White paper | Manufacturing

Single-use technologies

Single-use vs. stainless steel

The biopharmaceutical manufacturing debate

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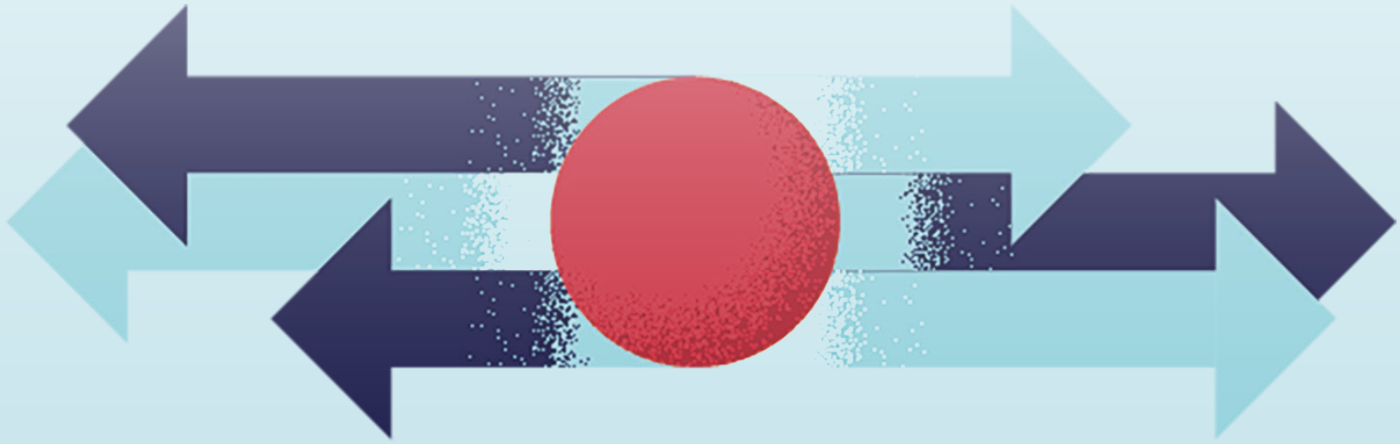
Introduction

Single-use technologies (SUT) and stainless steel are two widely used options in bioproduction. Original biomanufacturing processes were developed for producing sub-gram/L titers with a standard workflow that applied to most biologics manufactured. With sizeable patient populations and demand for large product volumes, commercial-scale manufacturing via stainless steel bioproduction dominated the market even after the first single-use bioreactor emerged during the late 1990s. Adoption of single-use technology was initially slow, with concerns regarding sustainability, operational equivalence, leachables and extractables, and scale limitations leaving companies skeptical about whether single-use was a viable option at the larger scale operations that were employed. As the therapeutic landscape has evolved with greater process intensification resulting in higher-yielding production, in smaller volumes, greater flexibility in manufacturing that single-use technologies offer has come to be seen as a superior option compared to traditional stainless steel systems. Single-use technologies offer several advantages in terms of flexibility, capital costs, and reduced downtime. They can be quickly scaled up or down, allowing for rapid changes in production volumes. Additionally, disposable elements of single-use technologies can be quickly assembled and disassembled, reducing the amount of downtime needed for cleaning, sterilization, and maintenance. This can allow for faster turnaround of the GMP equipment thus leading to faster production cycles and greater productivity. The ability to customize single-use technologies for specific production processes allows for greater flexibility in process development and optimization.

Here we outline several advantages and disadvantages of single-use technologies and stainless steel systems focused on performance, adaptability, and economics. We also highlight the continuous improvement opportunities offered by the flexibility of implementing single-use technologies.

Keywords
Single-use technology, stainless steel, bioproduction, biomanufacturing, sustainability, flexibility, quality, scale, modularity, risk mitigation, performance, differentiation, continuing improvement, DynaDrive, DynaSpin, harvest, bioreactor



Single-use vs. stainless steel debate

Biopharmaceutical manufacturing relies on a series of equipment within the overall bioproduction workflow, which can be made of either single-use or stainless steel materials. Evaluating these options in terms of sustainability, flexibility, scale, and cost is essential to choose the best fit for a specific application. The debate between using stainless steel and single-use technologies for bioproduction centers around the advantages and disadvantages of each option [1–5].

The argument for single-use versus stainless steel can be complex and depends on a myriad of scenarios, with factors including molecule type, range of titer, cell density, demand phase (i.e., pre-clinical, early-phase, late-phase clinical, commercial), patient population, single-product vs multi-product facility, the quantity of product, and facility type (i.e., new facility, existing facility, hybrid adoption, complete SUT adoption) weighing on the decision for one over the other. Other factors to consider are run rate and the number of molecules to change at the site, including tech transfer and downtime for the site involved.

Table 1.

Area of focus	Benefits of single-use	Benefits of stainless steel
Sustainability	Lower facility water and energy requirements, personnel time, lower contamination potential, quicker turnaround	Reusability, recyclability at end of life
Flexibility	Multi-product capability and process flexibility, quicker adaptation to newer technologies, easy reconfiguration with modular designs, no CIP/SIP validation required	Durability, higher capacity
Scale	Rapid scale-up, customization, reduced downtime, quicker facility design and commissioning	Large volume 10,000 L+ available, long-term durability
Quality	Supplier-centered change control, no batch-to-batch production contamination, no soil carry-over, consistent product-contact materials	Existing documentation and processes, end-user-centered change control, consistent product-contact materials
Cost/speed	Significantly lower capital expenditure, quicker facility build time, ballroom design with closed system processing increases efficiency of operations	Lower annual operating costs

Sustainability: Implementing circular economy concepts, such as recycling and reuse of single-use components, can mitigate the negative environmental impact of single-use technology [6]. Single-use bioreactors (S.U.B.s) have been shown to greatly reduce water consumption and facility energy use when compared to stainless steel bioreactors (SSBs). However, the disposal of single-use components raises concerns regarding waste generation and potential environmental impacts. Life cycle assessments (LCAs) comparing S.U.B.s and SSBs have shown that the environmental impact of both systems are highly dependent on manufacturing conditions and disposal practices [2]. Lastly, tremendous strides are being made in SUT sustainability from materials to packaging to regional manufacturing and distribution.

Flexibility: SUT offers increased flexibility due to shorter set-up times, lower cleaning requirements, and easier customization of reactor size and configuration. This is particularly relevant for research and development (R&D) applications, where process development is ongoing and production volumes are low. Making volume projections are difficult and variable without the knowledge and planning for large-scale manufacturing facilities to support the commercialization stages. The magnitude of investment required for a large-scale stainless steel facility build-out is substantial and requires a balance of both timelines for execution as well as the return on investment (ROI) for larger steel facilities. The modularity of single-use offers an alternative way to add flexibility into the timing for a build-out, deferring major capital thus allowing for the minimization of risk. SUT has been shown to be far more useful in multi-product facilities and in instances where process flexibility, in terms of volumes and product requirements, is paramount. While SU can still deliver great benefits for most large-scale molecule development processes, some of the largest commercial-scale molecules may see economic benefits of SS that may outweigh the flexibility benefits of SU.

Scale: SSBs are well-established for large-scale biopharmaceutical production. However, their size and installation requirements can limit flexibility, especially when considering production phases and required material for clinical studies. In contrast, SUT offers reduced immediate scale but can be easily multiplexed, allowing for the production of large batches while reducing the need for dedicated infrastructure. Facility setup and commissioning becomes simpler to accomplish with SUT, leading to easier adjustments and adaptation of newer technologies within the various unit operations.

Quality: Existing quality process controls can be implemented with either technology with adaptation depending on need. Consideration must be made about the supply chain and control around material availability. Stainless steel requires the end user to control and update their own processes and components. Whereas, SUT suppliers own the quality and documentation aspects of their own products, including multisourcing of reactor and single-use components removing this burden from the end user.

Cost: The choice between single-use and stainless steel technology can significantly impact capital expenditures (CAPEX) and operating expenditures (OPEX). The importance of considering both CAPEX and OPEX in decision-making suggests that a streamlined LCA approach can aid in evaluating the economic and environmental implications of different technology choices [7]. Single-use and closed systems processing allows for all unit operations to be housed within a ballroom clean room set-up, with unit operations consolidated into designated suites for either upstream or downstream bioprocessing. Stainless steel facilities by nature of cleaning, sterilization, and preventative maintenance procedures, necessitate systems to be open, creating the need for separate spaces to hold each individual unit operation. This more dispersed segmentation exhibits physical barriers and creates a need for changing gowns between spaces as well as slowing the redirection of staff moving from one location to another. This introduces inefficiencies to the overall operational workflow. Single-use facility design saves time and efficiency in cross-training, labor operations, and applies a better utilization of resources which over time may contribute to cost savings measures.

SUTs have a lower upfront CAPEX due to reduced infrastructure requirements but come with increased OPEX spend due to higher use of consumables that require disposal. It can be easier and quicker to obtain target return on investment (ROI) for single-use allowing for more rapid scale-up or scale-down depending on demand. In contrast, stainless steel technology requires significant upfront investment but can provide long-term cost savings due to its durability and reusability; however, OPEX spend with stainless steel systems is also significant in terms of water use, personnel time and validated clean-in-place (CIP) and sterilization-in-place (SIP) processes.

Manufacturers are constantly looking for options to improve the economics and sustainability of bioproduction. Advances in single-use consumables, products, workflows, and control schemes are being developed to further improve economics and sustainability. For example, next-generation S.U.B.s, which incorporate advanced sensors and automation, can reduce the risk of contamination and improve process control. Overall, the debate between using stainless steel and single-use technologies for bioproduction ultimately comes down to the specific needs and goals of the production process, as well as the economic and environmental considerations of each option.

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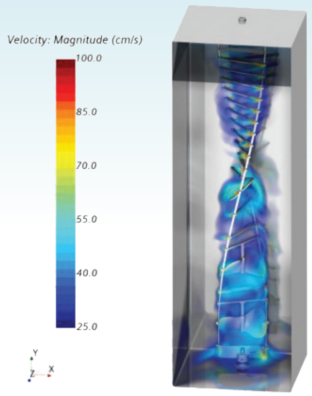

Figure 1a. Fluid velocity profile for the 500 L DynaDrive S.U.B.

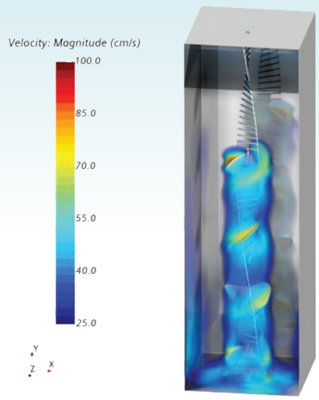

Figure 1b. Fluid velocity profile for the 5,000 L DynaDrive S.U.B.

Table 2.

Parameter	2,000 L S.U.B.	5,000 L S.U.B.	10,000 L Stainless
Gas entrance velocity	Low	Mid	High
Mean shear rate	High	Low	Low
Mean bubble residence time	Low	High	High
Gas hold-up	Low	High	Low
Bubble rise velocity	Low	High	Mid
Mean bubble diameter	Low	Mid	Low
Systemic k_La	Low	High	Low
Localized k_La	narrow	broad	broad
Localized fluid velocity	High, narrow	Low, narrow	High, broad

Performance

An ongoing consideration in the choice to use S.U.B.s ultimately lies in the performance of the reactor. Chosen operational parameters, including agitation and gas flow rates, affect numerous sub-parameters such as fluid velocities, liquid shear stress, and oxygen and carbon dioxide mass transfer. These are all affected by impeller size and design, sparger design and operating conditions, tank shape, and liquid column height. Most S.U.B.s are designed based on established principles developed in legacy stainless steel systems but are adapted to the unique limitations required by single-use manufacturing.

Each S.U.B. manufacturer strives to push the performance envelope, using stainless steel systems as a general benchmark while considering operational requirements set forth by customers. Studies to highlight these performance attributes can include mass transfer studies, mixing studies, and computational fluid dynamic analysis.

Higher more efficient k_La: A comparison of the 2,000 L Thermo Scientific™ HyPerforma™ S.U.B., the 5,000 L Thermo Scientific™ DynaDrive™ S.U.B. and a 20,000 L traditional stainless steel bioreactor was completed previously [8]. The presented CFD studies considered gas exit velocity from the sparger, mean bubble shear rate, bubble residence time, gas hold-up volume, oxygen mass transfer, and liquid velocity profiles (Table 2). For the DynaDrive S.U.B. specifically, the bioreactor design allowed low bubble shear effects while offering significantly longer bubble residence time and gas hold-up volume resulting in nearly a 2X mass transfer increase within the design constraints of each reactor type. Similarly, liquid velocity, which correlates to the amount of shear stress cells are exposed to during a process, was shown to be greatly diminished in the DynaDrive S.U.B.

Scalability: The authors highlight the need for a bioreactor to scale properly and the balance of operational parameters when considering control schemes. For example, the high performance of the DynaDrive S.U.B. allows for adjusting both mixing and gassing setpoints to tune the reactor for optimal mass transfer and mixing. This becomes important as a process is developed to allow for proper mixing of feeds and reagents to balance pH and nutrients. If a high-demand culture uses the maximum allowable performance of a bioreactor, tuning these parameters becomes a limitation. The maximum performance of the DynaDrive S.U.B. allows for this type of operation while the stainless steel system may display limitations.

Bioreactor scalability, both across vessel sizes and from various manufacturers, is important as processes are further developed, and larger quantities of molecules are required for clinical or commercial manufacturing. Several studies were completed showing the performance of the DynaDrive S.U.B. compared to various alternatives [9–11]. In each study, the DynaDrive S.U.B. was shown to easily provide sufficient operational conditions to achieve similar cell growth profiles while maintaining both product quantity and quality. Scalability from small volume to large volume with simple parameter adjustments leads to confident process transfer and scaling.

High density cell growth: Importantly, the DynaDrive S.U.B. has been shown to support high cell density processes in line with current process demands. Cell densities in excess of 200 x 10^6 cells/mL have been reported [12, 13] while using less than 50% of the maximum performance capacity of the S.U.B. Culturing at such high densities enables manufacturers to reduce operating volumes with intensified processes.

Differentiation

The benefits of SUT compared to stainless steel have been significantly highlighted in economic models comparing total cost of ownership or net present cost when considering capital purchases, recurring consumables costs, and facility buildout and resources. Hardware for SUT and associated facility footprint and utilities are significantly less expensive than stainless steel counterparts. The low upfront capital expenses and potential market exit costs of single-use facilities provide economic flexibility that stainless steel facilities cannot offer when considering total bioproduction capacity and molecule pipeline approvals.

For example, economic models comparing net present cost (NPC) for multiplexed 2,000 L HyPerforma S.U.B.s, 5,000 L DynaDrive S.U.B.s, and 15,000 L stainless steel systems are shown in Figure 2 [14]. The cost of build-to-suit bioproduction facilities, which can take several years to design, build, and qualify (IQ/OQ) are represented by the left-most point of the figure for each facility type. Here, single-use facilities show dramatically lower costs while facility development and deployment timeframes are also significantly shorter. The addition of new facilities as production demand increases are represented by stepwise increases seen in each curve. Concurrently, annual operating costs for each facility, including depreciation and discounting based on run-rate, are represented by the slope of each line. Factoring in molecule demand increases over time as well as these capital and operational costs, facilities based on the 5,000 L DynaDrive S.U.B. are shown to have reduced NPC over up to a 30-year lifetime or 6,000 kg/yr demand.

Another thing to consider when approaching final capacity demand is continuous product and process improvements. While a stainless steel facility must be a build-to-suit at maximum capacity, this can lead to complete standardization of process regardless of running from hundreds to thousands of kg/yr demand. While standardization can be beneficial to consistency of product, this can lead to eventual inefficiencies when considering advancements in bioprocess operations.

For example, if new technologies are to be considered to reduce costs or offer higher productivity or yield, these elements are very difficult to introduce into an established stainless steel facility. Conversely, as molecule demand increases and new single-use facilities are planned and brought online, state-of-the-art technologies can more easily be introduced.

When considering global expansion, bringing product manufacture close to patient populations, as well as diversification of operations to avoid single-point facility failure, the economics offered by SUT are clearly identified. Ultimately, biomanufacturers facing small pipelines and low production demands will rarely, if ever, reap the economic return of scale offered by large stainless steel facilities. Similarly, for larger biomanufacturing, single-use facilities can help reduce capital and annual operating costs while providing sufficient operational capacity to support even robust molecule demand.

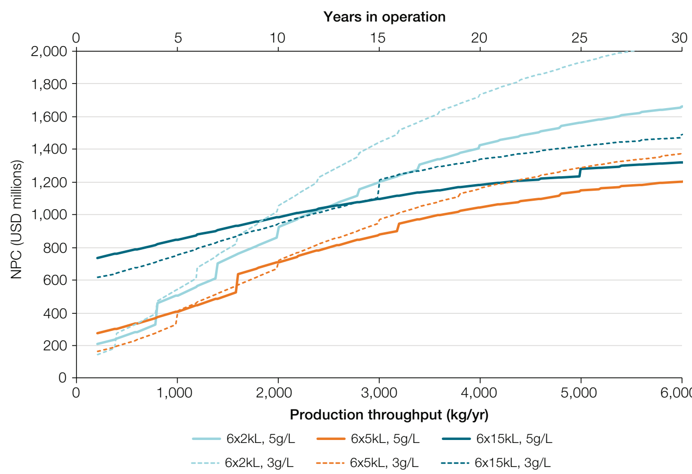

Figure 2. Perspective of total facility ownership costs in terms of net present cost (NPC); discounted operating costs are captured in the primary slopes of the lines. Steps in the lines represent discounted costs of a new facility required to support production demand. Data are at a 200-kg/yr/yr production ramp.

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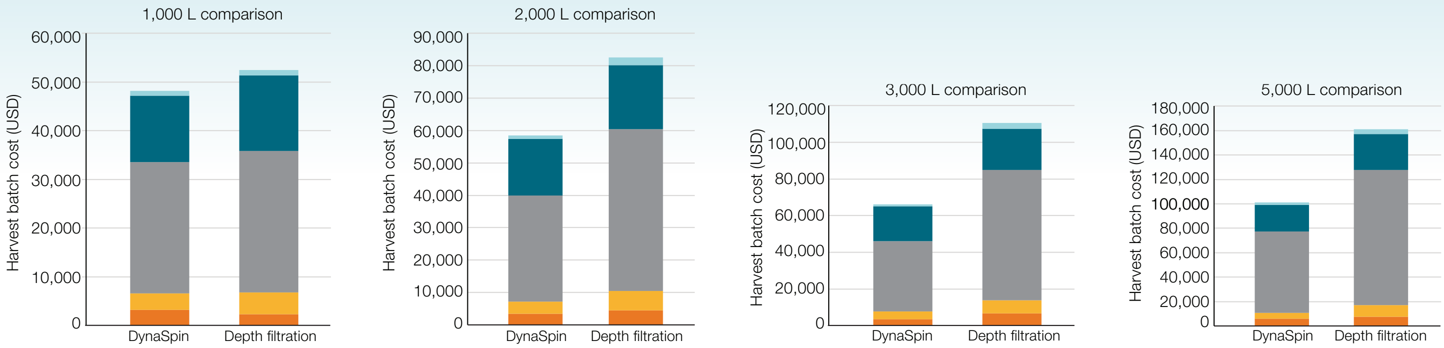


1,000 L	DynaSpin	Depth filtration
Total other	1,025	1,128
Total labour	13,589	15,548
Total consumables	26,948	28,996
Total materials	3,438	4,499
Total capital	3,195	2,331

2,000 L	DynaSpin	Depth filtration
Total other	1,070	2,292
Total labour	17,416	19,727
Total consumables	32,817	49,955
Total materials	3,685	5,947
Total capital	3,464	4,558

3,000 L	DynaSpin	Depth filtration
Total other	1,133	2,949
Total labour	19,083	22,576
Total consumables	38,420	71,254
Total materials	3,993	6,986
Total capital	3,587	6,688

5,000 L	DynaSpin	Depth filtration
Total other	1,928	3,793
Total labour	21,550	29,590
Total consumables	66,806	110,550
Total materials	4,717	9,465
Total capital	6,019	7,637

Figure 3. Harvest batch costs comparing DynaSpin versus depth filtration at various volumes.

Continuing improvement

Technologies continue to evolve, and manufacturers are finding better ways to increase cellular yield, efficiencies in bioproduction workstreams, and improved products to drive efficiencies for each unit operation. SUT offers distinct advantages, especially when considering time to expand facility capacity and evaluation periods for the newest technologies (15). Improvements for all aspects of single-use are constantly being sought to even replace other existing single-use offerings.

Increasing SUT harvest challenges: As processes intensify, resulting in higher cell densities or product volume increases, newer strains on the full bioproduction workflow have been realized. Intensification is especially impactful for traditional single-use harvest and clarification e.g. single-use depth filtration. Clarification in this instance is directly proportional to cell densities and process volumes which requires undesirable increases in filter surface area and equipment footprint to accommodate the newest high-intensity processes. New products, such as the Thermo Scientific™ DynaSpin™ Single-Use Centrifuge, can help alleviate some of the constraints placed on these processes. These efforts showcase vendors striving to offer continuous and automated approaches to assist in difficult unit operations.

Single-use centrifugation vs depth filtration: Comparing the DynaSpin vs traditional depth filtration options, the data in Figure 3 show clear cost savings, especially in labor and consumables [16]. This is highlighted well with the 5,000 L scale showing reductions of 37% in consumables costs and up to 33% in overall costs. Some of these savings are due to significant reduction in water use which further reduces energy costs of producing water and buffers for flushing the filters (Figure 4).

In terms of sustainability, one must consider liquid waste, solid waste, and facility footprint. Energy requirements to produce water and consumables, material production costs from a consumables and energy standpoint, energy requirements for facility HVAC all lead to significant economic and environmental impacts. The DynaSpin greatly assists in reducing floor space in modern facilities, further reducing facility energy costs.

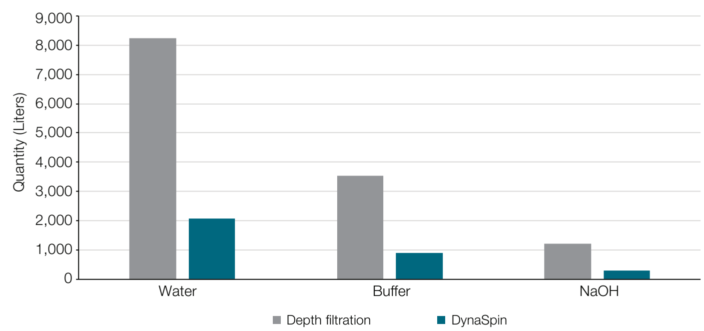
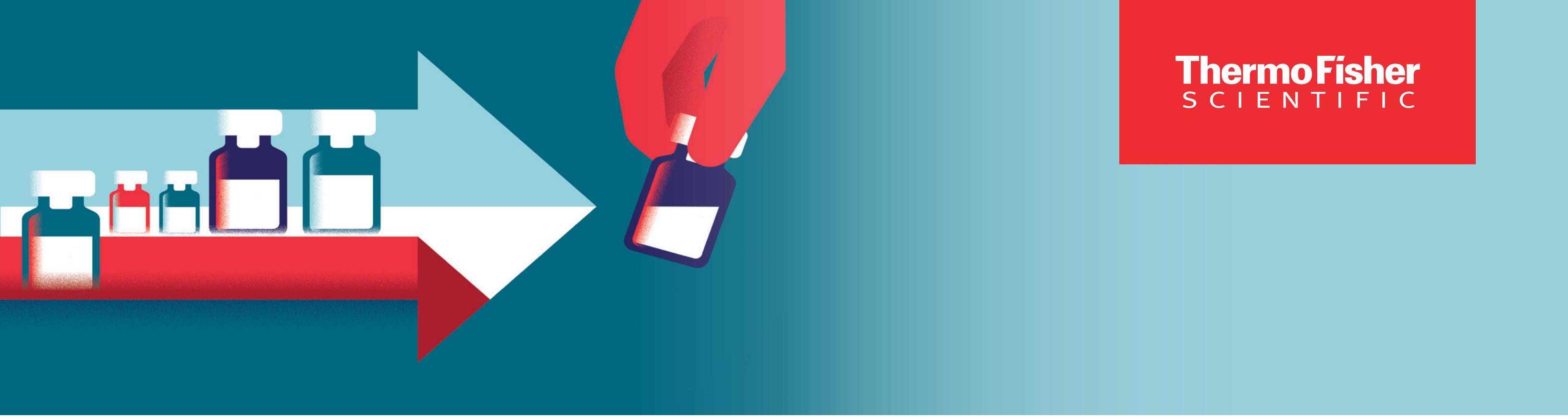


Figure 4. Harvest comparison: water, buffer, and NaOH reduction.



Conclusion

SUT has driven significant changes in the biopharmaceutical industry in recent years. The increasing use of SUT has been one of the largest contributors to process intensification and offers several advantages, including greater flexibility and cost-effectiveness while reducing the risk of cross-contamination. SUTs are seen as more sustainable than traditional stainless steel, as they require less energy and water, even with the understanding that their use does pose challenges, such as concerns about consumable and plastic waste. By utilizing single-use technologies, companies can alleviate risk and reduce costs associated with upfront capital expenditure, decrease the time needed for stainless steel facility construction, and minimize the financial burden of decommissioning a facility if a product fails to progress to clinical stages. Additionally, while there are still some concerns around potential impact and LCA, the benefits of flexibility, scalability, performance, and sustainability make single-use an attractive option for many biomanufacturers. Lastly, SUT suppliers are continuing to push for advancements in these technologies to improve performance and sustainability overall.

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