Optimizing Manufacturing Strategies for mAbs

Bioproduction Specialists from Thermo Fisher Scientific share their insight to support monoclonal antibody production

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mAbs: Making the Right Equipment and Process Decisions

How to identify the best equipment for your monoclonal antibody production

What is the best equipment for producing mAbs? What are the main key considerations? How do you decide between single use and stainless steel? We spoke with Matthew Zustiak, Director of the Bioprocess Collaboration Center at Thermo Fisher Scientific, to discuss the challenges of equipment choice.

What is your role at Thermo Fisher Scientific?

I am the Director of Research and Development for our Bioprocessing Collaboration Center. The Center and its team collaborate internally within different groups of Thermo Fisher Scientific as well as externally with other companies. My area of expertise is around upstream bioprocessing. During my career, I've spent several years in process development, covering everything from early to late stage development, and I have experience transferring those processes into manufacturing, which gives me a useful overview of the entire process. The Bioprocessing Collaboration Center is based in St. Louis, Missouri, adjacent to our pharma services group. We have a pilot lab, operating up to the 500-L scale, that we use to test new equipment and instruments at various stages of development to provide useful feedback on their development to increase speed to market and improve market adoption.

What specific equipment is needed for mAb production?

mAbs are primarily produced in mammalian cells, so for the upstream process – where you are growing cells – you require various culturing systems for small culture volumes out of cryopreservation with progressively larger systems used through the scale-up of the culture until a large bioreactor is used for the production stage. At the early stages of the seed train, you tend to see the use of shake flasks and rocker bags, which are single-use systems. In later stages, we generally see requirements in the 1,000–5,000-L range – the top end of this now enabled by Thermo Fisher Scientific's introduction of 5,000-L single-use products. However, as you scale the culture up, the demands of greater volume instruct the choice of equipment. A production scale bioreactor could be as little as a 500-L system, covered by single use products or all the way up to a 15,000 L production volume capacity using larger, stainless-steel bioreactors.

After the production phase, the supernatant needs separating from the cells, which requires a harvesting system, such as a centrifuge followed by depth filtration or a dual stage depth filtration system. From here, the product moves into equipment specialized for purifying the antibody out of the clarified culture fluid. This most often involves chromatography systems of various sizes, depending on the amount of material you are producing, along with the appropriate columns for your protein. From here, you will employ viral filtration, ultrafiltration and diafiltration steps, to provide buffer exchanges and formulate the product into a stable final formulation at the desired concentration.

For bulk drug substance, the product is often filled into bags or carboys and frozen or kept at 2-8 °C. For drug products, specialized filling equipment is required for sterile vial filling operations and, in some cases, lyophilization equipment as well.

How do equipment requirements change as development progresses?

The three main phases of bioprocessing, upstream (cell culture), harvest and downstream (separation, purification), and fill and finish, must all scale to meet a defined product output. How much material or product you need to produce is a critical question that companies should address early in the development process because it has a significant impact on equipment choice and requirements. It is not simply a matter of scaling the equipment in size; other choices can be made, such as stainless steel or single use. For anything sub 5,000 L, single use equipment can be employed, which brings discreet advantages to a process. Single use removes the need for certain steps (for example, cleaning and sanitizing), allowing manufacturers to swap between products efficiently

and without the need for a host of analytical methodologies to ensure there is no cross contamination. However, single use is only cost-effective at lower volumes and, when production demands increase, stainless-steel vessels become the better choice. Stainless steel may also be the better option if the manufacturer is concentrating on a single product because cleaning and sanitation protocols are simplified.

At what stage of development do companies need to start thinking about equipment and processing needs?

One important question that should be asked early on is, is it commercially attractive to set up a full-scale production plant, or is it better to contract out the work to a CDMO? The choice of building in-house capacity or using a CDMO needs to be considered early in the development process. In the early phases of product testing, especially at the clinical trial stage, commitment to a full-scale processing facility may not be as attractive as engaging a CDMO. This is effectively a de-risking position until clinical confidence in the product is gained and when there is certainty that no further process changes will be required.

If you do opt to build your own plant – which can have long-term benefits – then the earlier this is considered the better. However, it is important to have thoroughly defined your entire process before committing to a plant, which may mean waiting until in vivo testing of your product is complete. For instance, as you learn more about the product in its clinical setting, late-stage changes in processes are often discovered and these can bring about expensive modifications to the equipment required as well as changes in the accompanying regulatory approvals.

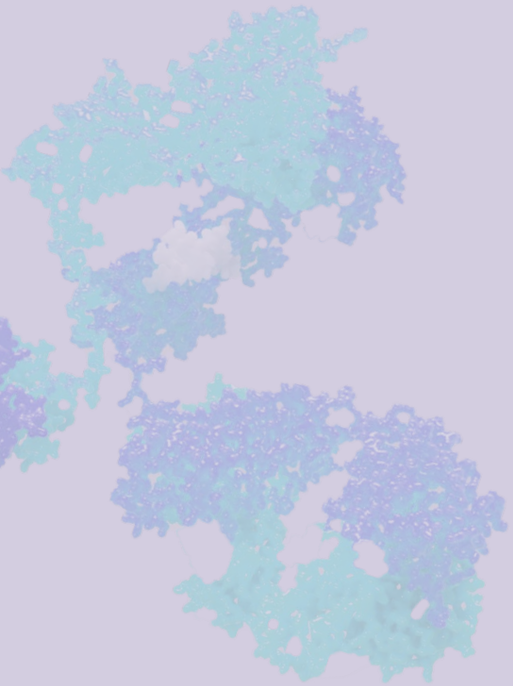
What is your advice when it comes to making final equipment decisions?

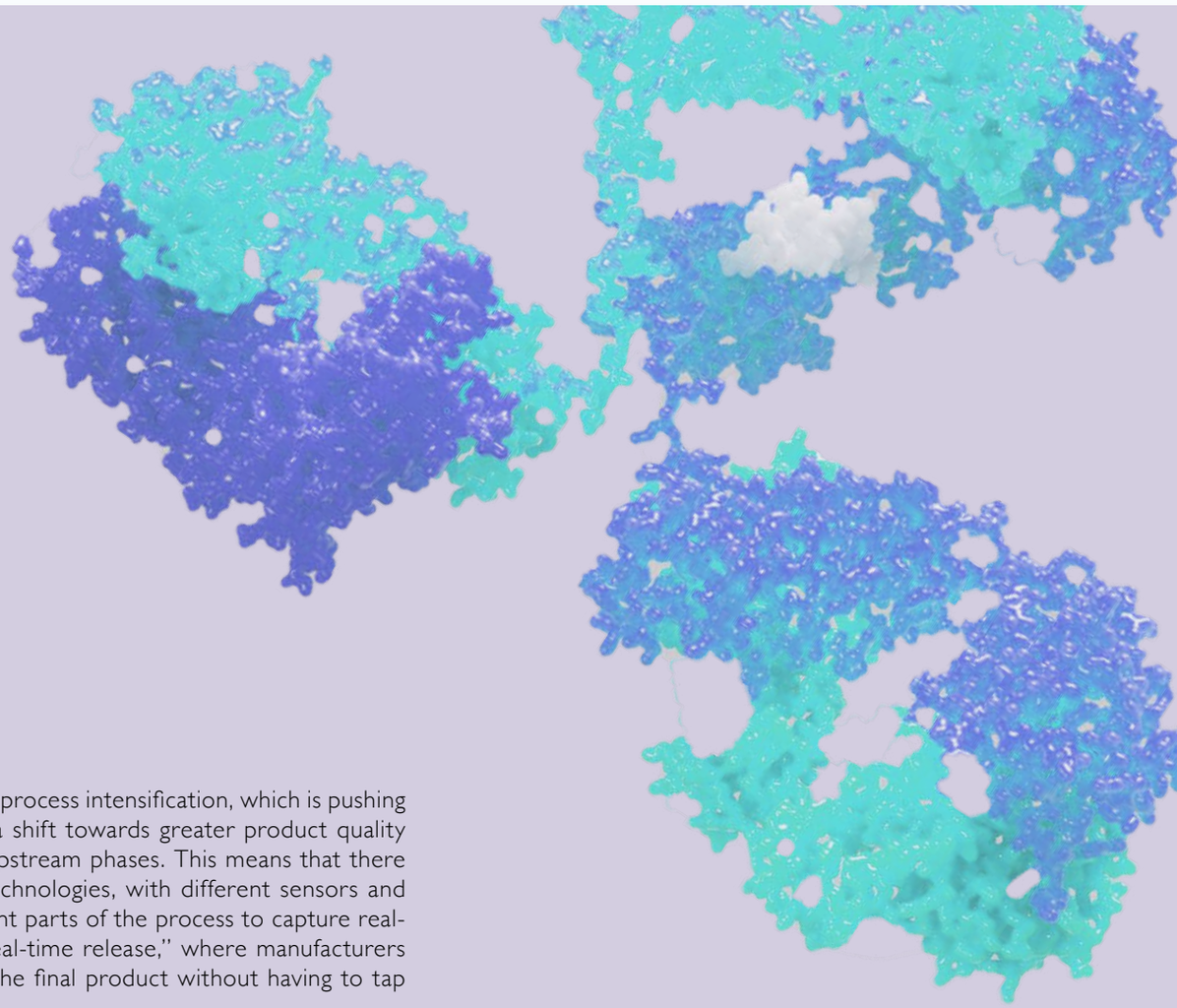
Market size for the final product is a critical starting point. Are you looking at 2000 patients a year or two million? You must build your capacity from the start to meet your market estimation, and this, therefore, dictates the type of equipment (and size) that will be required. You also need to consider how many batches per year will be required, and ensure you have the appropriate profile of equipment to meet that demand.

Occasionally, you find yourself on the borderline between single use equipment and more permanent stainless-steel vessels. In this space, you may find that the costs of single use begin to outweigh their benefits. In such cases, if you go back and look at the early stages of the process, there may be changes you can make that would have an advantageous effect later and help with equipment decisions. For instance, upstream host cell engineering may be able to double or triple the titer, ultimately making single use the way to go.

What about the vendor–client relationship?

To ensure you are choosing the right plant for your process from the beginning, it is crucial to work with a trusted partner that has experience with the complete system, including how systems scale from the early research phases through to production. At Thermo Fisher Scientific, our experience in the biopharma industry and continued investments in innovation means that we have extensive, important knowledge to





share with our clients. We can engage early in the process and collaborate to plan the optimum system, which is how we prefer to work with our clients. In my experience, once a well-considered system is up and running – and properly validated – it should be very robust. At the early stage, it pays to ensure that the appropriate equipment is chosen to meet the exact specifications and output of the proposed process, as changes later down the line become ever increasingly expensive.

We also recognize that many of the process steps are common to most – if not all – systems; by providing standardized units for these steps, we can expedite process development. Recently, Thermo Fisher Scientific launched its "mAb Process Playbook," focusing on single-use technology recommendations for production up to 2,000 L. The idea here is that a package of single-use components can be sent out to clients that can be readily incorporated into a manufacturing process, providing an almost end-to-end solution.

How do you expect technologies to continue to advance in the future?

Every change in the biopharmaceutical area has historically involved incremental improvements. Right now, a key trend is process intensification, which is pushing titers higher and higher. There is also a shift towards greater product quality and consistency, especially during the upstream phases. This means that there is a growing focus on new analytical technologies, with different sensors and probes that can be inserted into different parts of the process to capture real-time data. This will eventually allow "real-time release," where manufacturers can have confidence on the quality of the final product without having to tap samples for assessment.

Designing and equipping a manufacturing process efficiently and cost-effectively requires extensive planning. Knowing the end market use, having realistic production requirements, and determining whether to scale up or scale out are all critical factors; once in place, a manufacturing plant is very expensive to change. Thermo Fisher Scientific has the right depth of experience and is continually working at the forefront of improvements to methodologies and equipment. We welcome any company, regardless of size, that would like to discuss its ambitions early in their decision-making process.

Early Scale Up Strategies

Preparing for scale up in the early phases of monoclonal antibody development

Monoclonal antibodies (mAbs) are a key part of the biopharmaceutical landscape. Although their manufacture is well established, the sensitive nature of biologic products continues to give rise to challenges. Efficient and reliable scale up is a key component of mAb production – and there are several considerations that need to be understood and reviewed early on in the process. In this article, we explore scale up in the earlier phases of the product lifecycle with Kristina Pleitt from Thermo Fisher Scientific.

What is your role?

I'm a Senior Manager in the Bioprocessing Collaboration Center in Thermo Fisher Scientific's R&D Innovation team. While we sit in the Bioproduction Group, our team is actually the interface between two business units, Bioproduction and Pharma Services (a CDMO for recombinant protein production via mammalian cells). This allows us to have good exposure to most of what Thermo Fisher Scientific offers, be that equipment, single-use products, or services for clinical and commercial drug substance development and production. Our role at the BCC is to operate between these two business units and help fill gaps with products and strategies that currently don't exist. We also have the task of refining our existing products to help ensure we are providing the best end user experience. Our team members have extensive experience in mAb process development and scale-up for production, including full development and tech transfers for early and late phase molecules.

mAbs are well established in the industry, so does this mean that scale up is straightforward?

Scale up is viewed as straightforward, but this doesn't necessarily mean it is simple or easy. There is a great deal that needs to be considered. Of course, you need to determine the process itself, but you also must understand the at-scale requirements, such as the logistics of how it's going to be manufactured, the required equipment, the footprint of the plant, and any processing constraints or limitations that are introduced when you move from the bench into the production suite. You have to address many aspects in your development plan.

A few things to keep in mind as you consider the feasibility of scaling up, especially in the early phase, are time of development and process requirements versus equipment/facility capabilities. And cost is always seen as a major factor. I would advocate that, even at the earliest stages of development, it is important to remember the longer-term goal. Sufficient time and expense spent at the early phases will save both time and money in the long run once large-scale production begins. As you move into scale, cost savings and other aspects that have been identified and put in place at the early stages of process development are amplified. Building and applying process knowledge early in development and initial scale up batches becomes very valuable both short- and long-term. It plays a role in establishing more robust methodologies for your process through its lifecycle. It is essential to understand that the early phase work is a necessary part of building the process for the final, large-scale manufacture of the product. Being mindful of this will avoid focusing on data that is only relevant to these early steps in the larger process.

More broadly speaking, at the early stages of scale up, the focus should be balanced between essentials and on manufacturing robustness. It is important to gather as much knowledge as possible so that, when you reach the manufacturing stage, there will be less challenges related to scaling to overcome. Be mindful about the experiments you choose to perform, ensuring each one gives more knowledge towards the process space. Having an oversight of what will be needed at the next stage informs the choice of studies at this earlier stage, so it's important not to overlook experiments, such as stability, for example.

What are the biggest challenges during the early scale up stages?

When you are gathering process knowledge, you need to be as complete as possible, but this is time consuming and expensive – so there is a temptation to skip some of these steps. It is also tempting to cut back on data ranges within experiments. However, you must remember that any shortcuts could result in costly problems later as you scale! Issues can also be exacerbated by lead times; it is essential to plan far in advance to secure the appropriate supply chain. Sometimes his does not sit comfortably with those clients wanting

to chase aggressive timelines and move their programs along at pace.

In summary, simplicity is key. The simpler the process, the lesser the chances for errors as higher yields are sought through scale up. Consider, for example, manual processes; such steps carry a high risk of error because different operators may perform them differently, which adds complexity to your process. Time taken to reduce or eliminate these steps – steps that are seemingly benign at a small scale – will vastly improve your chances of having a more robust process for larger scale production. The object is to understand your system in as much detail as possible, while balancing the time and cost it takes to get there. With this in mind, it is also important to know what kind of facility you will be transferring the process into for manufacturing; it will also point to further key experiments that need to be conducted at small scale to facilitate the transition.

Are there any mistakes you see being made in early-stage development time and time again?

One mistake that can creep into early R&D is to ignore incorporating short experiments to improve the manufacturability of the process. By considering how the process will be performed in GMP, a few select experiments can provide insights on the design space and de-risk potential challenges at-scale. These could be simple studies to improve process ranges, reduce operator interactions, or removing process performance-based decisions.

Another common problem is neglecting to perform an engineering run at-scale. Yes, this is something that does take time and money, but it is a great way of de-risking the process – and can save you time and money later on in expensive investigations, held up lots, and burdensome change controls in full GMP systems.

What are your recommendations to save time and costs?

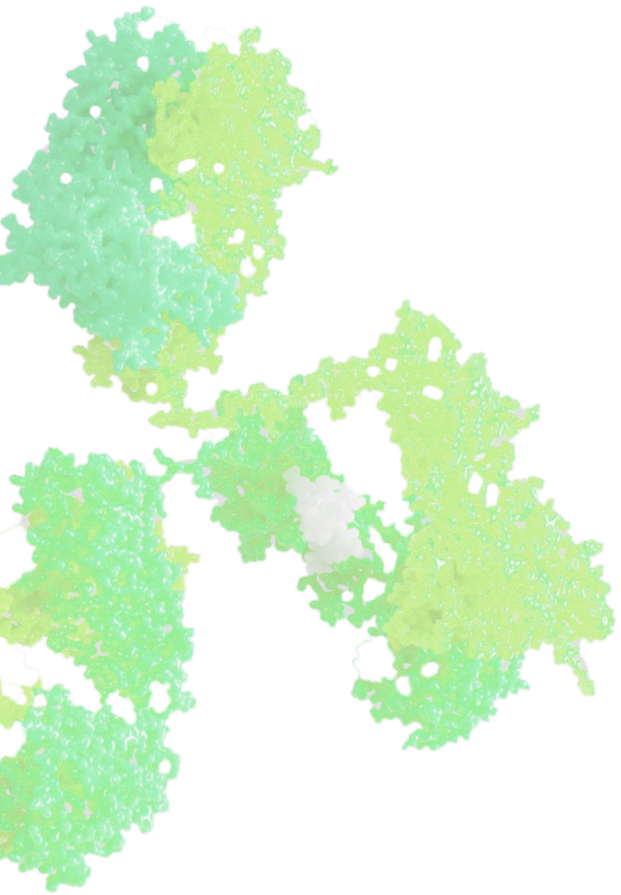
One of the easiest ways to condense timelines is to leverage an existing platform. There tends to be a great deal of similarity across processes providing a solid foundation of knowledge and standard practices. Attempt to use standard platform processes and practices wherever possible and leverage raw material stocks to avoid long lead times. Other ways to cut time are to be judicious in the studies you do and partner wherever possible. Ensure each development step is critical; ask whether you are adding to the process knowledge or de-risking the output. Much of these depend on you having full oversight of where you want to be and how you will reach that point – something only experience brings. Building on what's known allows you to focus effort on refining and optimizing critical parameters.

Cost is again a balance of the value from de-risking versus the cash spent. At the early phase, raw materials are particularly expensive and can have long lead times. Working with a trusted and experienced partner, can help where there are already existing stocks. It is also beneficial at this stage to consider both the immediate and longer-term view. For instance, how many cycles or batches do you anticipate producing with a specific chromatography column? Is it possible to use stock media rather than custom? While these may seem like more cost up front, a little additional knowledge to increase process robustness could help during production.

How can Thermo Fisher Scientific's expertise help support early stage scale up?

Thermo Fisher Scientific offers a lot of expertise and experience in this sector and has been working with companies throughout their scale-up programs for many years. Within our Pharma Services Group, we have two specific programs: "Quick to Clinic™" and "Quick to Care™". These platforms focus upon the development of manufacturing processes and encompasses a wealth of experience. Similarly, we have a considerable range of products, from media to single-use products that can scale with your program, and that means you can consolidate your efforts within one dependable partner. Partnering or collaborating with clients is very much part of our ethos. Not only does this better prepare the supply chain, but it also helps us identify ways to meet the clients' needs and facilitate their processes – both now and in the future.

Through our collective bioprocessing development and manufacturing proven experience, we have a complete overview of the pathway from the bench to manufacture with good process knowledge at every scale. Our clients can feel confident that Thermo Fisher Scientific will use its extensive expertise and experience to fully support them at every step of their journey.



Enter the Age of Modular Manufacturing

Thermo Fisher Scientific's standardized, modularized system provides individual building blocks that can be arranged in a customized fashion, while easing supply chain pressure.

Throughout the COVID-19 pandemic, Thermo Fisher Scientific has worked to help ensure robust supply chains for customers. But the company has also been busy developing further novel solutions and strategies, including modularization, that offers many benefits to biopharma customers. Rob Hendrix, Manager, Systems Design Engineering at Thermo Fisher Scientific, tells us more about these exciting developments.

What is your role?

I work on single use and system design within the Bioprocess Collaboration Center. I am part of the Thermo Fisher Innovation Team and my primary role concerns modularization strategies and how to achieve more economical manufacturing efficiencies for customers at commercial scales. To really make an impact in this area, you must look at the process requirements and systems for manufacture, and also evaluate the impact of business decisions that affect investment in this area and de-risk both process and business-based factors.

How do standardized, modularized systems benefit supply chains?

Modularization, at its core, allows us to use the minimum chain of single-use manifolds at a high volume, whilst retaining the maximum number of degrees of freedom in your process design. Modularization may involve a little loss of efficiency during the unit operation optimization process, but this is more than made up for later on. As a business case, these small shifts in efficiency can ultimately have a significant impact. Modularization allows the same component (stock item) to be used for multiple unit operations within a multi-unit operation end to end process. This single component with multiple different uses design philosophy solves several challenges that affect supply chain management, as it is based on ordering of a smaller subset of materials compared with custom processes. It promotes manufacturing robustness through the stocking of common materials within multiple manufacturing suites, allows standardized deployment across multiple manufacturing sites, and decreases the risk of supply shortages for individual stock items.

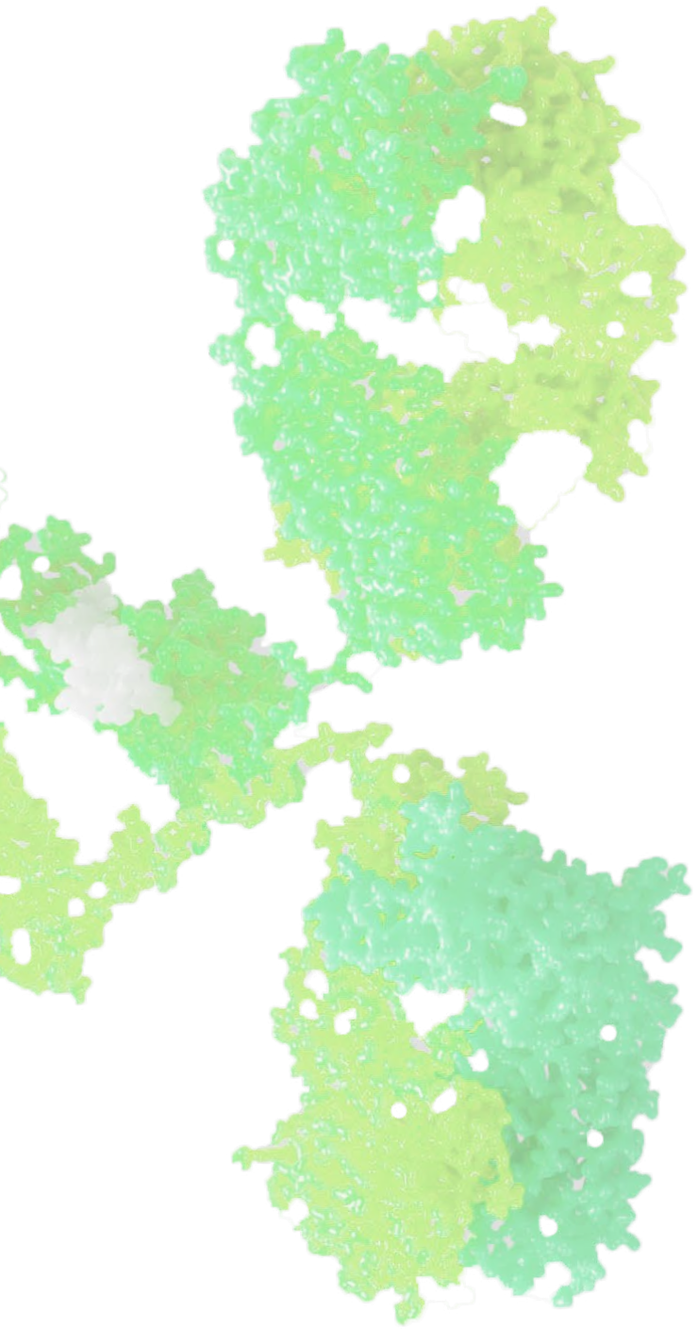
Standardization of the manifolds offered through our mAb Process Playbook Modular Manifold Library™ allows the designer to seamlessly piece together their unit operations regardless of polymeric construction materials. It's our equivalent of building blocks ! Building blocks always connect regardless of which piece you have. Our components are also designed to remove the potential for errors, which might normally arise when stacking various process steps together or trying to transition between polymeric materials of construction to meet other mechanical requirements within a given process.

Modularization through standardized subcomponents helps to also build additional levels of human factor engineering into a manufacturing design to further reduce manufacturing errors. One of the underestimated benefits of this type of modularization strategy is that it transitions the manufacturing mindset away from one of custom every time but "right-first-time" to one of "right-first-time" with a never changing connection process. This allows for specialization of operator tasks around a repeated subset of operations and thus an observable drastic reduction in errors associated with uniqueness.

Why should manufacturers think about modularization early in the life cycle of a molecule?

Modularization via standard manifolds is a design approach that brings efficiencies at all scales but increases drastically as a firm moves toward commercial scale manufacturing. It is of utmost importance that clients transfer this philosophy into their development in the early stages of a molecule's lifecycle.

One of the pitfalls of many organizations is that the development drives information and process requirements in a one directional workflow from Development to Commercial. However, this can lead to over optimization toward unit operation



specific yields and an end-to-end workflow design that does not translate efficiently at a commercial scale when manufacturability of the process is considered.

To help clients adopt this design approach at earlier process scales within the development pathway the modular manifold library is designed to offer the same engineering and design strategy starting from the bench top and then transitioning the whole way through commercial scale components. Maintaining the same components and design approach through the life cycle of the molecule from development to commercialization offers additional efficiency potentials for a firm including earlier troubleshooting and evaluation of engineering performance of the molecule with the subcomponents and polymers as well as an easier pathway to other manufacturing efficiencies such as batch record standardization and templating. This inherent combination of flexibility and efficiency is something not seen in customized, single-use processes.

What are the risks?

Our studies have shown that adopting the standardized modular approach does not increase errors associated with connections.

Foremost, modularization of an end-to-end manufacturing process introduces a small increase in the total number of process connections within each unit operation. While the actual number of connection unit operations has been shown in other publications to not be large this accepted increase in the number of connections runs counter current to the accepted design ethos of minimizing the number of connection points within the process boundary. To further evaluate the potential impact of this connection, an increased statistical analysis was performed that evaluated the elevated connections within multiple same 2000L liter scale processes. This analysis demonstrated that at a 98 percent success criteria the processes whether modularized or designed with fully custom and minimal connection single use manifolds behave statistically the same. This analysis was published by Thermo Fisher in a white paper titled Analysis of engineering manufacturing risk utilizing a modularized and standardized single-use manifold design approach.

What are the upsides?

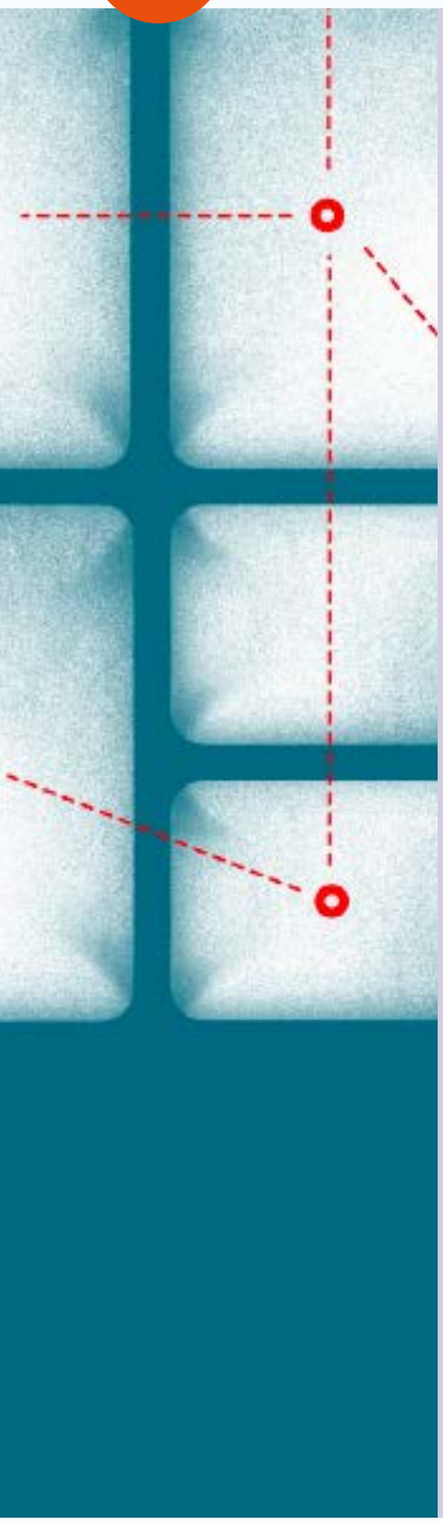
Our standardized, modularized system provides individual building blocks that can be arranged in a customized fashion. This reduces the need to turn to a custom solution since the customization can be achieved by just rearranging the pieces. These building blocks, by their very nature, remain constant, which simplifies supply and stocking. Standardization, therefore, leads to supply chain resilience by reducing the number of unique stock items required. There are also other benefits; for example, it can significantly reduce process design, as well as address the complexities of component management, all without limiting process capability. It also simplifies upfront design time, resulting in time- and cost-savings for manufacturers. We believe that using a consistent approach to design increases manufacturing success rate because it allows companies to focus on increasing production instead of managing complexity – highly valuable in terms of saving time and cost.

Adoption of this system is straightforward and requires very little change in company operating practices. Ultimately, its adoption should reduce the administrative burden of purchasing and stocking.

Why partner with Thermo Fisher Scientific?

We are the ideal partner to collaborate within this field for several reasons. We have put a great deal of resources into developing our modularization options and strategy, particularly during the pandemic, and we have designed a system that simplifies, de-clutters, and improves supply chain performance. We also have a trusted and experienced presence worldwide and can deliver these subcomponents reliably.

Our innovation in this area is a great example of how Thermo Fisher Scientific works at its best. We actively seek opportunities to work together with our clients. We believe in establishing a trusted partnership led by collaboration and open communication to evaluate, assess, and plan, while finding the appropriate solutions early in your journey.. Through this philosophy, we keep evolving and growing alongside our clients. It is exciting to see how this system will be deployed across the industry – and where it will take biopharma manufacturing in the future.



Value of standardization modularized manufacturing strategies for single-use technologies

Authors

By Robert Hendrix, Staff Engineer, Systems Design, Kayla J. Spivey, Content Specialist III, BioProduction, and Levi M. Larsen, Market Intelligence Analyst III, BioProduction, all at Thermo Fisher Scientific

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.

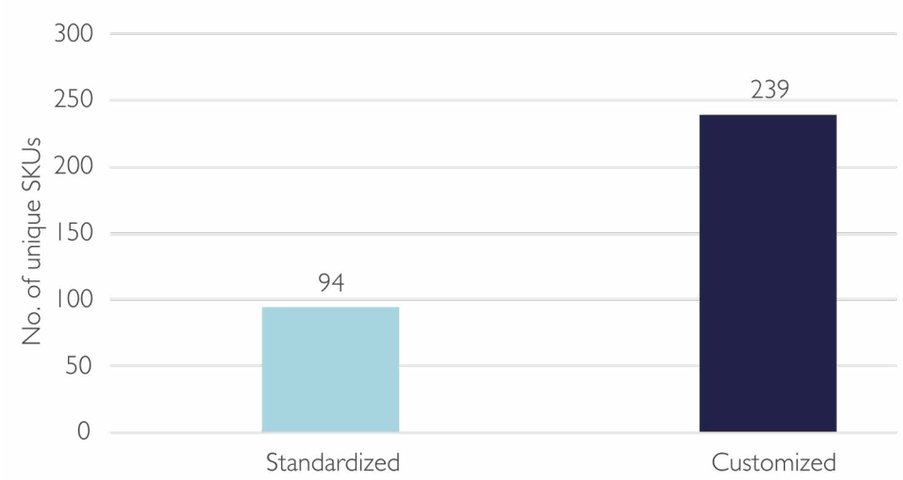
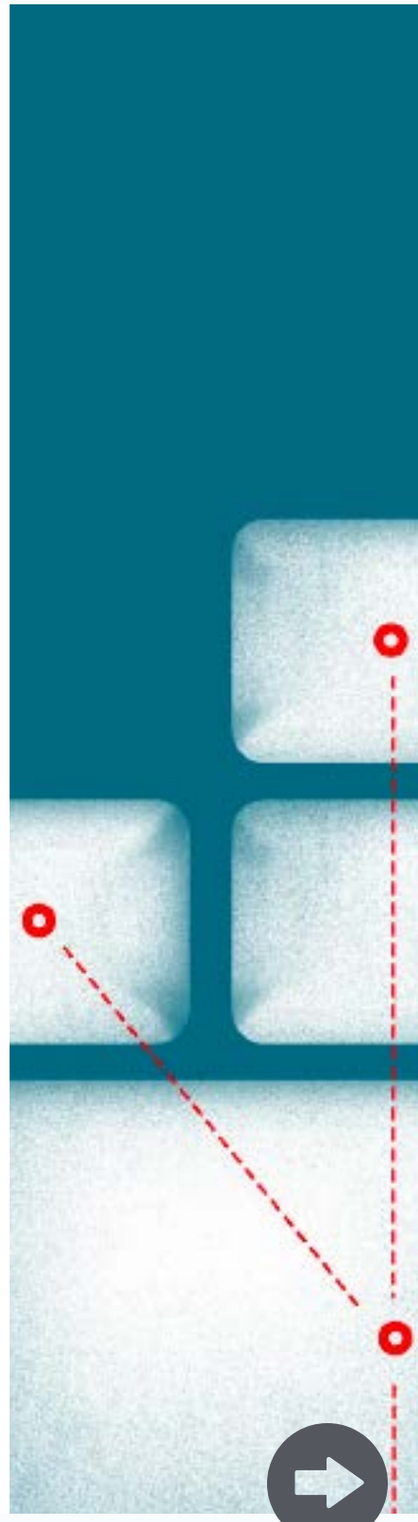


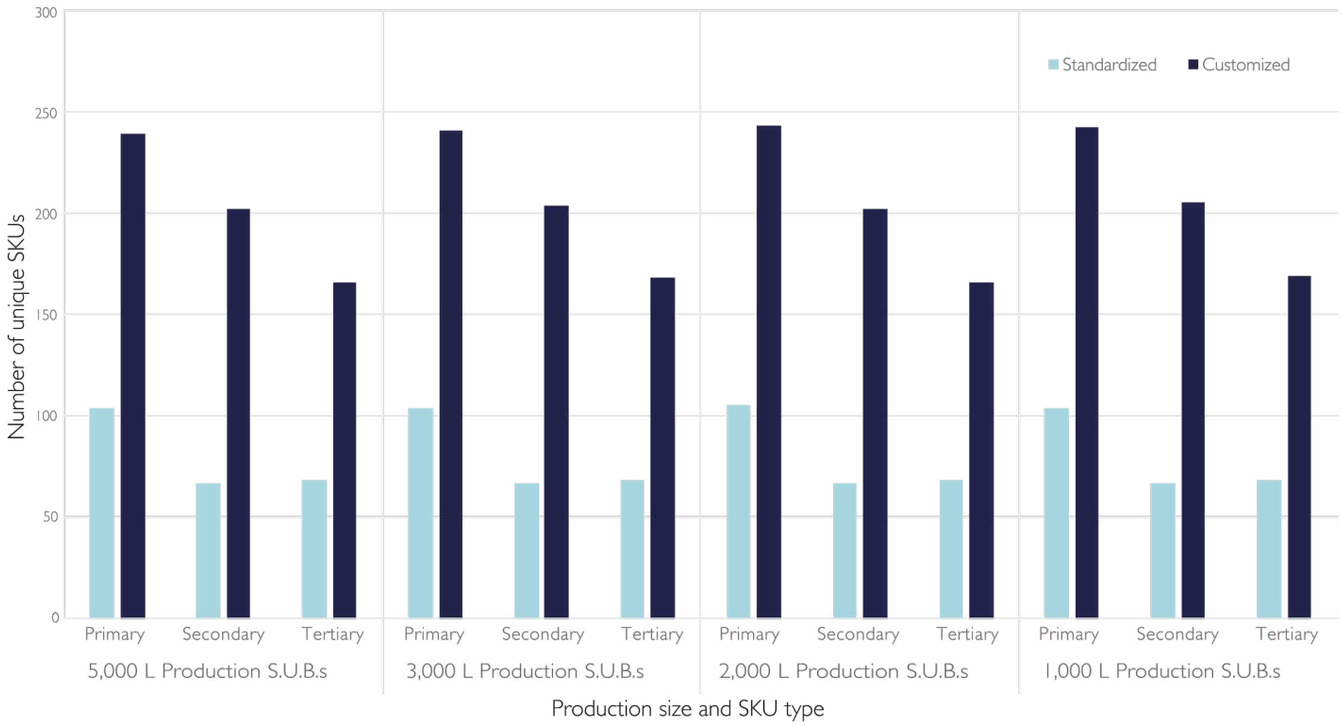
Figure 1. Primary quantity of unique SKUs required to perform unit operations.



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.



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 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.

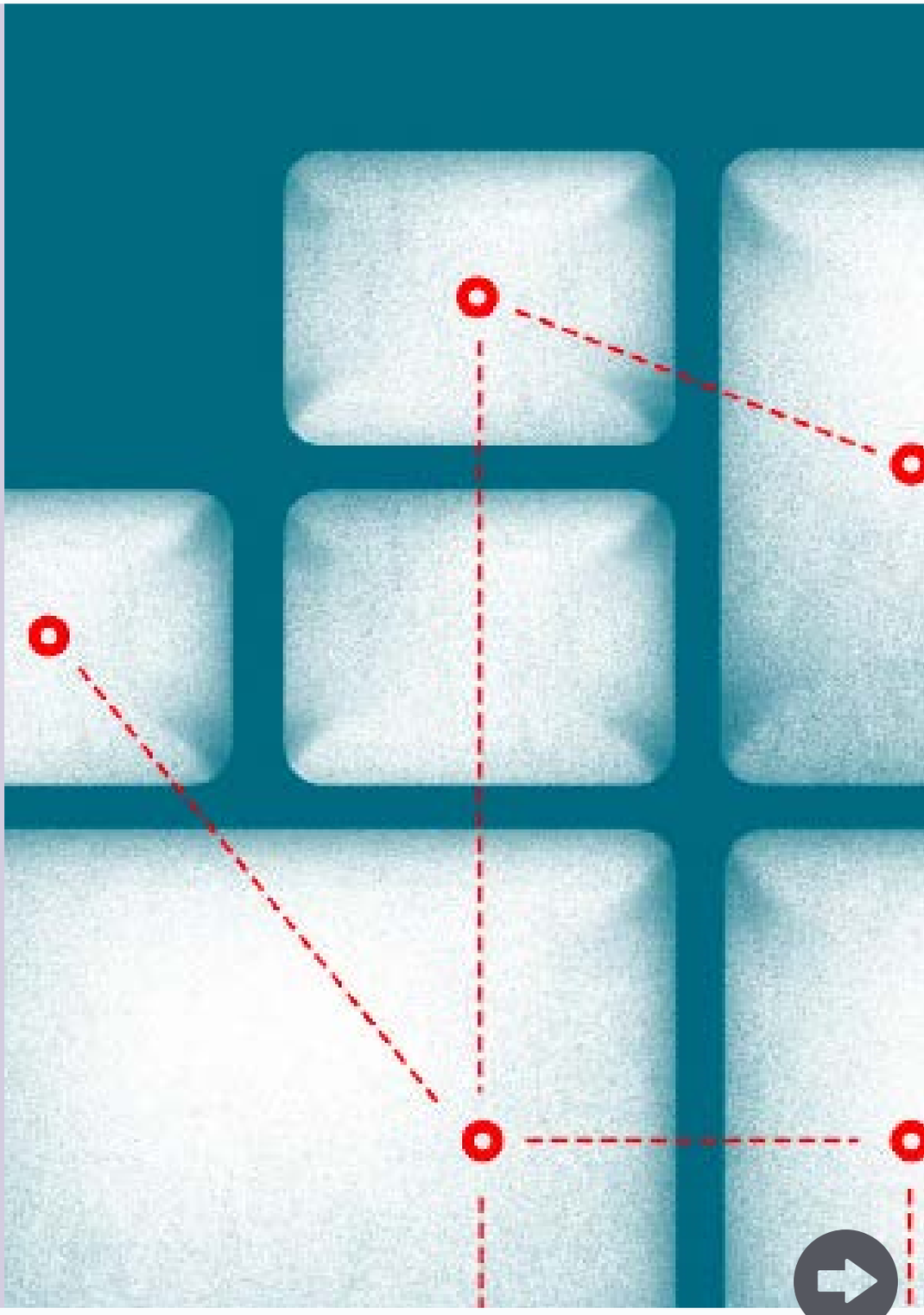
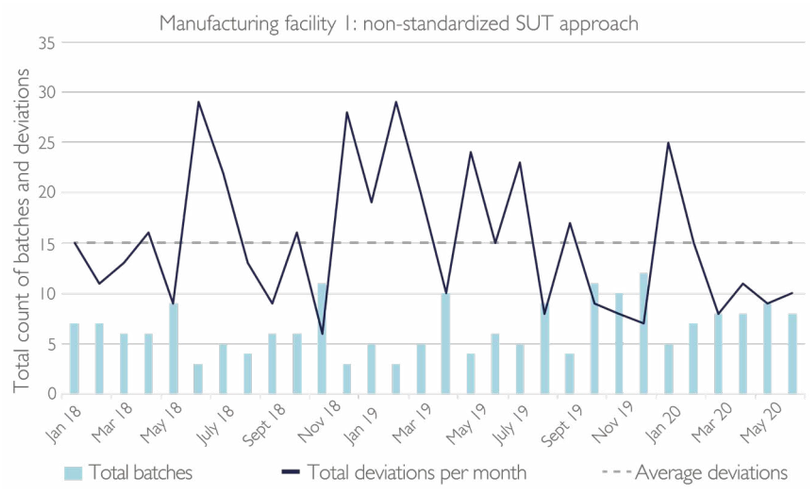
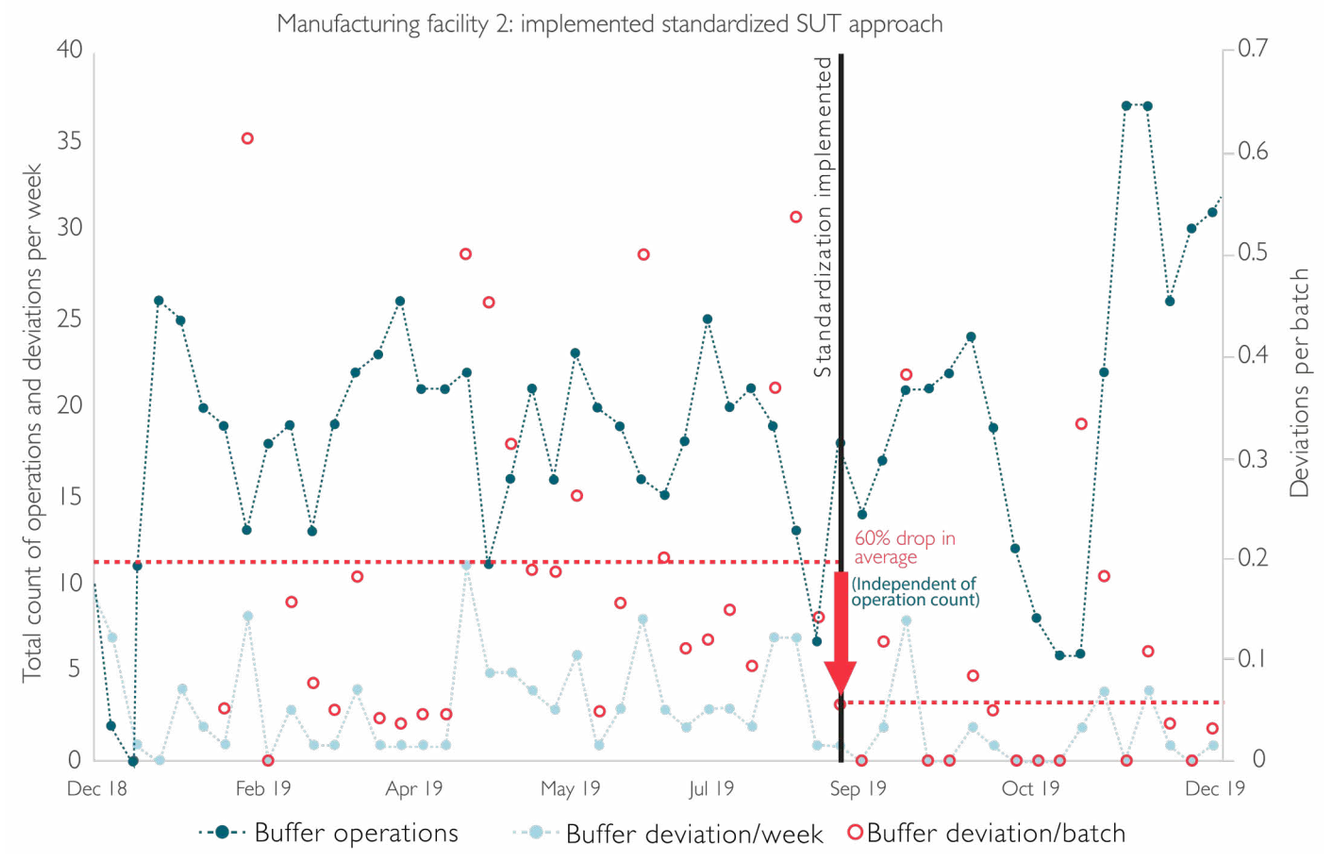


Figure 3. Manufacturing site comparison of non-standardized and standardized SUT approaches. Upon implementation, manufacturing site 2 deviation reduction accounts for a 5M–7M dollar opportunity in back-end remediation costs when compared to manufacturing site 1.



	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



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

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.

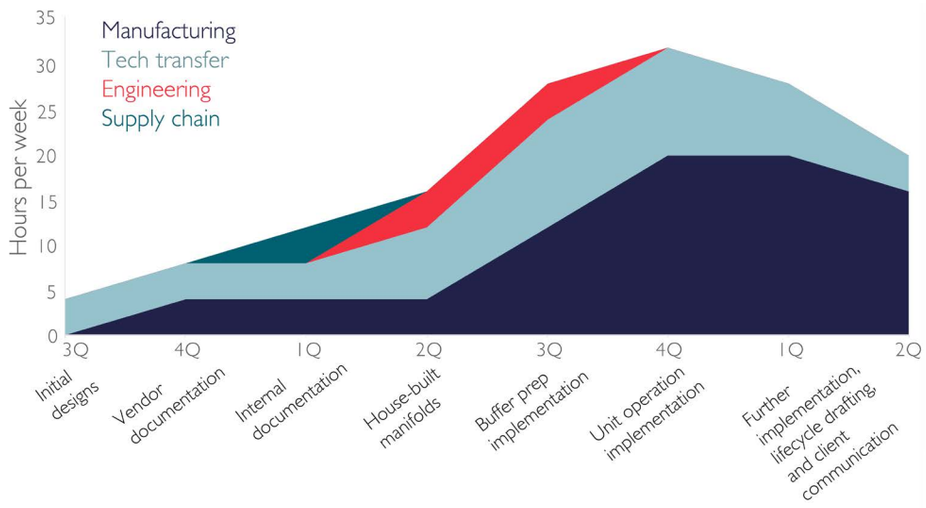
Figure 4 shows tracked hours needed by different departments from the start to the end of implementation. Throughout the 1.5-years it took to fully switch the process to the modularized single-use engineering approach, there was never a point when a department required a full-time employee. At its busiest, 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.

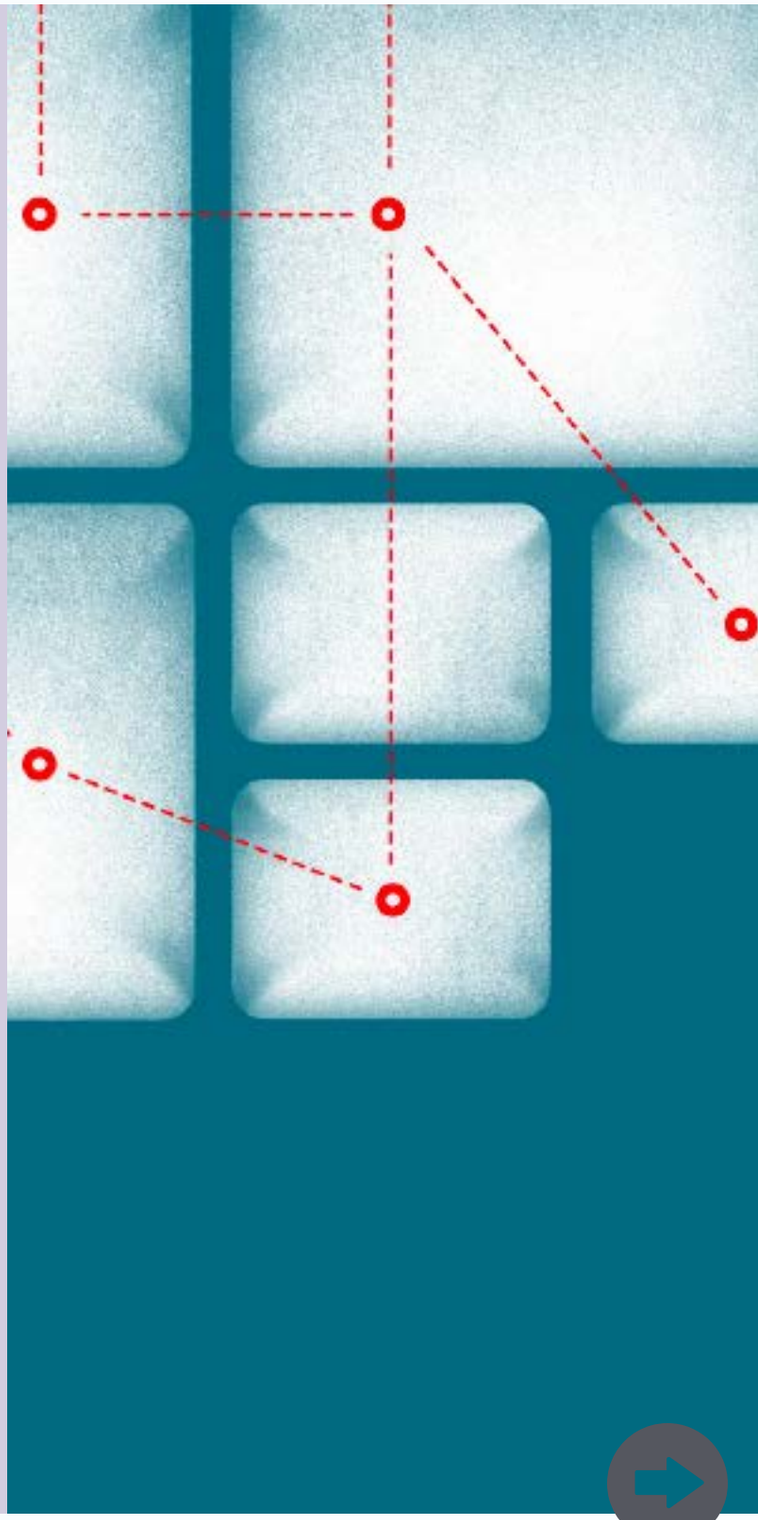
As a way of investigating the additional risk associated with implementation, we performed an analysis examining the engineering manufacturing risk using the standardized single-use design approach based on the mAb Process Playbook Modular Manifold Library. The subsequent paper from this additional research 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.

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.

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.

Learn more at thermofisher.com/mabprocessplaybook

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