in less exposure. 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. Selecting one type of technology and process over another requires an assessment of facility operations, cleanroom space, labor expenditure, ongoing cost support, and upfront capital expenditure investment.

Sustainability

Using this perspective to evaluate the harvesting step of bioprocessing allows us to determine what process technologies lead the charge in the sustainable harvest.

Time

Time is associated with process efficiency, such that, the higher the process efficiency, the lower the time required to complete a run, and the less energy is expended over the length of the workflow.

Cost

Keeping costs low is essential to achieving return on investment (ROI) and margin targets.

Space

When selecting a harvest technology, a company must be cognizant of how much space is required to properly run the harvest, store the materials needed for each run, and accommodate room for additional inventory to alleviate supply concerns.

Scale

The ability to use the same technology across all phases of the development cycle is desired, but different solutions may only be optimal for specific volumetric ranges.

Sustainability

Sustainability is becoming a more critical topic within the biopharmaceutical industry. Using this perspective to evaluate the harvesting step of bioprocessing allows us to determine what process technologies lead the charge in the sustainable harvest. When it comes to creating products and processes that support sustainability, a few contributing factors make up most of the overall usage, including energy consumption, plastic usage, and chemicals required for processing. Finding tangible ways of reducing each of these areas can result in cost and efficiency savings over time.

Depth filtration requires a vast amount of water, buffer, plastic packaging, and labor, all of which increase linearly with processing volume. This means that filter reduction is vital to achieving an organization's sustainability goal.

Sustainability focal points within consumable reduction, harvest space reduction, and material reduction are areas that conscientious process design could immediately address. For both filtration and centrifugation harvest steps, the use of consumable filters is required. See Figure 1a–b for a visual description of the filters required for both depth filtration (Figure 1a) and centrifugation (Figure 1b) processes.

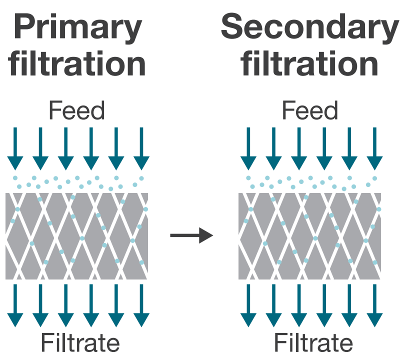

Figure 1a. Depth filtration process.

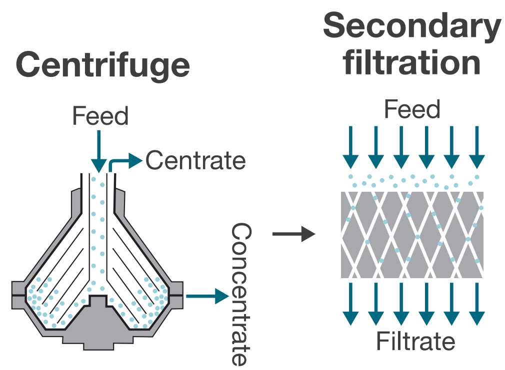

Figure 1b. Centrifugation process.

Consumable requirement

Within consumable usage, there are both direct and indirect factors that contribute to the sustainability of a harvest process. For example, filters are directly tied to the sustainability of your harvest step due to their requirement to complete operational processing. Alternatively, the amount of buffer and consumables used for buffer preparation (i.e., single-use mixer bags) would indirectly contribute to plastic usage.

Depth filtration naturally has a higher consumable counter due to the use of filters in both primary and secondary filtration steps. Centrifugation limits consumable usage, with complete elimination in some processes and reduction in others. Additionally, the better the separation a given centrifuge can achieve, the fewer filters are required to process the full volume. When choosing a specific technology, a firm needs to seriously consider how many filters will be required to harvest a product, and how consumable usage compares to alternative products that may reduce the number of filters needed to support the harvest process. This decision can make or break the goal to limit plastic usage for sustainability efforts.

Harvest suite space requirement

The sustainability perspective within bioproduction needs to be shifted to account for the highest percentage of contributing factors; therein lies an avenue for meaningful cost and efficiency savings across the overall workflow. As shown in the research [1], the biggest contributor to environmental impact is the electricity used to operate a plant. The authors suggest that any reduction in plant size or time to produce a product can result in lower energy required per dose of the final therapeutic product. Cleanroom footprint investment per stage of the production workflow can translate to smaller physical space required for top operational efficiency, and therefore a lowered overall facility energy expenditure. Filter stacks may be vertical or horizontal in orientation within the harvest shell. The surface area reduction of that equipment can be significant, especially in horizontally oriented depth filters within harvest technologies. The type of filter you select is process-dependent, and switching from horizontal to vertical filter orientation within the same unit type is impossible.

Careful consideration of filter orientation based on unit type will allow for optimization of the cleanroom footprint in models that have a horizontal filter orientation. This logic means that minimizing the cleanroom space needed for the harvest unit operation is pivotal to a firm's carbon footprint associated with operations geared toward that specific process.

Buffer requirement

Material usage, much like consumable usage, also has an area of impact in terms of sustainability. Material usage is skewed depending on the technology type used, depth filtration verses centrifugation, and whether the process uses stainless steel systems or single-use technologies. Direct contributors include buffers used to flush filters, water for injection (WFI), and clean-in-place (CIP) and steam-in-place (SIP) systems required to sanitize any stainless steel equipment. Indirect contributors could include any supportive auxiliary equipment used for harvest sterilization. Process design to reduce materials required to support traditional harvest methods is yet another key factor in having a green harvest.

> "Effective processes must achieve harvest within a reasonable and designated time period based on the needs of each particular cell line."

Time

During the product harvest step of bioprocessing, the longer a substance sits waiting for separation, the higher the increased risk of aggregation and settling. Time is associated with process efficiency; the higher the process efficiency, the lower the time required to complete a run, and the less energy is expended over the length of the workflow. Effective processes must achieve harvest within a reasonable and designated time period based on the needs of each particular cell line. Time from a process molecule perspective is about limiting protease and DNase activity in the culture that may begin to degrade the product. As cells die, their internally stored proteases and DNases are released into the cell culture and they can begin to damage the molecule of interest. The overall theme is the greater the time, the greater the risk to the process. Some processes have a room-temperature stability requirement to harvest, while cell viability is still high enough to eliminate any waste present in the culture that may pose a threat to the integrity of the product and to get the product through and away from any threats as quickly as possible. Beyond viability, a firm must also consider the rational implications of having a particularly prolonged harvest span of two different operations shifts, adding room for communication breakdowns that lead to unintended deviations and potentially jeopardize the integrity of the final product.

Speed of harvest is a factor measured by the influence of a few key variables depending on the specific type of technology used (i.e., centrifugation versus depth filtration). In traditional depth filtration, flux, measured in liters per minute per meter squared, is the determining factor for how quickly a product can be pulled down from a bioreactor. As the flux increases, the rate at which the contents of a reactor can be harvested increases in parallel. However, achieving a quicker harvest with depth filtration means one must either use more filters (and thus more space) or achieve a higher flow rate without compromising the product or the process.

In centrifugation, the key variable is flow rate, measured in liters per hour. Higher flow rates translate to a quicker harvest. However, centrifugation will have a range of revolutions per minute (RPMs), with different cell lines having different optimal ranges. This range is designed to minimize product shear and turbidity, as well as to ensure that operational safety of the instrument is maintained.

Cost

Cost is a crucial factor in picking the right harvest process. Keeping costs low is essential to achieving ROI and margin targets. Some technologies may be more capital-heavy, while others have high consumable costs per batch.

The cost of depth filtration is driven, in part, by the consumable expense associated with each batch. Filters are only used once, then must be disposed of properly. Because certain depth filtration processes require a primary and secondary filtration step, a substantial number of filters are required to meet process needs for both steps. The setup and takedown of these filters also incur significant labor costs, as filters must be placed in housing, wiped down, connected to tubing, and flushed before being used. After use, the filters must be disconnected from their tubing, removed from the housing, and transferred to their next location for disposal.

Centrifugation can be done with either stainless steel or single-use systems. Single-use centrifugation leverages a consumable, filters, and tubing that can only be used once. The stacks or filter housings are present to hold any additional filters that may be required for operation. For stainless steel processes, the CapEx of the centrifuge is on a 7- to 10-year depreciation schedule, the filter stacks are equivalent in cost to the single-use alternative, and the capital depreciation on inline pumps adds to the overall cost of investment and continued operation. For stainless steel systems, capital is the most significant expenditure. These systems require little to no consumables per run but must be meticulously cleaned with CIP and SIP systems after each run and incur follow-up validation runs to confirm cleanliness. This requires additional auxiliary equipment to ensure proper sterility. This capital-intensive technology requires a firm to invest more money upfront but may result in lower batch costs due to the lack of required consumables. For single-use systems, capital investment is much lower, and CIP and SIP systems are not needed because rotors are replaced after each run. This requires more per-batch consumable spending but is significantly less than what is required for traditional depth filtration.

It is important to note that centrifugation is followed up by secondary filtration, which is typically done using depth filters. Thus, from a cost perspective, one must consider if the primary filtration step is less expensive using depth filtration or centrifugation. One must also consider how each technology might impact the filter performance and subsequent cost needs of the secondary filtration.

“The more consumable-heavy a process is, the more space is needed to meet all these needs.”

Space

When selecting a harvest technology, a company must be cognizant of how much space is required to properly run the harvest, store the materials needed for each run, and accommodate room for additional inventory to alleviate supply concerns. The more consumable-heavy a process is, the more space is needed to meet all these needs. In that sense, companies must consider how the need for extra space might impact the size of the manufacturing facility and its warehouse, and the costs associated with building, operating, and maintaining these spaces.

Depth filtration, which has already been established as a consumable-heavy technology, is likely to have the most significant space requirement. Depth filtration scales linearly with the size of the operation, while centrifugation does not. Given this, large-scale manufacturing requires a sizable suite to accommodate a considerable number of filter housings, as well as space to operate them. Larger cleanroom space will inevitably be associated with higher utility costs and incur an increase in the construction bill. Additionally, a high number of depth filters would need to be stored in a warehouse and would take up extra space as the process size increases.

Centrifugation, however, does not require nearly the same amount of space, as it replaces the primary filtration stage and can cut back the number of filters required for the second filtration stage. This generally makes centrifugation more advantageous at a large scale.

In the case of single-use centrifugation, additional rotor consumables would need to be stored; and for stainless steel, it’s possible that the needed auxiliary cleaning equipment may require additional space (example: hold-and-kill tanks as well as space for additional CIP and SIP equipment that will be needed).

Space is a crucial factor to consider because it directly correlates with cost. Beyond cost, some companies may need to minimize the footprint of their plant because they operate in areas with a high metropolitan density (example: building a manufacturing site in Logan, Utah, USA vs. Boston, Massachusetts, USA).

Conclusion

A major challenge with late-phase production of any molecule is determining what type of processes will work best based on individual operational bioprocessing needs. Stainless steel centrifugation requires significant capital and facility investment, with CIP and SIP systems taxing both the facility during installation and, once finalized, the labor for operational expenditures. The value of stainless steel centrifuges is not recognized until significantly larger volumes are reached, and, therefore, ROI is deferred until the facility reaches the preplanned maximum volumetric capacity. These challenges have led many customers to single-use systems as a more sustainable and cost-effective alternative to stainless steel.

The standard depth filtration process consists of two filtration stages, one for primary filtration and a second to reach the purification parameters required for each specific molecule. Depth filters are challenged at this scale due to the sheer number of filters required, regardless of the manufacturer. Massive numbers of depth filters always translate into a heavy dependence on supply chain, increased complexity in facility logistics and storage, increased cleanroom footprint requirements, significant buffer requirements (and associated components e.g., water for injection, mixing vessels, filters), and increased labor and manual contact at every step. Considering the perspective of sustainability, time, cost, space, and scale will allow companies to thoroughly evaluate the key harvest considerations that contribute to cost and operational efficiency savings.

Reference:

1. Budzinski K, Constable D, D'Aquila D, Smith P, Madabhushi SR, Whiting A, Costelloe T, Collins M. Streamlined life cycle assessment of single use technologies in biopharmaceutical manufacture. *N Biotechnol.* 2022 May 25;68:28-36.