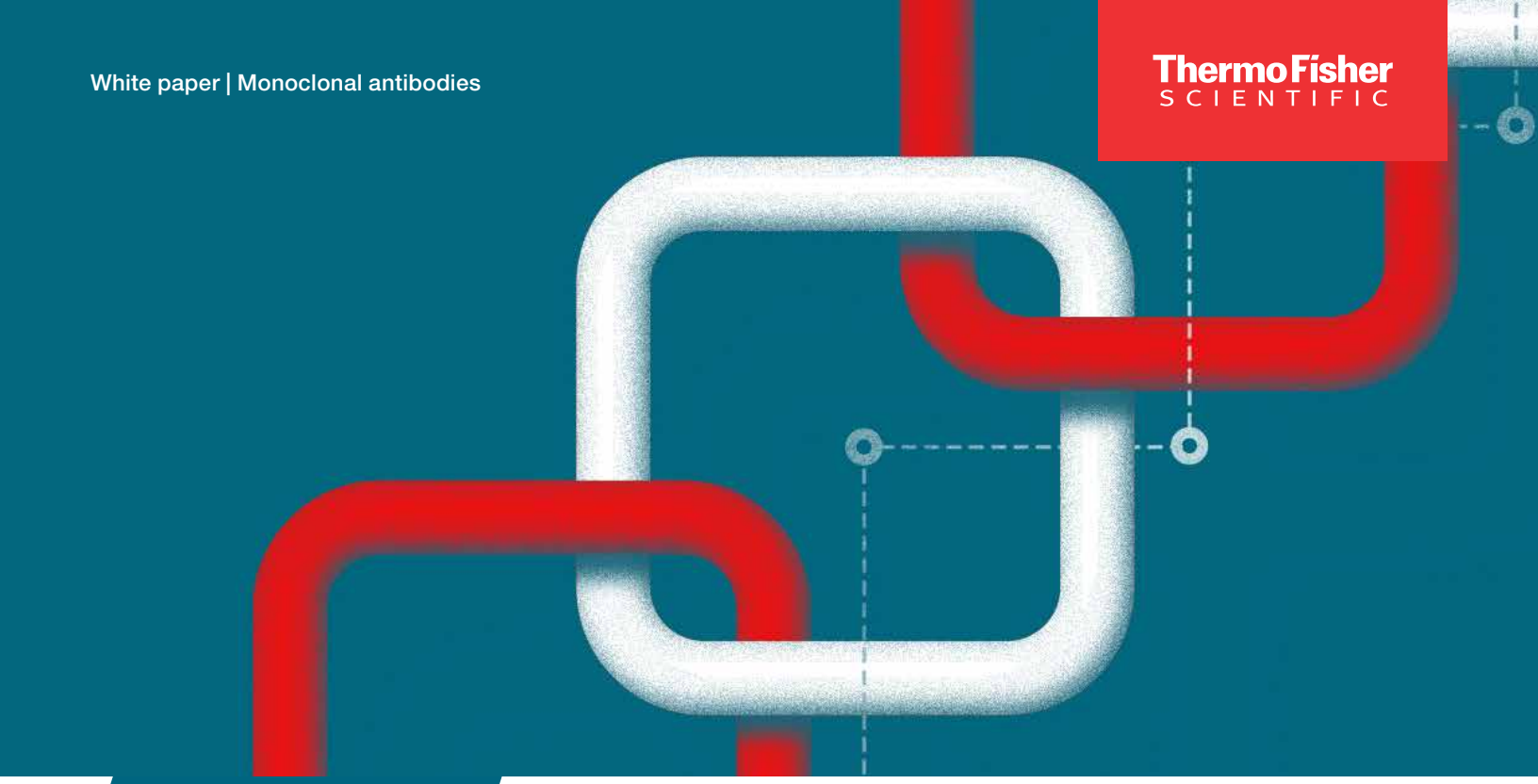

Single-use technology

Analysis of engineering manufacturing risk utilizing a modularized and standardized single-use manifold design approach

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Abstract

We present a manufacturing risk analysis for a novel standardized and modularized single-use manufacturing strategy for 2,000 L scale single-use recombinant protein production using the mAb Process Playbook Modular Library developed by Thermo Fisher Scientific. We evaluate manufacturing risk of this approach by calculating engineering risk profiles for 10 unique end-to-end 2,000 L processes and evaluating these risk profiles against a 98% manufacturing success rate standard. When analyzing the calculated manufacturing risk profiles, the results suggest that the use of the standardized and modularized single-use engineering strategy does not generate excess engineering risk at a 98% success rate standard. In fact, the standardized and modularized engineering approach performs well enough on average that each individual program analyzed should be expected to perform better than the 98% success rate criterion.

Introduction

Process design for the production of recombinant proteins becomes an increasingly important focus for the commercialization and delivery of a variety of rapidly expanding pharmaceutical modalities including monoclonal antibodies, cell therapies, and gene therapies. Process design is also important for the successful manufacturing of critical subcomponents to support processes for mRNA vaccines. Manufacturing processes are customized for the manner of terminal sterilization of the product; therefore, a thorough understanding of proper aseptic design and low bioburden design practices is required to safely mitigate risks for the targeted patient or mitigate manufacturing risks for subcomponent contamination in downstream processes. Specifically, the risk of potential ingress of adventitious agents or nonviable particulates that can copurify with the product must be mitigated in the design of the process.

Biomanufacturers need to understand how the production environment and equipment used influence system quality and operations, and ultimately, mitigate the most common contaminants. This means mitigation of four common contaminants potentially introduced to the process:

Particulates

Dust, elastomeric debris, dirt, hair, etc.

Chemicals

Endotoxin, impurities in raw materials, leachables and extractables, and cross-contaminants

Viral matter

Retrovirus-like particles (RVLPs), murine minute virus, etc.

Microbes

Bacterial, yeast, fungal, etc.

These common contaminant classes can be introduced into the manufacturing process by the bioprocessing environment including:

Raw materials

used as components in manufacturing

In-process materials

such as buffers

Consumables

including single-use containers, bags, tubing, and filters, as well as contaminants from utility services, air, WFI, O_2, CO_2, N_2, and clean steam

The manufacturing environment

Shared clean-in-place (CIP) systems

when these are not self-sanitizing

Traditional single-use (SU) manufacturing mitigates these environmental risks by appropriately defining sterile boundaries within critical unit operations and designing unit operation–specific subcomponent manifolds. Prior to use, manifolds are sanitized or sterilized using chemical sanitization, gamma irradiation, or steam sterilization, depending on the unit operation and facility procedures. Historically, additional engineering controls including welding and sealing of single-use tubing, have facilitated functionally closed manufacturing connections downstream of 0.2 µm sterilizing grade filters.

A customized SU manufacturing strategy is effective because it assures lower failure rates; however, a case-by-case design approach is a substantial time investment. Customization increases upfront design and execution times while generating the need for highly specific one-off single-use manifolds. Given these manifolds must then be custom assembled by a supplier, preassembled manifolds diminish supply chain optimization.

If a supplier experiences supply chain issues, something SARS-CoV-2 has made the world extremely familiar with, it is not surprising that the most common products would be given priority. Thus, the true tradeoff comes fully into perspective. Does a firm risk potentially higher contamination rates using a modular standardized manifold approach that yields additional connection points, or does it opt to customize its products and reduce the number of connections within the process, but maintain a larger and more unpredictable supply chain risk?

Building workflow micro-efficiencies into a manufacturing process helps to lower cost, speeds up return on investment, and decreases the overall time to bring a drug to market. When assessing even small operational modifications, it is critical to ensure that efficiency solutions are supported by experimentally relevant data that establish confidence in providing high-quality and consistent results. The benefits of implementing a standardized modularized design strategy, like the one offered by the mAb Process Playbook Modular Manifold Library, creates a more efficient supply chain, faster technology transfers, more robust designs, and documented standardization with fewer products. The downfall of the modularized and standardized single-use design approach is that it results in additional points of connection within the overall workflow, which could increase risk within each unit operation. In this study, 10 representative 2,000 L single-use processes were analyzed with the modularized and standardized design strategy to calculate manufacturing risk profiles for a modular design approach. Risk profiles were calculated based on failure rate data for single-use connections and welding based on sampled nonconformance engineering data normalized against total batches manufactured over a 4-year historical period. The goal of this evaluation was to observe potential differences in overall manufacturing engineering risk when comparing a standardized and modularized manifold design strategy to a traditional customized manifold design strategy.

Analysis

To evaluate the performance of the standardized and modularized manifold design approach, the 2,000 L bioreactor manufacturing processes of 10 clients were redesigned using the mAb Process Playbook of standard modular products. The 10 client programs that were redesigned and subsequently analyzed in this study were randomly selected from a sample of manufacturing processes from various industry-recognized pharmaceutical manufacturers. For the purposes of this study, they have been designated as Client 1–10. During the redesign of each end-to-end process, modular products from the mAb Process Playbook were chosen to maintain engineering equivalency within each unit operation; the unit operations were not changed. The processes were then analyzed to calculate an overall manufacturing risk score for the new modular process by measuring the new total instances of failure and multiplying those instances of failure by the historical failure rates observed within the manufacturing facility for those specific types of connections.

For the purposes of the analysis, the connections were first categorized into three different subgroups.

Connection type	Classification	Example
Briefly exposed connector	Connections that are not intended to be closed	Tri-clamp or MPC connection
Functionally closed connector	Designed to maintain a sterile boundary during and following the connection	AseptiQuik™ or Kleenpak™ connection
Weld*	Welding connections using an end-to-end weld at the point of connectivity	–

* These connections were an aggregation of connections performed using a variety of commercially available welding technologies.

The connection-specific subgroups were then organized into two categories: business risk failure points, which were defined and classified as connections upstream of the designated critical process sterile boundaries; and critical connection points, defined as single-use connections or welds designed to be functionally closed and critical to the sterile boundary within a given unit operation within a process. Within the process flow diagrams (PFDs), failure points for specific unit operations sub-steps within each unit operation were categorized as individual and unique points of failure in the process due to the batch nature of each process analyzed. Each subunit operation represents a unique instance in which an individual connection could fail within a given unit operation.

Table 1. Client programs, types of connection points, and theoretical total potential failure opportunities by connection type.

Connection type	Client 1	Client 2	Client 3	Client 4	Client 5	Client 6	Client 7	Client 8	Client 9	Client 10
Briefly exposed	554	373	508	744	381	385	328	568	448	858
Functionally closed	228	174	211	250	226	148	204	275	262	332
Welding	66	64	68	53	78	89	39	65	58	80

Table 1 summarizes the number of instances of potential failure within each of the 10 client programs for each specific subgroup defined on the previous page.

Failure rates for each of the connection subgroups, briefly exposed, functionally closed, and welding, were also calculated by aggregating failures observed over 4 years of manufacturing nonconformance data sets for each connection type in the end-to-end manufacturing workflow. Failure rates were determined by dividing the number of unique incidents of failure associated with each subgroup by the total number of batches manufactured. Calculated failure rates for each subgroup are summarized in Table 2.

Table 2. Aggregated failure rate by connection subgroup.

Connection type	Connection failure rate
Briefly exposed	0.45%
Functionally closed	0.48%
Welding	0.50%

Two risk profiles were calculated combining the total number of connections and the failure rates per connection subgroup for each process analyzed. The risk profiles were classified as a total manufacturing risk (TMR) failure rate and a product quality risk (PQR) rate.

The TMR rate was calculated using Equation 1.

Equation 1: $TMR_1 = xf_1 + (yf_2 + zf_3)$

The PQR rate was calculated using Equation 2.

Equation 2: $PQR_1 = (yf_2 + zf_3)$

Where xf_1 is equal to briefly exposed connections upstream of the defined sterile boundaries of each process and thus can be viewed as business risk failures with minimal risk of product quality impact, and $(yf_2 + zf_3)$ is the total connections specifically designed to be functionally closed connections and welds and thus have a high degree of probability for directly affecting critical quality attributes. These are viewed in this study as a product quality–specific manufacturing (PQSM) risk rate.

Table 3 displays the calculated total manufacturing risk and product quality risk profiles of each of the 10 client programs above, using data from Tables 1 and 2 and Equations 1 and 2.

Table 3. Calculated total manufacturing risk and product quality risk for 10 clients.

Connection type	Client 1	Client 2	Client 3	Client 4	Client 5	Client 6	Client 7	Client 8	Client 9	Client 10
TMR rate	3.917	2.834	3.639	4.813	3.189	2.888	2.650	4.201	3.564	5.855
PQR rate	1.424	1.155	1.353	1.465	1.475	1.155	1.174	1.645	1.548	1.994

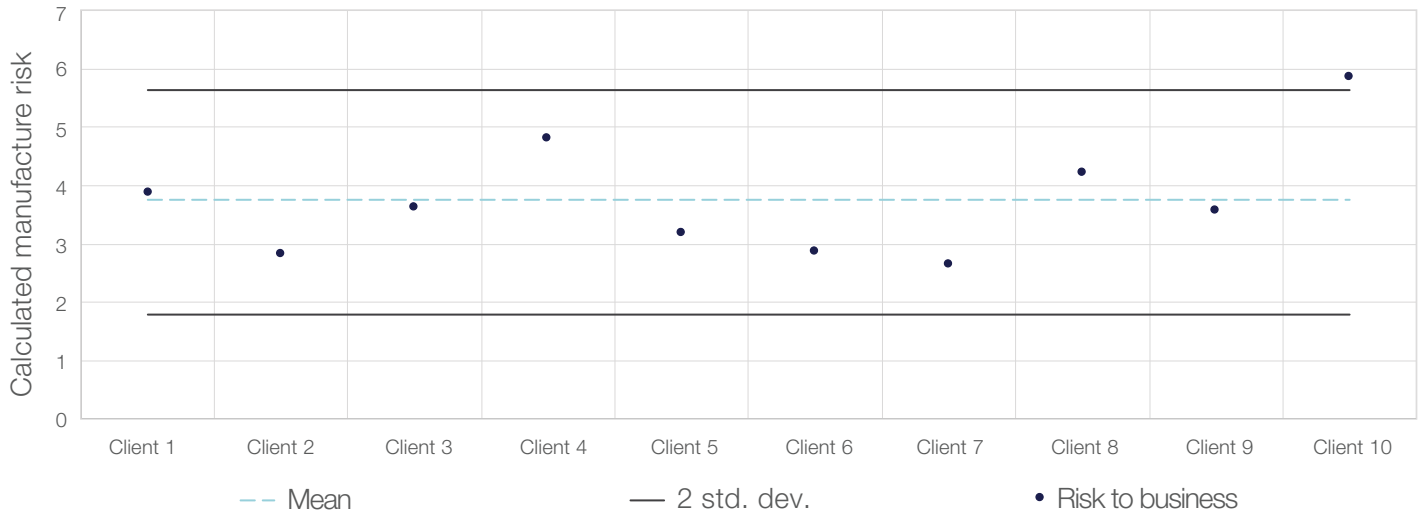


Figure 1. Total manufacturing process risk. Risk to business = total manufacturing risk (TMR) failure rate.

After calculating TMR and PQR, the impact of standardization was assessed by statistical analysis using XMR plots. Within each XMR plot the sample data and mean were charted along with the upper and lower bounds, defined as two standard deviations (std. dev.) from the mean. A comparative analysis is made by contrasting the XMR plots for TMR and PQR using the observed failure rates and a theoretical manufacturing success rate of 98%. While using the theoretical manufacturing success rate, Equations 1 and 2 change as shown in Equations 3 and 4.

Equation 3: $TMR_2 = xW_1 + (yW_2 + zW_3)$

Equation 4: $PQR_2 = (yW_2 + zW_3)$

Note the only difference is the previous observed failure rates f_1, f_2, and f_3 are now replaced with a 2% manufacturing failure rate for failure rates W_1, W_2, and W_3. This can be directly illustrated if the redesigned programs using the modularized and standardized engineering approach would theoretically push a given client's manufacturing success rate statistically past the success rate criteria of 98%.

Figure 1 shows an XMR plot, with the mean and upper/lower bounds for the calculated theoretical failure rates for each redesigned client process. The y-axis represents total theoretical manufacturing risk, with a higher score representing a greater associated risk of failure within a given end-to-end modularly standardized process. When plotted, the data were grouped close to the mean with only one outlier, client 10, located beyond the upper bound. For clients 1–9, the slight increase in connections due to modularization when compared to each other added little overall increase to the theoretical failure rate. In this analysis, client 10, a more complex perfusion process, served as the only outlier in the study due to the process's increased upstream complexity that pushed the overall risk score just outside of the upper bound. Client 4, which had roughly 200 more total connections than the sample average, was the only point that is above the upper first standard deviation. This was also due to a slight increase in complexity, and subsequently more connection points, to accommodate a more complex bioreactor feeding strategy, and a more complex chromatography unit operation sequence. However, even with the additional complexity and 200 more potential instances of failure, client 4 is still within the boundary of statistical control limits when compared against the other 9 client programs. While a myriad of factors could contribute to additional variation between clients, the consistent manufacturing risk scores suggest that utilizing the standardized modularized design approach does not significantly raise manufacturing risk irrespective of the slight increase in the number of connections within each unit operation.

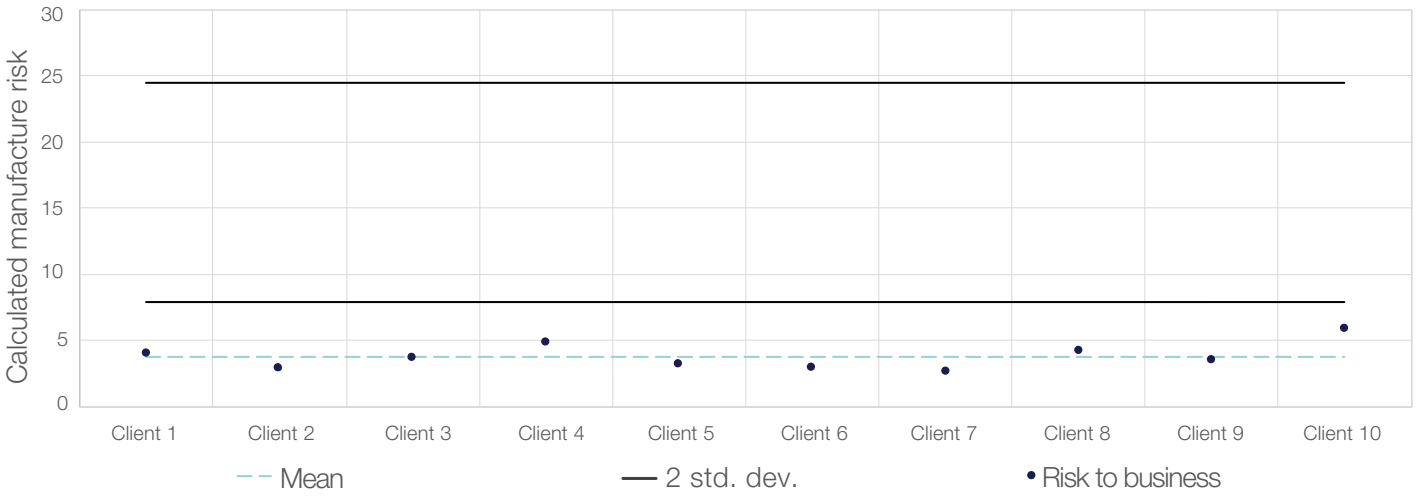
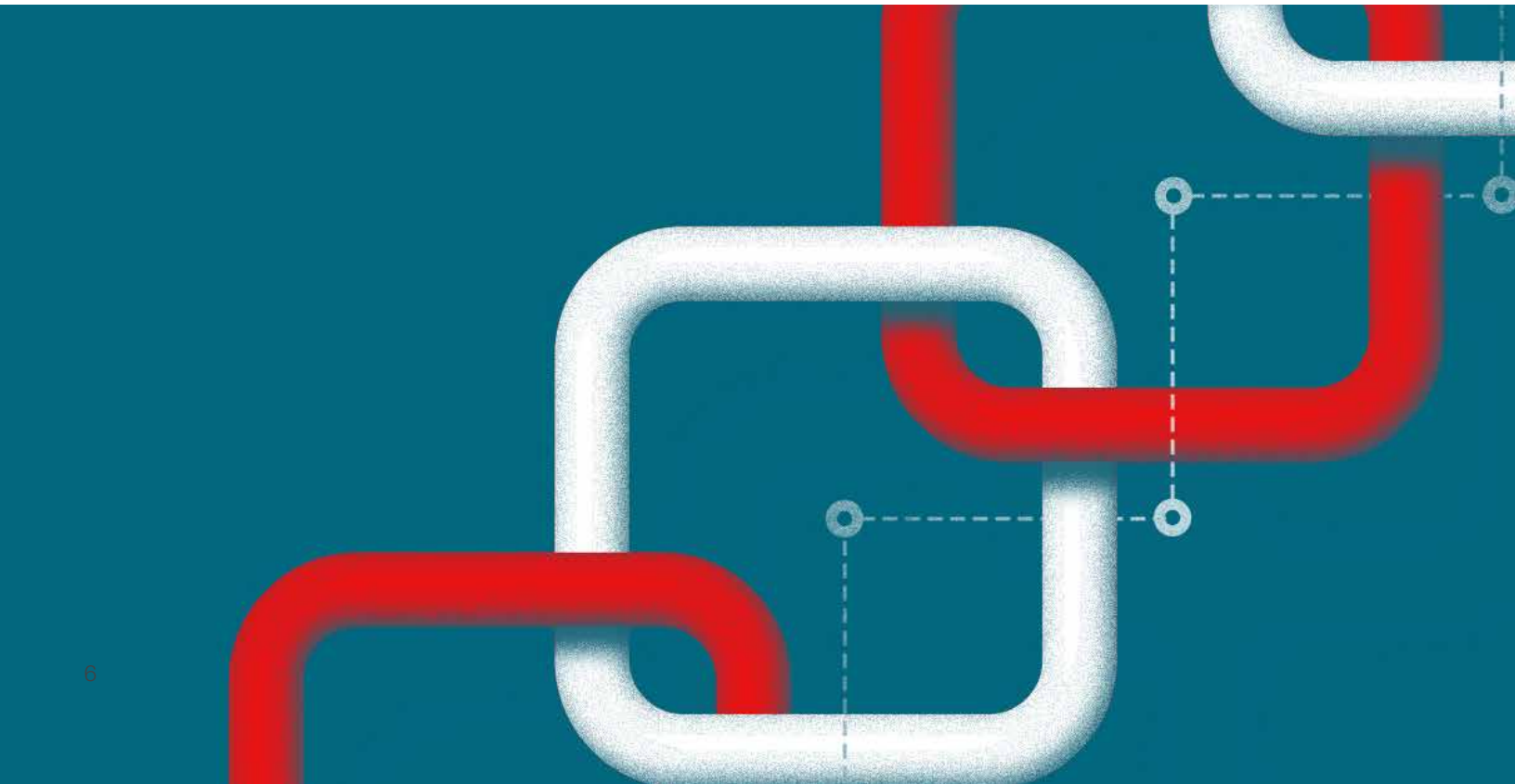


Figure 2. Total manufacturing process risk XMR plot adjusted limit: 2% failure rate. Risk to business = total manufacturing risk (TMR) failure rate.

In Figure 2, the sample data and mean were plotted the same as in Figure 1, but a 2% failure, i.e., 98% total manufacturing success rate, was used to define the upper and lower statistical bounds (see Equations 3 and 4). This compares the standardized modularized engineering design approach to a real-world manufacturing success rate target. In Figure 2, all the client data are well below the lower bound, demonstrating that the standardized modularization approach outperforms the 98% success rate criterion. In this case, even client 10, the outlier who is above the upper second standard deviation in Figure 1, is several risk points below the lower second standard deviation suggesting that the approach is also robust enough to maintain a consistent 98% success rate target regardless of additional complexity from a perfusion-based process.

Considerations made when selecting a type of connection for the bioprocessing workflow affects the potential for direct product contamination. Undetected product contamination puts patients at risk, and detected contamination leads to rejected batches; therefore, safety measures are a pivotal component to consider. Current risk mitigation strategies are focused on avoiding operator error, materials considerations, packaging, biocompatibility, sterility and leakage validation level, and minimizing the number of connections made within the critical sterile boundaries of unit operations.



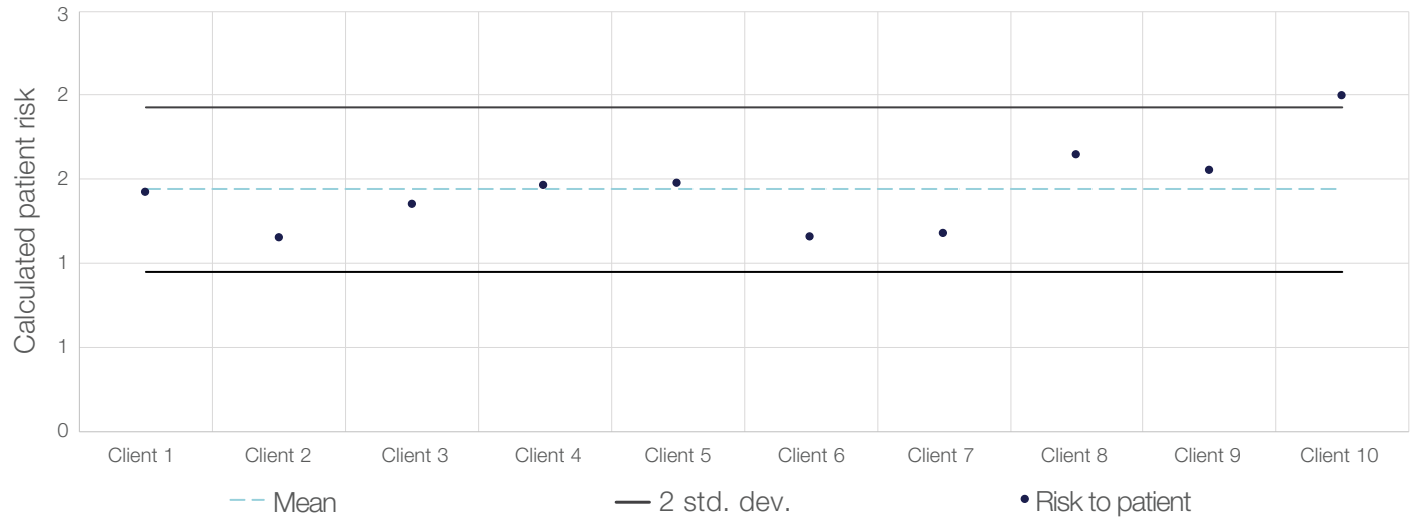


Figure 3. Total patient risk XMR plot. Risk to patient = sterile + welding calculated risk failure rate (PQR).

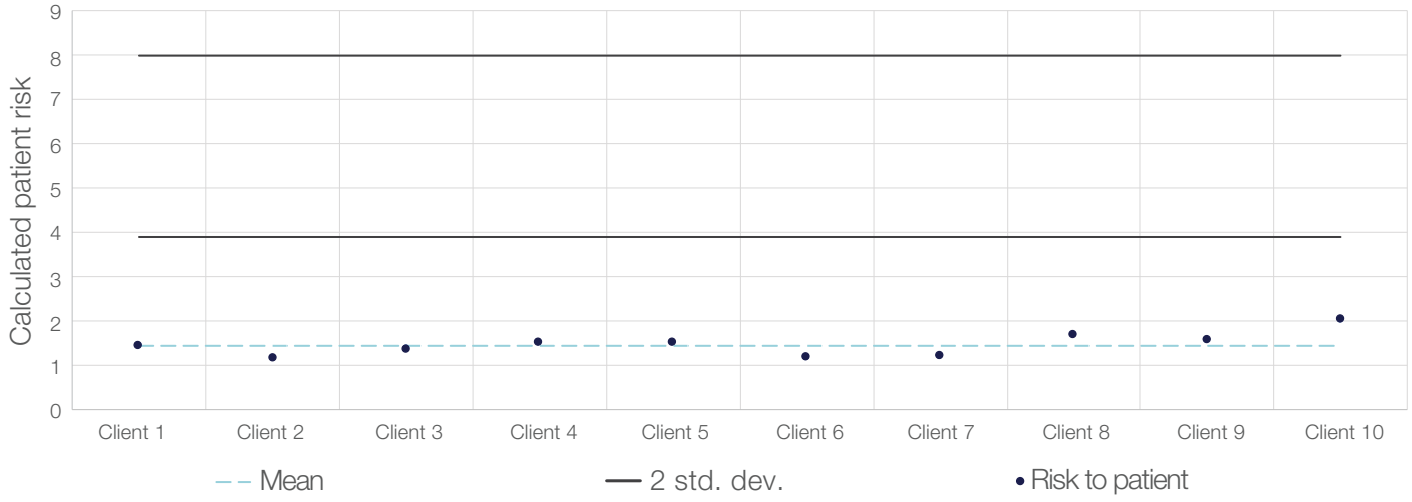


Figure 4. Total patient risk XMR plot adjusted limit: 2% failure rate. Risk to patient = sterile + welding calculated risk failure rate (PQR).

Connections downstream are integral to maintaining a sterile process boundary within each unit operation. PQR rates are displayed in Figures 3 and 4. Recall that PQR calculated previously only factored in failures of functionally closed single-use connections and welded connections. The XMR plot in Figure 3 exhibits similar behavior to the manufacturing risk XMR plot in Figure 1. In this instance, the data are grouped closer together, and again, client 10 (the more complex perfusion process) is the only process outside of the upper bound. Similar conclusions as to why this is the case can be drawn as stated above. PQR rate using the modular standardization approach analyzed did not vary greatly and was primarily grouped around the mean.

Figure 4 shows the same comparison as Figure 3, where a 2% failure rate is used to define the upper and lower bounds. The results and subsequent conclusion are almost identical.

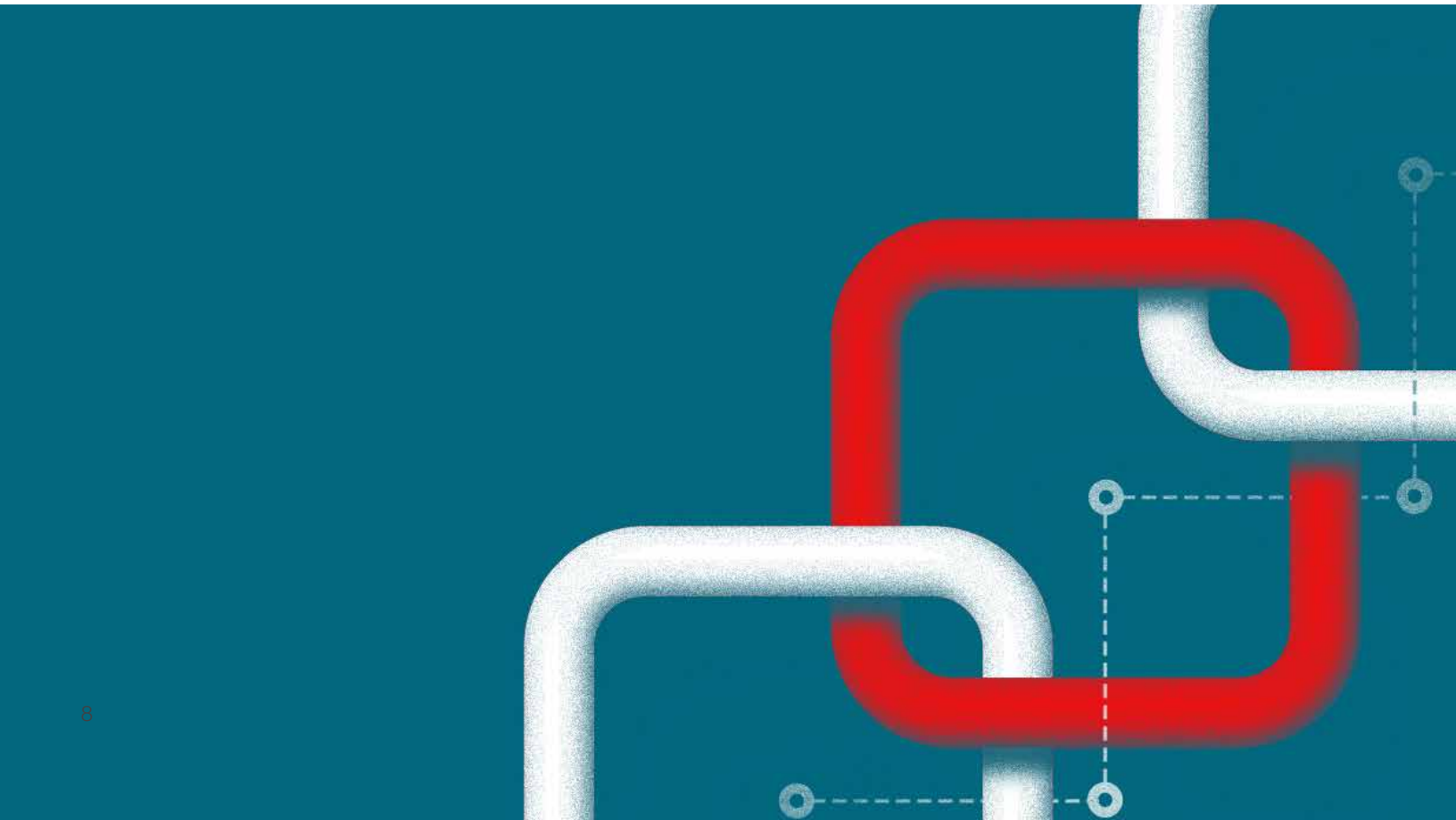
The modularized and standardized single-use engineering approach does not generate processes with significant added risk to the predefined critical sterile boundaries within each unit operation for each of the client processes analyzed. In fact, it outperforms by on average at an even lower amount of risk than the lower second deviation. The similarity in results suggests that the connection types do not adversely affect the outcome of patient risk.

Figures 1–4 illustrate that within the sample population, the modular standardized manifold engineering approach does not generate excessive failure rate risk. However, the data show that the number of connections could increase the amount of risk a firm is exposed to. Hypothetically, there should be a given number of connections that will not only push standardization into the average risk bounds of Figures 2 and 4, but beyond the upper bound.

Table 4 shows where this limit is by maintaining the sample average failure rates, but increasing connections proportionally, until the TMR and PQR rates calculated above are approximately the same as those shown in the 98% manufacturing success rate column. This fringe example was calculated to show the overall robustness of the engineering approach and the failure limits of the design strategy for the mAb Process Playbook Modular Manifold Library at a 98% overall manufacturing success rate. It represents the point at which the risk factor would exceed a 2% failure rate manufacturing standard. The two variables that impact risk are the number of connections and failure rates. Given the correlation of these values with TMR and PQR, if one is maintained, the other must increase to drive up risk. In the fringe example, connections had to increase by approximately 4 times the sample average to reach process risk rates at the second standard deviation statistical limit for the 2% failure rate manufacturing standard.

Table 4. Comparative example of sample average, world-class standards, and fringe examples for connections, failure rates, and risk profiles. Assuming the sample average failure rates remain the same as processes scale up, the number of connections needed to surpass the average business risk is more than 4X.

	Sample average	98% success rate	Fringe example
Connections			
Open connections	515	514.7	2,193
Sterile connections	231	231	984
Weld connections	66	66	281
Failure rates			
Open connections	0.45%	2%	0.45%
Sterile connections	0.48%	2%	0.48%
Weld connections	0.50%	2%	0.50%
Business risk			
Mean	3.8	16.2	16.0
Upper bound	5.6	24.5	—
Lower bound	1.8	7.9	—
Patient risk			
Mean	1.5	5.9	6.0
Upper bound	1.9	7.9	—
Lower bound	0.9	3.9	—



In Figure 5, the fringe example is expanded upon in a more robust fashion. The heat map demonstrates how changes in the number of connections for each of the three categories could impact risk. The areas shaded in light blue represent levels of risk that surpass the mean risk levels shown in Figure 5, where a 2% failure rate is present. Dark blue boxes are values that surpass the upper bound. The three axes in Figure 5—the number of open connections on the top, the sterile connections at the left, and the weld connections at the bottom—allow visualization of where processes land based on type and number of connections.

The existence of a fringe example means that there may be manufacturers that should not use the modular standardized single-use design approach. Given that failure rates are not anticipated to differ drastically from those seen in the sample population, the determining factor would be processes with overly large numbers of connection points within each unit operation. However, the number of connections needed to push risk levels to the 98% success rate second deviation (shown in dark blue) is so high there are no current processes studied in this analysis that match that criterion.

Number of open connections

Number of sterile connections	250	500	750	1,000	1,250	1,500	1,750	2,000	2,250	2,500	2,750	3,000
100	2	3	4	5	7	8	9	10	12	13	14	15
200	2	3	5	6	7	8	10	11	12	13	15	16
300	3	4	5	6	8	9	10	11	13	14	15	16
400	3	4	6	7	8	9	11	12	13	14	16	17
500	4	5	6	7	9	10	11	12	13	14	15	17
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1,200	7	8	10	11	12	13	15	16	17	18	20	21
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2,000	11	12	13	15	16	17	18	20	21	22	23	25
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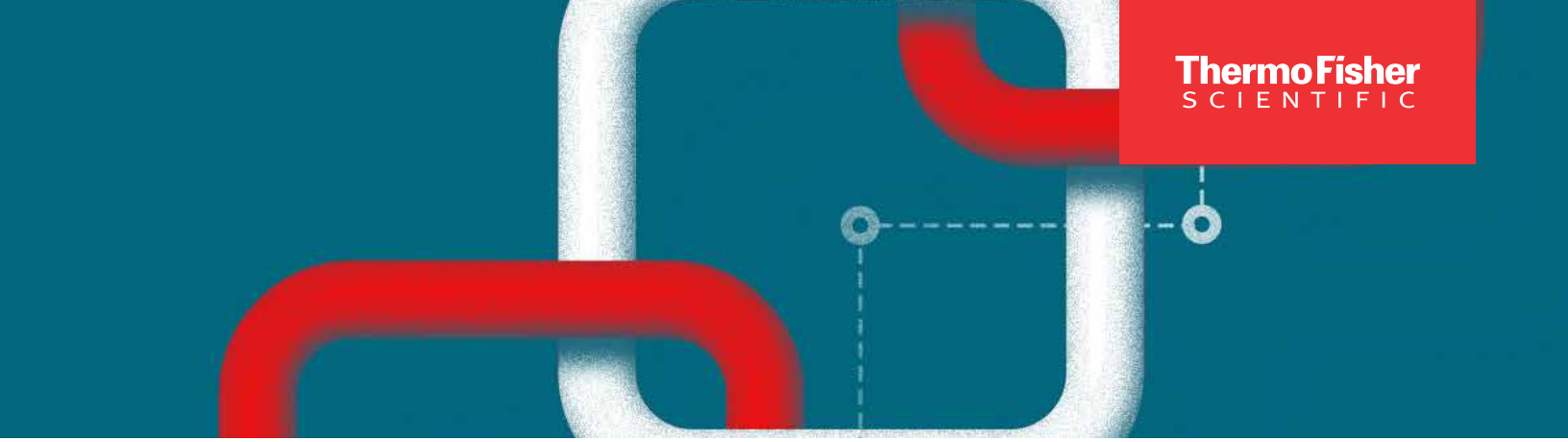
2,700	14	15	17	18	19	20	22	23	24	25	27	28
2,800	15	16	17	18	20	21	22	23	25	26	27	28
2,900	15	16	18	19	20	21	23	24	25	26	28	29
3,000	16	17	18	19	21	22	23	24	26	27	28	29
	25	50	75	100	125	150	175	200	225	250	275	300

Number of weld connections

Figure 5. Heat map of total manufacturing risk comparison of open, sterile, and weld connections. Light blue cells represent processes where the total manufacturing risk surpasses the average expected risk by world-class industry standards. Dark blue cells represent processes where the total manufacturing risk surpasses the acceptable expected risk by world-class industry standards.



Conclusion

Utilizing the modularized and standardized single-use design approach offered by the mAb Process Playbook Modular Manifold Library does not result in additional risk to either the firm or the patient. When using customized manifolds, firms often attempt to combat supply chain risk by stockpiling resources, but this results in the need for increased storage and higher warehouse costs. Modularization and standardization mitigate this problem by allowing a firm to purchase and utilize a smaller and pre-engineered set of single-use products at higher volumes. These standardized single-use products mitigate the supply challenges of customization because of their ability to be utilized within the designs of multiple unit operations and for multiple process variations. The cost of utilizing this engineering strategy is the slight increase in the number of connections made within each unit operation. The modularization and analysis of client processes presented here show the risk associated with the slight increase in connections is relatively small. Additionally, the design approach outperforms a success rate of 98% or better in every example. Thus, from a risk standpoint, a manufacturer can feel confident about being statistically within acceptable risk ranges when utilizing the modularized and standardized single-use design strategy.

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