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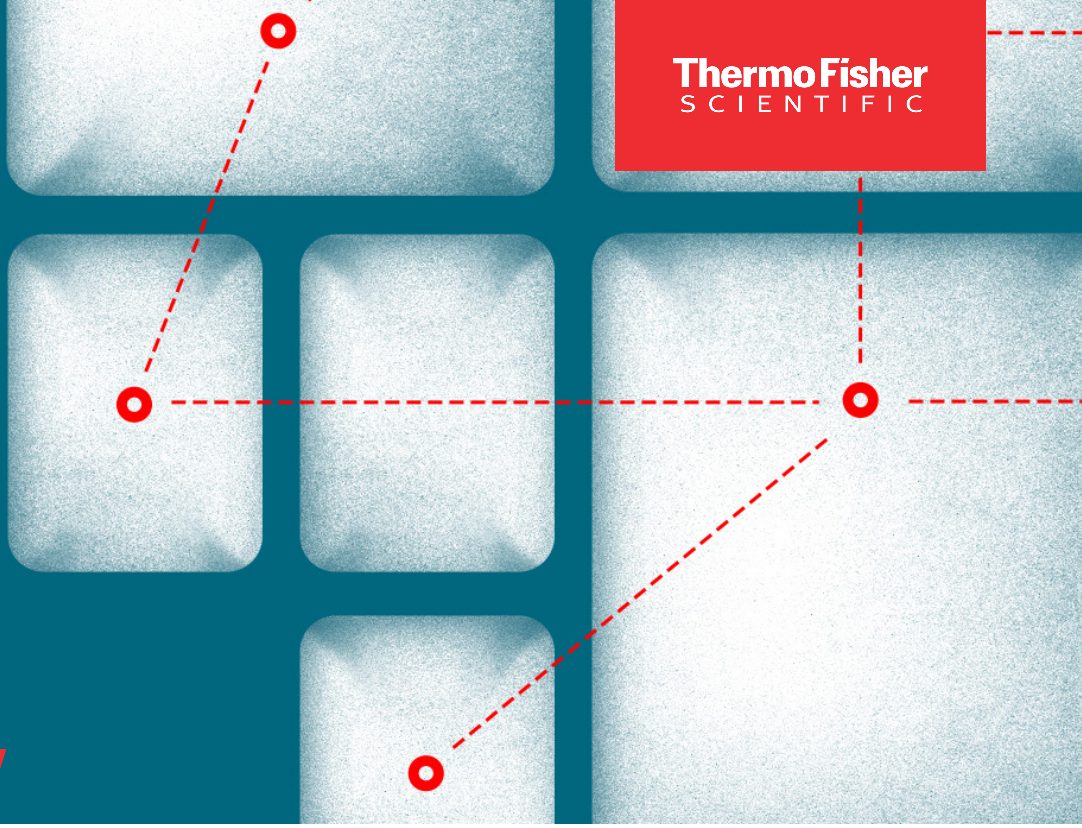

Single-use technologies

Value of standardization modularized manufacturing strategies for single-use technologies

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Introduction

Single-use technology (SUT) has been a long-standing choice for biopharmaceutical manufacturers striving to reduce the time and cost needed to bring their products to market. SUT is a viable option across all phases of a biologic's lifecycle, from R&D, to development, to clinical and commercial manufacturing. Its benefits have been well established, with users realizing reduction in manufacturing costs, increased productivity, and faster time to market. Beyond individual biologics manufacturers, SUT has also found significant traction from companies engaged in multi-product manufacturing. In this space, the added flexibility of rapid facility turnaround and reduced risk of cross-contamination enables increased production efficiency over other more traditional alternatives. As a result, the demand for SUT has continued to significantly grow yearly for both individual manufacturers and contract development and manufacturing organizations (CDMOs).

While the promise of reduced costs, flexibility, and faster pathways to market has continued to grow, the industry's appetite for single-use materials continues to increase. The traditional approach taken in single-use design has driven biopharmaceutical manufacturers to leverage risky single-source supply chain strategies for the design and sourcing of complex, optimized, custom single-use solutions, to meet a wide range of process-specific applications, even when unnecessary. This has been further complicated by design philosophies that, born from historical constructs, are not reflective of the recent gains by improved manufacturing processes for single-use manifold subcomponents. The perils associated with complex, one-off, limited-application, or sole-sourced products were why many supply chains failed to meet customer demands during the SARS-CoV-2 crisis.

Can supply chain assurance be maintained while offering an array of possibilities to achieve complex process designs? The standardized and modularized single-use design approach offered by the mAb Process Playbook Modular Manifold Library developed by Thermo Fisher Scientific allows us to deliver on both flexibility of design and supply chain assurance.

The following case studies present the potential power of a modularized and standardized single-use manifold design approach offered by the mAb Process Playbook Modular Manifold Library. Since modularization is able to impact a wide variety of business-critical areas including supply chain optimization and robustness, quality improvements by human factor engineering principles, and technology transfer efficiencies, what benefits would a modularized and standardized single-use design approach give to your organization?

Case study 1—supply chain optimization by standardized modularization

A design approach that centers around optimization through marginal yield increases enabled by highly specific single-use manifolds opens a firm to additional supply chain risk. It introduces the arduous task of managing the procurement, stocking, and supply chain of a myriad of one-off, highly specific manifolds for each product within their manufacturing pipeline. During the SARS-CoV-2 crisis, marginal process optimization at the consequence of supply chain risk was a strategy that left many firms spending significant labor hours designing one-off custom solutions to keep processes afloat as they waited for delivery of the originally specified custom materials.

Modularization of the single-use design approach can break this cycle and offer firms a significant supply chain advantage by leveraging manifolds that are designed to be utilized within multiple unit operations in the end-to-end workflow. This ensures that a firm can stock a limited number of individual single-use SKUs that can always plug into a unit operation to keep the process moving. The mAb Process Playbook Modular Manifold Library takes this approach one step further by employing a standardization strategy for the subcomponent connections, allowing firms the opportunity to seamlessly piece together SKUs regardless of polymeric construction materials.

To illustrate the potential improved robustness offered by this type of modularized engineering approach, the mAb Process Playbook Modular Manifold Library was analyzed against a traditional custom SKU design approach in an end-to-end workflow at 1,000 L, 2,000 L, 3,000 L, and 5,000 L manufacturing scales. This comparison demonstrates the level of SKU reduction in an equivalent end-to-end process using the modularized design approach of the mAb Process Playbook Modular Manifold Library (Figure 1). For all scales analyzed, a design approach built on modularized manifolds with standardized subcomponents delivered an almost 3-fold reduction in unique process SKUs.

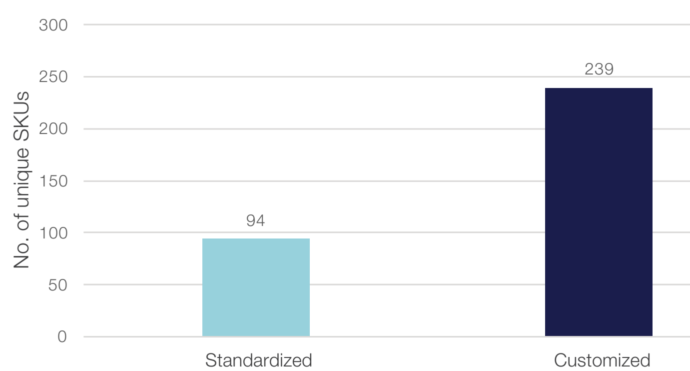


Figure 1. Primary quantity of unique SKUs required to perform unit operations.

> **This modularization and the use of the same SKUs for multiple unit operations solves several challenges:**
>
> - It delivers a supply chain that is based on ordering of a smaller subset of materials when compared to the custom optimized SKU process.
> - It allows for additional manufacturing robustness through the stocking of common materials within multiple manufacturing suites.
> - These common SKUs can be utilized at multiple manufacturing sites with similar scales.
> - It facilitates minimal redesign or adjustment in the stocked SKUs by the end user.
> - The use of standardized SKUs reduces strain on suppliers and ultimately increases SKU availability due to higher rates of consistent production, as compared to highly customized SKUs that are scheduled for special production in advance.

The results from Figure 1 were extrapolated further to show unique SKU reductions across different scales. Figure 2 shows the difference in total unique SKUs required for a standardized versus a customized process across vessel sizes and SKU groups. Groups are divided into primary (ideal polymer and process configuration), secondary (meets engineering specifications, but not first choice), and tertiary (meets engineering requirements).

When designing using the mAb Process Playbook Modular Manifold Library, customers can choose to use either ideal modular components for each unit operation, or substitute with SKUs that are mechanically similar and able to perform the unit operation, but are not necessarily the primary choice. In the latter case, the reductions reported below can be 2–5% more by substituting some unit operations with SKUs that are not the primary choice.

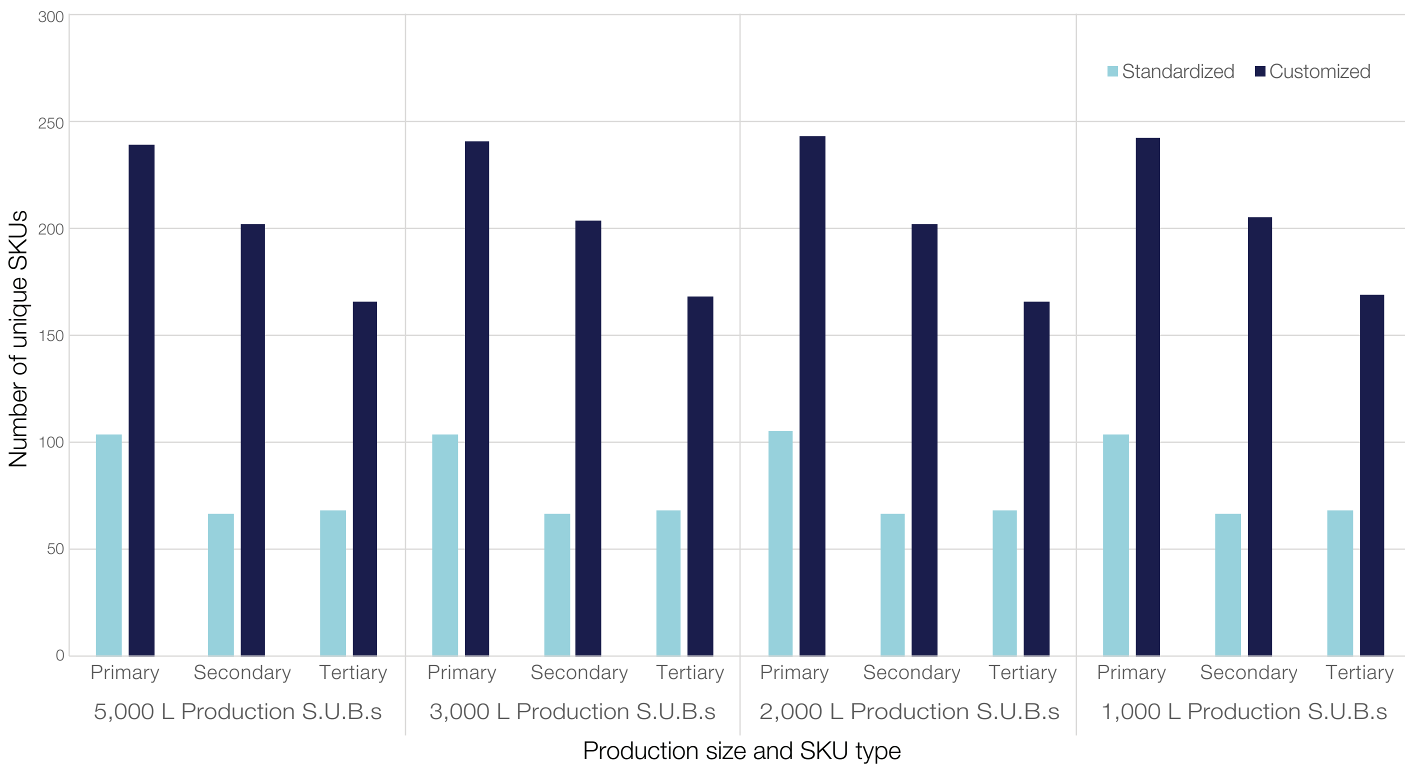


Figure 2. Quantity of unique SKUs required to perform unit operations.

The results from the modeling performed in Figure 2 highlight the following key advantages of modularization with subcomponent standardization:

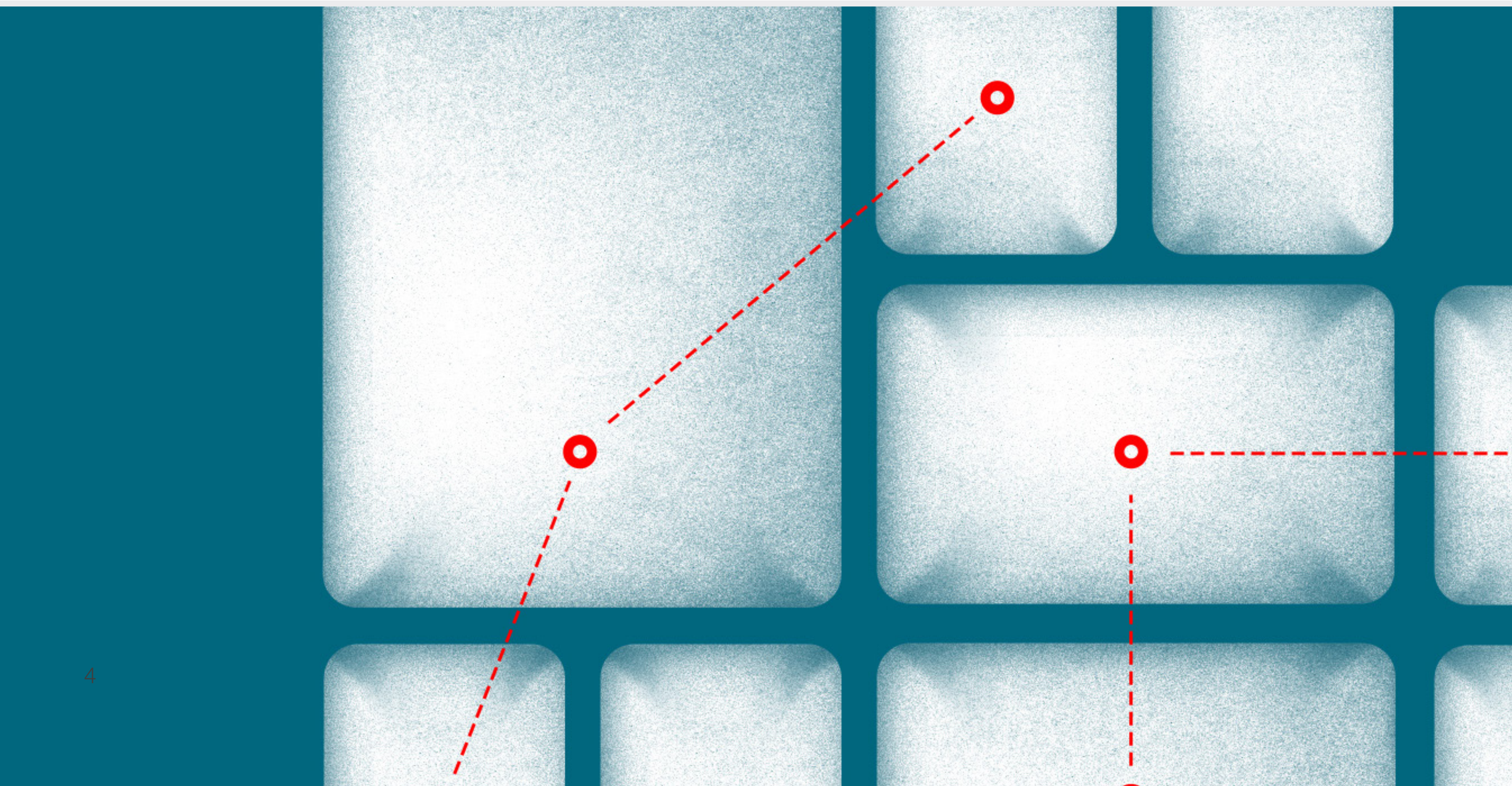
- There was an average reduction of 65% in unique SKUs among all SKU groups and production sizes. Note that this does not mean a firm will have to order fewer total manifolds, but that the same process can be performed with 65% fewer unique SKUs.
- The unique SKU reduction has the potential to reduce cost and complexity associated with planning, order management, quality management, and stocking.
- Many of the SKUs ordered will be useable in multiple parts of a process, which can help prevent bottlenecks from supply chain backlog.

Supply chain disruption is inevitable. Preemptively mitigating the associated risk can be the difference between keeping a production line running or shutting down completely due to missing components. The mAb Process Playbook Modular Manifold Library is designed to help a manufacturer keep their production running regardless of supply issues. The standardized modular manifold designs limit the strain on suppliers due to the reduced unique SKU demand and ability to incorporate modular pieces seamlessly. When manufacturers leverage the efficiencies of the mAb Process Playbook Modular Manifold Library, they can expect to see a more robust supply chain with a simplified operations strategy.

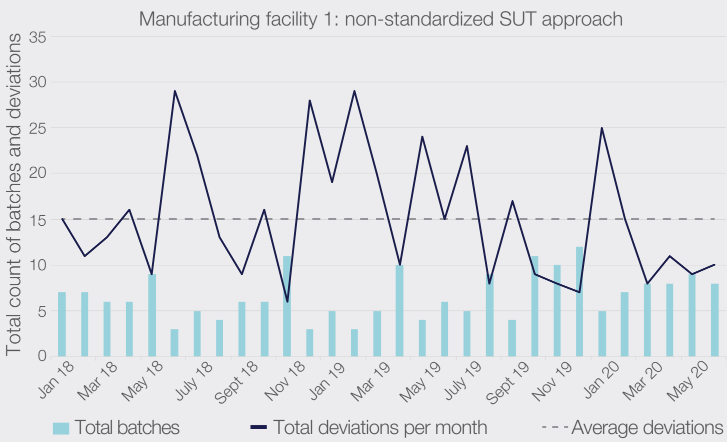
Case study 2—modularization and standardization of subcomponents maximizes human factor engineering principles to deliver increased quality

Human factor engineering principles are built upon the core concept that error reduction is built through simplicity, similarity, and familiarity of tasks. The traditional design approach of single-use workflows, built through custom, highly specific manifolds for specific unit applications runs countercurrent to human factor engineering principles. In this traditional design approach, engineers often place their manufacturing counterparts in the precarious position of right-first-time execution with a manifold, style of connection, or other application-specific variations that looks nothing like the previous product.

Modularization through standardized subcomponents solves the human factor engineering problem by simplifying the connection of single-use manifolds down to the same, consistent subcomponent connectors. Regardless of the manifold application or product-specific process configuration, the manufacturing operator is always asked to connect a set of modular pieces in the same way. This design simplification, realized through standardized subcomponent manifold modularization via the design approach of the mAb Process Playbook Modular Manifold Library, leads to powerful reductions in human factor–induced quality errors.



Reduction in human-induced quality error can be seen in the comparison of quality-related deviation resolution costs between two manufacturing facilities (Figure 3). Manufacturing facility 1 utilized a traditional fully customized and non-standardized single-use design approach, which represents what is most employed today. Manufacturing facility 2 implemented the modularized design approach using standardized subcomponents. Quality data over a similar manufacturing period showed that manufacturing facility 2 increased their operations capacity by 3x while exhibiting an almost 60% decrease in single-use deviations following implementation of the standardized modularized approach. This reduction equated to an almost 5-to-7-million-dollar labor efficiency benefit over manufacturing facility 1 when comparing each facility cost for an equivalent batch output and associated deviation rates over the same period.



	Average deviations (dev./batch)	Cost/month ($)	Cost/year ($)
Current state	15	510K–1M	6M–12M
Opportunity (60% reduction)	6	100K–400K	1M–4M
Opportunity savings	—	—	5M–7M

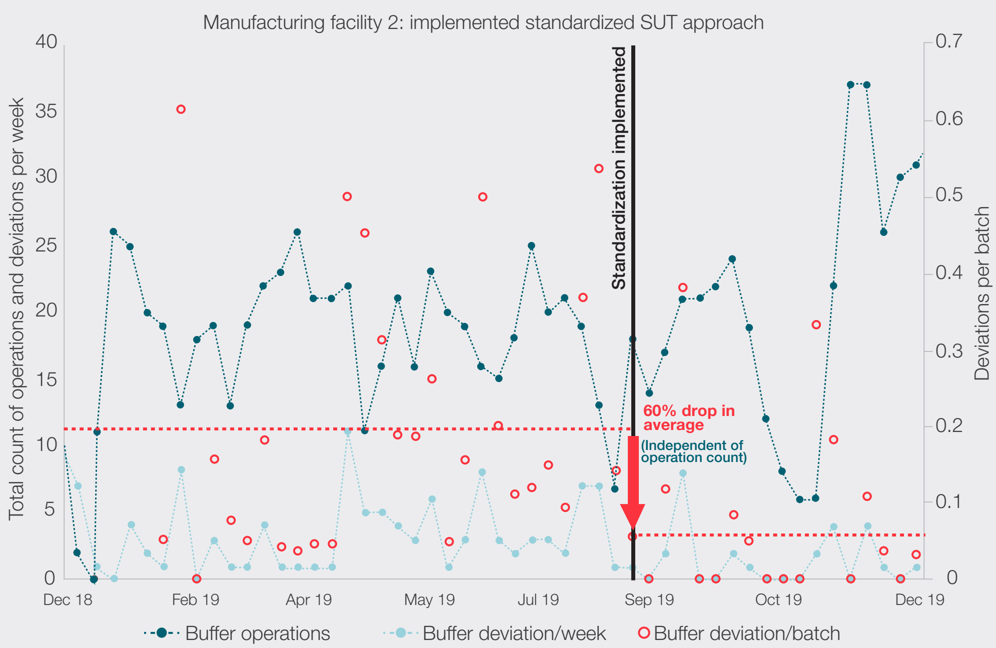


Figure 3. Manufacturing site comparison of non-standardized and standardized SUT approaches. Upon implementation, manufacturing site 2 deviation reduction accounts for a 5M–7M dollar opportunity in back-end remediation costs when compared to manufacturing site 1.

Case study 3—technology transfer efficiencies using modularized design with standardized subcomponents

Modularization based on standardized predefined subcomponents not only benefits business quality but can also play a significant role in the upfront reduction in labor hours associated with designing and planning for a program.

To illustrate this potential benefit, we evaluated the engineering design time associated with producing two equivalent harvest processes for unique programs that used a comparable approach within the harvest unit operation (Table 1). When the process engineer was asked to design the unit operation from scratch using the traditional customized design approach, the engineer was tasked with having to design 15 unique manifolds to produce the harvest operation step. The process took approximately 30 manifolds total to complete, used 17 welds, and due to the customization of the manifolds, required 4 autoclave cycles to sterilize the materials prior to use. A subset of the 15 unique manifolds were built internally, and the remainder were sourced as low-volume one-off requests from the facility's preferred single-use supplier. This labor did not only include design time. It also included the time the engineer spent contacting the local supplier, articulating the design, approving the draft manifold design from the supplier, and working with procurement to ensure that the appropriate sourcing system was correct and that order quantities for the campaign were appropriate. This context illustrates the complexity and total time spent in the initial design phase of a single unit operation using the traditional customization-based approach.

Due to the complexity and uniqueness of the manifolds and the time needed to build and autoclave several of the manifolds used in the process, the total process time for this unit operation was 12 hours in total labor across multiple departments.

For the second process, the engineer utilized a modularized design approach where they constructed the equivalent harvest unit operation from a set of predefined, pre-engineered, gamma sterilized, modular single-use manifolds with standardized subcomponents. While the total number of manifolds increased from 30 to 40 in the design of the new modularized process, the design time for the process was only 2 hours. This represents an 83% decrease in process design time. Additionally, the manufacturing time to set up the operation decreased 83% from 12 hours to 2 hours. This decrease in design time and manufacturing setup time can be easily explained. In designing the second harvest operation utilizing principles of modularized standardization, the engineer only had to spend time picking the appropriate manifolds from a predefined list of manifolds that have already been standardized to seamlessly be pieced together. This is a significantly more straightforward design task than designing customized manifolds from scratch. In utilizing the modularized and standardized design approach, the engineer was also able to eliminate the need for autoclaving (replacing autoclaving with gamma irradiation) for welding. Replacing welding with single-use connections can be performed in seconds.

The data from this comparison can be extrapolated further to determine total savings for different-sized manufacturers. Assuming staffing costs range from $100 to $120 an hour, and the number of unit operations per program ranges from 20 to 25, one can predict the labor costs for each customized versus standardized process.

Table 1. Additional benefits to the modular single-use approach.

Design	No. of manifolds	No. of unique manifolds	Setup time	Welds	Autoclave cycles	Design time
Legacy	~30	15	12 hr	17	4	>12 hr
New	~40	6	2 hr	0	0	2 hr

Given these aforementioned staffing and operations assumptions, cost estimates are as follows:

- Using a customized process, for a single technology transfer the lower bound estimate is $24,000 with an upper bound of $36,000. Furthermore, a CDMO with 10 technology transfers a year may spend $240K to $360K a year on design labor alone.
- By contrast, a standardized process that uses the same total manifolds and price of labor ranges in cost from $4,000 to $6,000 per technology transfer. For a CDMO with 10 technology transfers, this is $40,000 to $60,000.
- Total savings by switching to standardization is $20,000 to $30,000 per technology transfer. Again, a CDMO with 10 clients would see that number increase 10 fold.

Labor reduction is one of the most significant cost-saving opportunities for manufacturers who use a standardized modular design. By using the mAb Process Playbook Modular Manifold Library, significantly less labor is required for both design and setup of a given process. This benefit adds to the numerous ways in which the playbook simplifies a process supports the financial benefit of standardization.

By using the data from case study 3 to feed the hypothetical example above, switching to a standardized manifold approach resulted in an 83% decrease in both design time and cost for the manufacturing processes setup. This represents a significant cost savings, positively benefiting the bottom line of the manufactures and CDMOs alike.

Conversion to the modularized design approach is not impossible for anyone

Our research shows that using a modularized single-use engineering design approach with standardized subcomponents has clear benefits for both individual manufacturers and CDMOs. Those that would benefit the most from the standardized modularized engineering approach are those with new processes who are deciding between customization and modularization, and those with existing processes considering switching over. The former has obvious labor, time investment, and cost-savings opportunities, whereas the latter must consider the implementation hurdle of converting an existing process.

Conceptualizing converting to a standardized approach can be overwhelming, and given the benefits across various elements of the business, a firm might still be tempted to keep their original customized approach. The fear associated with the labor investment involved in change controls and process improvement implementation is a rational pain point for customers weighing their options for future bioprocessing. To evaluate the challenges of implementation, we performed a case study evaluating a firm that was able to accomplish this change to a modularized and subcomponent-standardized engineering approach using minimal non-dedicated staff.

Figure 4 shows tracked hours needed by different departments from the start to the end of implementation. Throughout the 1.5-years it took to fully switch the process to the modularized single-use engineering approach, there was never a point when a department required a full-time employee. At its busiest, the implementation took just over 30 hours a week by the manufacturing science team and engineering team; one person per department could handle the workload needed for that specific phase. The resulting time required in the case study suggests that the investment to switch is relatively small. Imagine how quickly implementation could be accomplished, and timelines compressed further, with a dedicated team.

As a way of investigating the additional risk associated with implementation, we performed an analysis examining the engineering manufacturing risk using the standardized single-use design approach based on the mAb Process Playbook Modular Manifold Library. The subsequent paper from this additional research presents a manufacturing risk analysis for a modularized and standardized single-use manufacturing strategy at the 2,000-liter scale by evaluating risk profiles against a 98% success rate standard. These additional data when combined with the case studies presented in this paper stand as a practical evaluation for manufacturers and CDMOs alike to weigh the risks and benefits of moving from customization to standardized modularization for single-use technology supported processes.

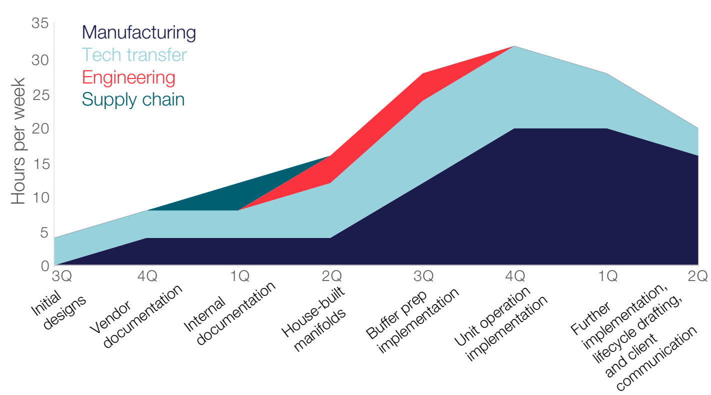
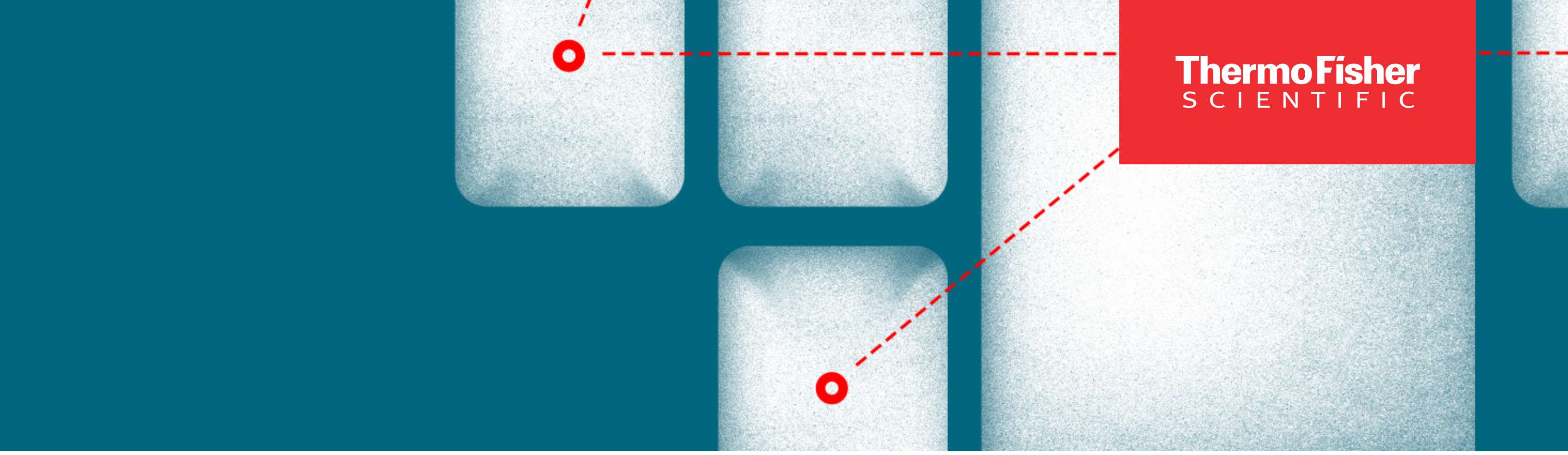


Figure 4. Time investment per department for implementation.



Conclusion

More than ever, biomanufacturers are seeking support to quickly and efficiently produce a variety of therapies to meet the growing population's needs. SUT has consistently provided flexibility and efficiency, but it has come with its fair share of weaknesses. Thermo Fisher has developed an innovative playbook to overcome these shortcomings and make SUT an even more viable option for individual manufacturers and CDMOs alike.

For manufacturers that elect to switch to standardized processes, the benefits described in these case studies are widely applicable regardless of scale and infrastructure, enabling consistency and simplicity in technology transfers. Standardization leads to supply chain resiliency by reducing the number of unique SKUs. This in turn reduces the time-consuming activity of process design and reduces unnecessary associated component management without limiting process capability. It also leads to a decrease in impactful deviations and upfront design time, resulting in time- and cost-savings for manufacturers. The versatile, standard offering can drastically reduce the time-consuming upfront activity of process design and limit unnecessary associated component management while not restricting process capability. Using a consistent approach to design increases the success rate on the manufacturing floor, which directly translates to savings in time and money, and frees up capacity for added focus on increasing production instead of managing complexity. Potential workflow options adhere to current best practices and standard engineering principles while meeting the needs of your processes. Playbook designs easily accommodate a wide range of processing strategies by leveraging decades of experience in designing process solutions across the industry. It is the needed, next major innovation that will help keep SUT as not only a viable option for future process designs, but also the best option for many manufacturers.

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