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Application Note 02

Sustainability of single use technologies in biopharmaceutical manufacturing

Joris Van de Velde, Matthew Peters, Caitlin Wold and Carolina Riba,*
3M Separation and Purification Sciences Division, 3M Center, St. Paul, MN

Introduction

Over the past years, the understanding and awareness of climate change and sustainability has continued to increase. Companies in all sectors, including biopharmaceutical manufacturing are evaluating their operations and have committed to take action and set more ambitious goals for reducing their environmental impact. At the same time, the amount of single use technologies being utilized in bioproduction facilities continues to increase [1]. Single use products offer many benefits in biopharmaceutical manufacturing, including more flexibility, lower capital investments and less cleaning requirements. However, single use products typically result in more raw material consumption and waste generation. When considering the flexibility, affordability and maintenance benefits of single use systems in biopharmaceutical manufacturing, it's important to account for their environmental impacts relative to traditional systems through a life cycle perspective. It should be recognized that multiple environmental factors (e.g. carbon emissions, water consumption, energy use, etc.) should be accounted for in assessing relative product sustainability. There are often trade-offs between environmental factors and rarely does one product have lower environmental impacts across all impact categories than an alternative.

The first section of this document provides a general comparison of single use technologies in biopharmaceutical manufacturing (SUT) versus the traditional, reusable technology and is based on a review of available literature on this topic. The second part of this application note describes a case study for a fully single use facility and is based on process modelling. It includes an evaluation of advanced single use 3M products and solutions, and their impact on PMI and other parameters. The last section suggests potential strategies for reducing the environmental footprint during the use phase of biopharmaceutical manufacturing. The evaluation of single use technology in this document refers only to the manufacturing of recombinant protein therapeutics and does not apply to other industries or applications.

Part 1: Single use versus reusable technologies in biopharmaceutical manufacturing: review of literature

Single use versus reusable technologies in biopharmaceutical manufacturing: summary

- Several studies reported that the SUT scenario had lower environmental impacts than a stainless-steel system, particularly in water and energy consumption during the use phase. A very large part of the environmental impacts for both systems occurs in the use phase [2] [3].
- Traditional facilities typically consume substantially more water and energy in the use phase than facilities using SUT due to the energy used to operate equipment as well as to produce and supply water-for-injection and steam for cleaning and sterilization [4].
- SUT typically incur larger environmental impacts during both supply chain and end of life phases due to raw material extraction, processing, manufacturing, transportation, and waste management of consumables [3].
- The location of the facility significantly affects environmental impacts, especially climate change, due to its implications on energy grid mix, water scarcity and proximity to logistics hubs [3] [5].

*Contact: Joris Van de Velde at jvandevelde1@mmm.com

Multiple studies showed lower impacts across different environmental impact categories for SUT compared to traditional systems. This may sound counterintuitive but has been the conclusion of different scientific studies [2] [3] [4] [5] [6].

The impact can be split into multiple life cycle stages: supply chain phase, use phase and end-of life. The supply chain phase includes the material sourcing, manufacturing, and distribution of consumables. The use phase is the therapeutic protein production process, including the sterilization and cleaning. End-of-life is the disposal and/or recycling of consumables and equipment.

In traditional systems, most of the environmental impacts occur in the use phase. Steam-in-place (SIP), clean-in-place (CIP) and water for injection (WFI) preparation are highly energy-intensive and are responsible for the bulk of the facility footprint. The unit operations with the highest PMI are typically the support CIP/SIP system, followed by the protein A column and the production bioreactor, according to literature [2] [4]. SUT minimize the need for cleaning, thereby reducing energy and water consumption in the use phase [3] [6]. One study for a model, single-use facility demonstrated 87% reduction in water use, 30% lower energy use and occupied 38% less space than its stainless-steel alternative. As a result, a 25% carbon footprint reduction can be expected [7].

SUT generally have a higher impact than stainless-steel operations in terms of material sourcing, manufacturing of consumables, distribution, and end-of life phases. One life cycle analysis (LCA) study found that the supply chain and end of life may represent less than 10% and 1% of the total life cycle impacts, respectively [4]. Another study attributed a higher impact to the supply chain (>50%) but concluded that end-of-life had a negligible contribution [3]. Due to its relatively minor impact on the overall results, diverting materials from landfill towards recycling or waste-to-energy may have minimal effect on the overall results.

Environmental impacts, particularly climate change, are highly sensitive to the location of a biopharmaceutical manufacturing facility. Geography determines how the electricity in that region is produced (high vs low CO2 emission energy sources), as well as the distance between the facility and its suppliers [3] [7]. Local water availability and access will determine its priority among other environmental impacts.

Part 2: Process modelling case study of a single use facility

3M single use technologies

3M offers a variety of single use products for the biopharmaceutical manufacturing industry, including depth filters, membrane filters, chromatographic clarifiers, and membrane chromatography devices. The newest 3M technologies were designed to enable advanced process intensification and compression. This section will explain how advanced SUT can make processes more efficient, thereby reducing their environmental footprint in the use-phase.

- **3M™ Harvest RC Chromatographic Clarifier** is a single stage clarification solution for CHO cell cultures. The technology uses charge rather than size for separation, allowing cells, cell debris and DNA to be cleared in a single step [8]. It allows users to step away from the traditional multi-stage clarification approach and simplify the harvest operations, as shown in Figure 1.

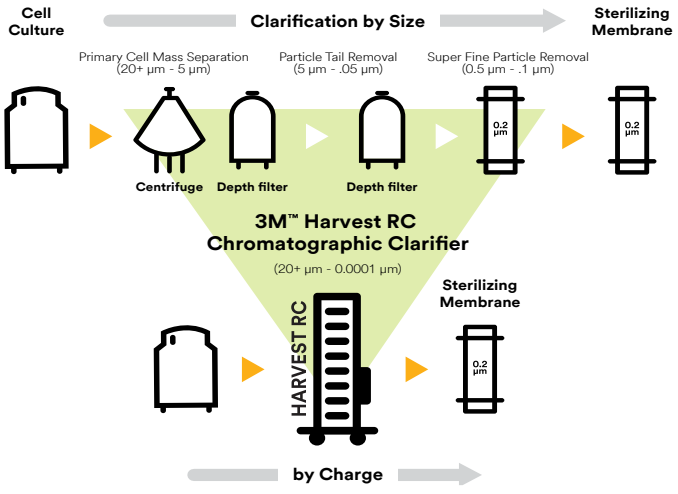

Figure 1: 3M™ Harvest RC Chromatographic Clarifier reduces the harvest and clarification to a single stage unit operation.

- **3M™ Polisher ST** is a single use flow-through solution that replaces a traditional multi-use AEX polishing column. The capsules combine two complementary AEX-functional media: a quaternary ammonium (Q) functional nonwoven and a guanidinium-functional membrane [9]. The non-woven provides a tolerance for the turbidity that may be observed after virus inactivation and neutralization. This allows the elimination of a depth filter and membrane step, which reduces the number of steps and the floorspace in production, as shown in Figure 2.

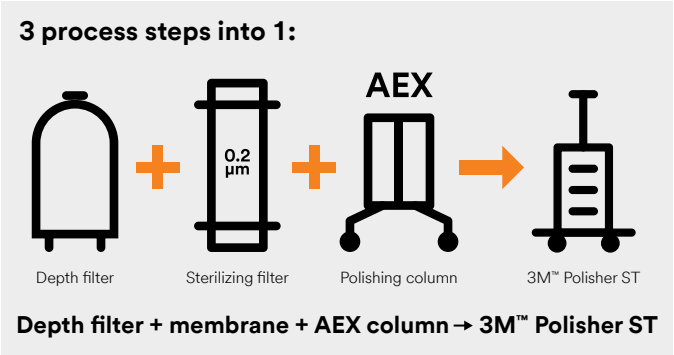

Figure 2: 3M™ Polisher ST allows compression of 3 process steps into one single use capsule.

Process modeling

For an evaluation of 3M SUT, we modeled a typical single-use large scale mAb manufacturing facility using the commercial Biosolve Process™ software package (version 8.3) from Biopharm Services Limited. The model assumes a setup with 6 bioreactors of 2000 L working volume and a facility output of 100 batches per year.

Figure 3 shows the process steps per scenario in a schematic overview. The base scenario has a two-stage depth filtration train for the clarification and includes a resin-based AEX column after the capture step and low pH hold. The column is protected by a depth filter and a membrane. In scenario 1, the depth filter, membrane and AEX column in the DSP are replaced by a 3M™ Polisher ST capsule. The effect of replacing the 2-stage clarifying depth filters by a single stage of 3M™ Harvest RC Chromatographic Clarifier is also modeled. Scenario 2 includes both those changes.

All scenarios are based on a single use facility model that includes single-use bioreactors, tubing, buffer hold bags and filtration capsules, which eliminates cleaning requirements for steel vessels, piping, and housings. The resins of the chromatography columns are used for 150 cycles in the models. Stainless steel facilities are not modelled in this analysis.

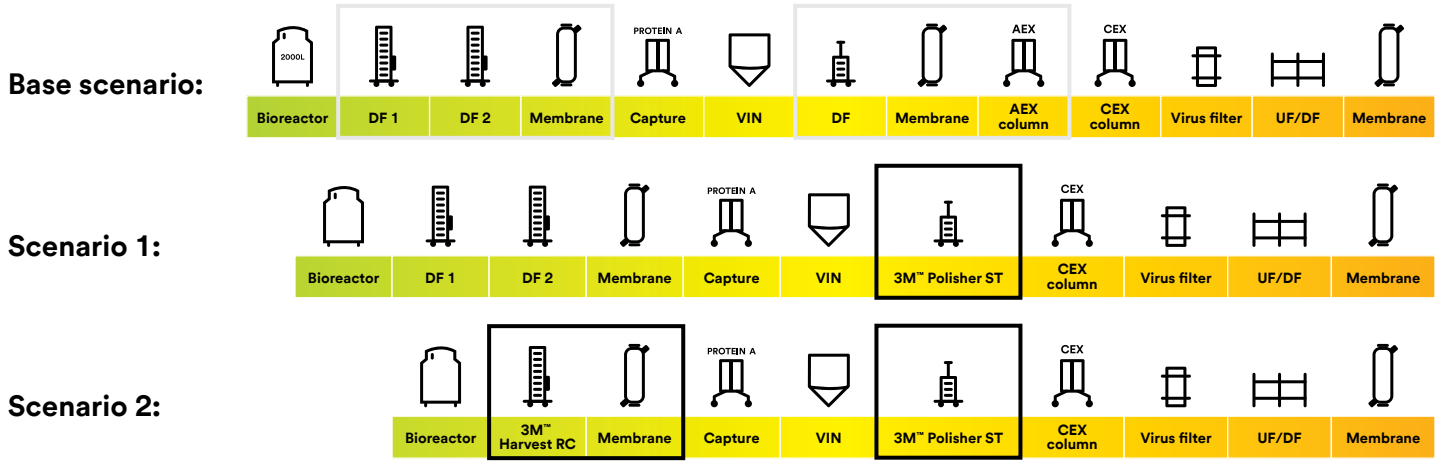

Figure 3: Schematic overview of the modelled scenarios, showing the different unit operations.

Process Mass Intensity

The process mass intensity (PMI) value is a key performance indicator that can be used to evaluate the resource efficiency of a process. It is defined here as the total mass of materials going into the process (including consumables, process water, buffers etc.) divided by the mass output of final product [10] [11]. The PMI value is weight-based and does not consider differences in environmental impact between, for example 1 kg of water and 1 kg of plastic, or between 1 kg of water and 1 kg of a hazardous chemical. Nevertheless, it is a useful metric to track, especially in combination with other parameters. PMI should be understood as a measure of resource use efficiency and not as a direct or absolute measurement of environmental impact.

mAb and other biologic processes typically have PMI values of thousands, meaning that thousands of kg of inputs are required to produce 1 kg of product. Water consumption is the largest driver for those high values [11] [12]. Chemical processes typically have PMI values that are orders of magnitude smaller [13]. Although biologics processes may never reach that low, there is certainly room for improvement.

Figure 4 shows the PMI value of the total process for the different model scenarios. The advanced single use technologies presented here allow process intensification and simplification by combining multiple steps into one. The PMI of the intensified scenarios decreases significantly compared to the base, demonstrating that the process becomes more efficient and consumes less resources. The PMI drops due to a combination of reduction in water use, consumables, and an increase in product recovery. The next paragraphs describe those factors in more detail.

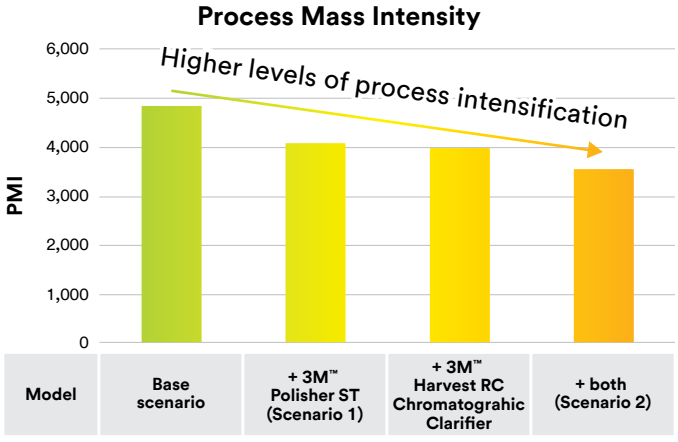

Figure 4: Process mass intensity results for the modelled scenarios.

Liquid and solid waste per process step

Our models correspond to a single use facility, including disposable bioreactor bags, product hold bags and encapsulated filters. Figures 5 and 6 show the solid consumable waste and liquid process waste per process step. Liquid waste from cleaning is not included since the facility relies heavily on single-use bioreactors and product hold bags. It must be noted that solid and liquid waste are just two metrics that are part of a facility's footprint.

Clarifying depth filters are the largest contributor (60%) to the total solid process waste. While the pre-use flush volume of the depth filters can be significant, it is small compared to the liquid process waste generated by the chromatography columns. The fed-batch bioreactors also require large volumes of water, but this is not categorized as liquid waste because it contains the product.

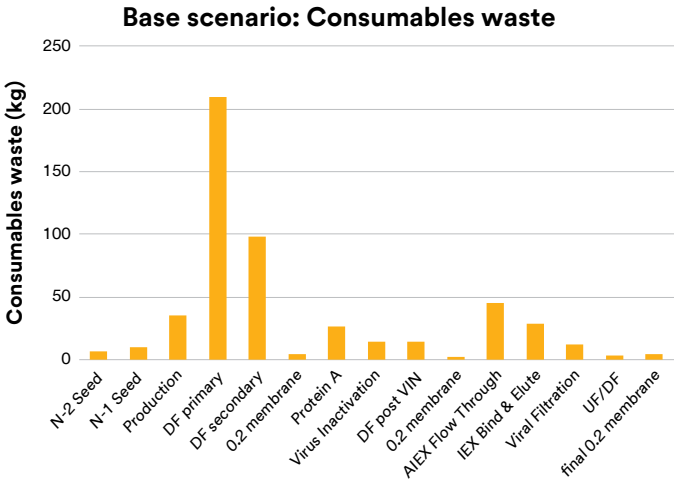

Figure 5: Consumable usage per process step

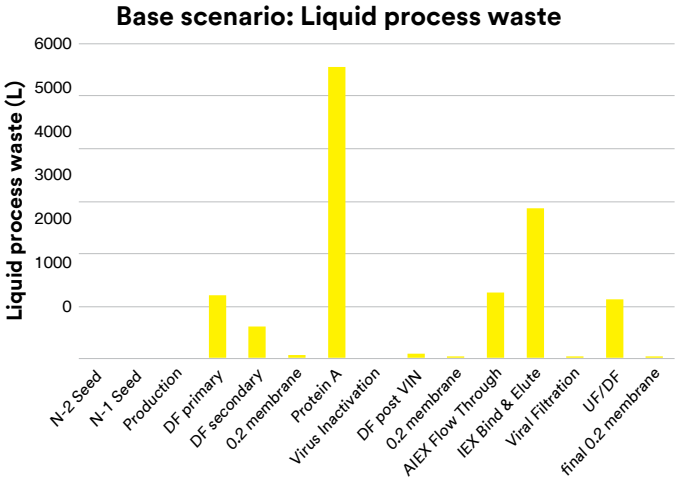

Figure 6: Process water usage per process step

Effects of 3M single use technologies

3M™ Harvest RC Chromatographic Clarifier is designed for harvesting CHO cell cultures with a packed cell volume (PCV) of 5-8%. The typical throughputs for that range are 60-100 L/m² [8] [14]. In our model, we assume that a first stage depth filter at 100 L/m² and a second stage depth filter at 200 L/m² are replaced by 3M™ Harvest RC Chromatographic Clarifier operated at 100 L/m². In doing so, the total number of capsules is reduced from 21 to 14, and the capsule weight is reduced from around 300 kg to 200 kg, as summarized in Figure 7.

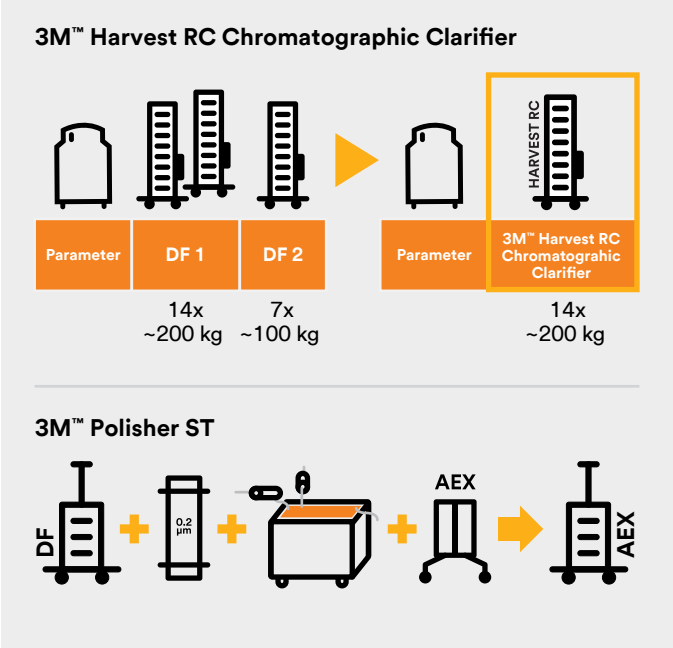

Figure 7: Reduction in consumables by combining steps

3M™ Polisher ST typically requires only one 1.6 m² production capsule per 2000L batch. That capsule has roughly the same weight as the depth filter capsule used after the virus inactivation step. The membrane stage, the resin and any bag assemblies used for product hold in between those steps are eliminated, as shown in Figure 7. The AEX column typically requires multiple different buffers and cleaning solutions for equilibration, chases, elution, and regeneration. Each of those solutions will require a separate single-use bag assembly. With 3M™ Polisher ST, the same buffer is typically used for equilibration and chase, which further reduces the number of bags required.

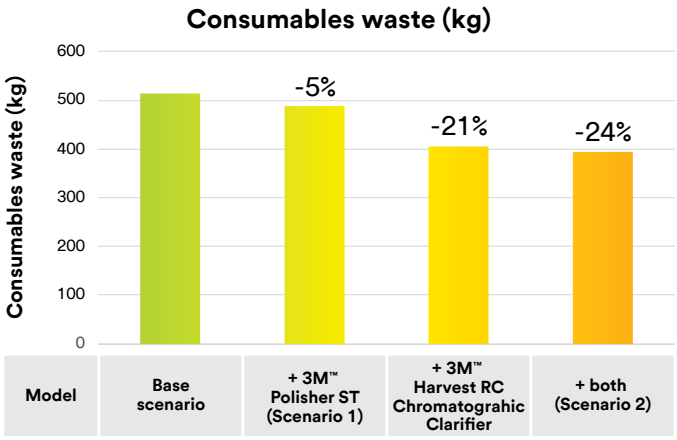

Figure 8: Total solid process waste of consumables per scenario

Implementation of 3M™ Polisher ST results in a 5% decrease in the total consumable waste of the process, while 3M™ Harvest RC Chromatographic Clarifier results in a 21% reduction, compared to the base scenario. Combining both technologies reduces the solid waste of the process by almost a quarter.

3M™ Harvest RC Chromatographic Clarifier is fully synthetic and has a reduced flushing requirement of 25 L/m², compared to traditional depth filters that may require 50-100 L/m² flushes prior to use. 3M Polisher ST is a single use AEX flow-through step that eliminates the need for elution, sanitization, storage, and re-equilibration between cycles or batches. Omission of these regeneration steps, together with its smaller size can reduce the volume of buffers and solutions by 80% compared to a traditional column.

3M™ Polisher ST reduces the liquid process waste by 9%. The reduced flush on 3M™ Harvest RC Chromatographic Clarifier corresponds to a 4% lower liquid use. The combination of improvements in clarification and DSP results in a total water saving of 12%, as shown in Figure 9.

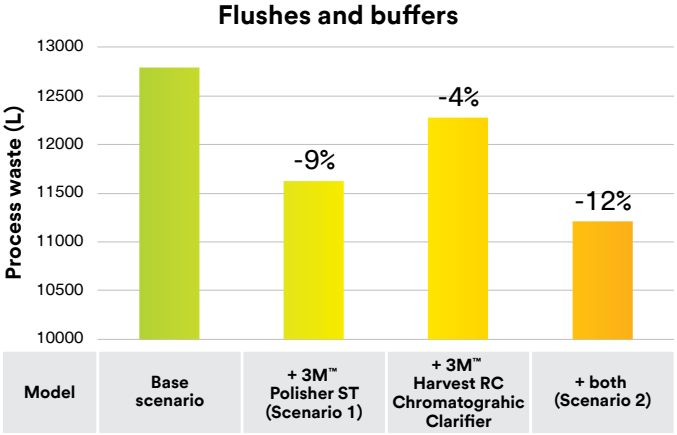

Figure 9: Total liquid process waste numbers per scenario.

Product recovery

Product loss is a form of waste that may be easily overlooked when assessing process efficiency, yet it is a very important one. Imagine two facilities with a similar setup and the same bioreactor productivity. Facility A has a total DSP product recovery of 75%, while facility B achieves only 50%. Both facilities probably have similar water and energy consumption, use equal amounts of consumables etc. However, the product output of facility A will be 1.5 times higher than that of facility B. At roughly the same footprint and environmental impact, facility A can get 1.5 times more doses delivered to patients. If demand rises, facility B will be the first to require the production of additional batches or installation of new production lines, both of which will further increase the process inputs and environmental impact.

Advanced SUT allow process simplification and unit operations with a lower resource consumption. Reducing the number of steps means less product can be lost in those steps, and higher process output will be achieved. 3M™ Harvest RC Chromatographic Clarifier and 3M™ Polisher ST both allow higher recoveries than the legacy technologies they replace, driving up the overall DSP recovery [8] [9] [14]. Figure 10 shows how their implementation affects the annual plant capacity and the number of doses produced. Increased outputs will also directly affect the PMI value and the cost of goods in terms of manufacturing cost per kg of protein produced.

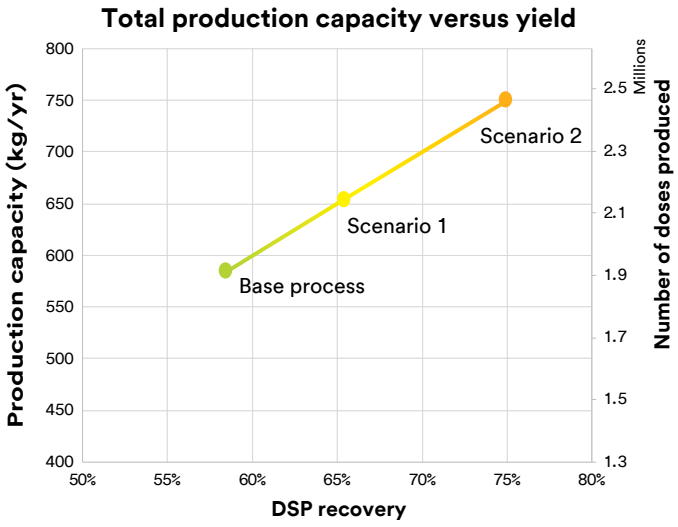

Figure 10: DSP recovery for each model scenario, and the resulting production capacity.

Reducing resource use in biopharmaceutical manufacturing processes

In this section, several ideas and options are listed to reduce resource consumption of manufacturing processes. The effect of these actions will vary between facilities and would need further detailed evaluation by the end user. Here are some proposals to consider:

- Start with an LCA study to understand the main drivers of the environmental impacts across material sourcing, manufacturing of consumables, distribution, and end-of life phases [5].
- Target protein loss is an important form of waste. Optimize processes for maximum product recovery. Failed batches and product rejections should be minimized for the same reasons.
- Cleaning, sterilization, and purified water preparation are very demanding operations [4]. Evaluate how SUT may reduce energy and water consumption in the use phase, compared to the traditional reusable technologies. Transition to SUT where reductions in environmental impacts align with the company's environmental priorities.
- Avoid overdesigning process steps or applying excessive safety factors. Over dimensioning increases solid and liquid waste and can result in higher product loss. Instead, carefully evaluate and select technologies that scale reliably and provide consistent performance [8] [14].
- In stainless steel facilities, most of the environmental burden lies with the drug manufacturer. In single-use facilities, the responsibility is shared between the suppliers of consumables and the end-user [3]. Ask your suppliers about their programs and commitments to reducing environmental impacts of their products. Good relations and communication with suppliers make operations run smoothly and can avoid supply chain disruptions or the need for carbon-intensive, last-minute air shipments.
- Innovation is key for making biologics processes more sustainable. Continuous manufacturing is one way to eliminate waste and decrease the PMI index. While batch manufacturing is still the standard for biologics, drug manufacturers increasingly invest in the development of continuous processing, which would result in lower energy use, lower water and buffer use, less waste and a smaller facility footprint [15] [16] [17]. For batch processes, scientific breakthroughs in SUT or operational improvements like in-line buffer dilution can offer large gains [18]. Whatever direction is chosen, the goal should be to do more with less.

Conclusion

Production processes for monoclonal antibodies and other biologics are demanding and typically have a very high PMI index. The utilities, cleaning and sterilization operations are strong drivers of the environmental impact of these processes. Although SUT may increase the consumption and waste disposal, it has the potential to also reduce energy and water demand.

LCAs are the industry standard for comprehensive analysis for the environmental impacts of processes and products. Detailed process modeling and key performance indicators like the PMI index can offer a simpler starting point.

Biosolve Process™ software was used to model a typical mAb production process and assess the effects of introducing advanced SUT. 3M™ Harvest RC Chromatographic Clarifier combines multiple clarification stages into one, thereby reducing the number of capsules required and associated waste. The synthetic media reduces flushing requirements and water use. 3M™ Polisher ST replaces multiple steps in the DSP process and offers around 80% reduction in buffers and solutions compared to a traditional AEX column. Both technologies demonstrate better product recovery than their current alternatives, which further drives the PMI down and the productivity up. The recovery is an important factor for the facility efficiency and the environmental impact per kg of protein or per dose produced.

Ultimately, the biopharmaceutical industry will require extensive innovation and continued technology improvements to become more efficient and sustainable. Strong collaborations between producers, suppliers and regulatory bodies will be imperative to success. There are several routes to consider, but all solutions will require doing more with less. Process intensification and simplification with advanced SUTs can offer significant gains that can be part of the trajectory towards sustainable production of biologics.

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Sustainability is an important part of the culture of 3M Company. We back initiatives that foster sustainable communities, including projects that protect threatened ecosystems, support local economies, enhance livelihoods, and promote science-based environmental education. We are approaching our goal of 50% renewable electricity at all global sites by 2025 and are committed to going 100% carbon neutral by 2050. For more information, visit our website at Sustainability and ESG | Overview and Commitments | 3M, where you can download 3M's 2023 Global Impact Report.

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3M Separation and Purification Sciences Division
400 Research Parkway, Meriden, CT 06450 USA

Phone 1-800-243-6894 1-203-237-5541
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