



Custom Single-Use Assemblies

How to Reduce Complexity for Biomanufacturers



ENGINEERING YOUR SUCCESS.

Custom Single-Use Assemblies

If more than 85 per cent of your single-use assemblies are customized, you are likely overcustomizing at the expense of time, performance and quality.



Guy Matthews

Guy has worked in the biopharm industry for the last 20 years starting his career as a scientist at a well-known CMO in the UK before moving to more commercial roles. During this time, he has been involved in many projects implementing single-use technology in both upstream and downstream bioprocessing.

Guy now works as division marketing manager at Parker Bioscience Filtration where he is focused on bringing Parker's expertise in motion and control to bioprocessing to create robust solutions in single-use technology that enable customers to improve the quality and accessibility of biopharmaceuticals.

Excessive customization is a key challenge of implementing single-use technology (SUT) in biomanufacturing. Customizing adds six to sixteen weeks or more to lead time, increases costs and potential for quality issues, adds complexity to inventory control, and compromises supply chain security.

Industry experts estimate 80 per cent of assemblies for new processes are customized - a number that has the potential to be reduced to approximately 15 per cent.

History of the "Customize Everything" Mentality

Since its introduction more than 20 years ago, the benefits of SUT have been well recognized and adoption has been swift.

What started out as a simple bag for holding buffers or cleaning solutions has evolved to thousands of single-use products and entire processes run in single-use format. The explosion of products is causing challenges. The industry is calling for standardization.

How did we get to this state of excessive customization? The message to end users for more than 20 years has been to customize a solution for every operation, every scale and every product.

That was, and still is, an attractive proposition compared to the fixed stainless steel facilities SUT replaced.

In the past, customization (modification of stainless steel plants) required time-intensive, costly engineering and revalidation work.

With the introduction of SUT, customized designs became more affordable. But now, customization has gone too far.

Customized assemblies are being used when there is no need or benefit. There was a report of one biopharm organization having more than 2,000 different assemblies in use. Upon recognizing the need to standardize, the number of assemblies was reduced by approximately 80 per cent.

But standardizing on the back end is not the solution. The decision to standardize or customize an assembly should be made on the front end where up-front time and costs can be avoided.

Consequences of Excessive Customization

Too much customization creates complexity. One challenge is the need to stock and control many low-volume items, including managing and writing-off expired stock.

Lead times for products are increased due to low-volume production runs and the changeover processes between products. The potential for quality challenges increases in smaller production runs due to the complex assemblies and customized parts.

Finally, costs are higher because of the time required for the design, testing, and management of single-use systems.

All of these factors add up to longer implementation times, and potentially higher cost of goods.

Customization, on average, adds a minimum of 16 weeks to a project, compared with only 10 weeks for a configured device. Why is this important? Speed to market is critical when a manufacturer patents a drug - the clock starts ticking. When you have a blockbuster drug, every day of missed sales can be worth millions of dollars.

How does customization lead to longer implementation times? Imagine a scenario in which an end user has a project and a need is identified. The solution is customized with a part that has not been used in an assembly before.

The end user approaches a single-use systems provider. At a minimum, quality and safety issues must be met, and a number of issues should be resolved before the new device is built into the assembly. These issues take time, both for the vendor and the end user. The end user must be aware of the time requirements - time that may not be included in the project plan.

For vendors, customization requires time to:

- **Ensure product safety and compliance**
- **Verify supply chain reliability**
- **Confirm fit with manufacturing capabilities**
- **Manage parts and components supply time lines**

For end users, customization requires time to:

- **Manage the design review process**
- **Coordinate specialist knowledge or training**
- **Plan ahead for any lead time issues for smaller quantities of customized items**
- **Perform quality checks on a higher quantity of smaller incoming batches**

When is a Customized Solution Necessary?

A customized solution should only be used when the process absolutely demands it.

If other ways to run the process have been considered and nothing else works, then there is a case for customization. The decision should be driven by the process needs and quality requirements.

What may seem to be a new process requirement to the process development engineer has likely been encountered previously by the supplier. This expertise should be exploited as much as possible.

The absolute need for a customized part is going to be rare. An example of when a customized assembly may be required could be for process reasons such as material compatibility issues or non-standard quality requirements.

Since customization adds time, cost and complexity for end users, Parker recommends asking the following questions when considering a customized solution:

- **Is the decision to customize driven by a process or quality need?**

- **Can the need be filled by a standard or configurable assembly? Have you asked your SUT supplier this question?**
- **What benefit does the customized option offer that the standard or configurable option does not?**

End users must have the discipline to resist customization when it is not necessary.

“Speed to market is critical when a manufacturer patents a drug - the clock starts ticking. If you have a blockbuster drug, every day of missed sales can be worth millions of dollars.”

Alternatives to a Customized Solution

Standard Solution:

A standard solution is one your vendor already has on the shelf and is available immediately. It is one built to the vendor's validated design specifications.

This should be the first consideration for a solution. If a standard solution can meet the process requirements, it will be the most timely and cost-effective.

Configurable Solution:

In the absence of a standard off-the-shelf solution, the second option is a configurable solution. Configurable solutions use parts from the vendor's design space (described below).

If the customer needs a design that is not met by the vendor's standard offerings, a solution configured from validated parts in the toolbox will take six to eight weeks - a significant time improvement over the customized piece which can take on average a minimum of 16 weeks.

Making the compromise of choosing from a limited toolbox offers the benefits of time, performance and quality.

Design Space Concept:

What is a Design Space?

The design space is a toolbox of validated parts and assemblies. The customer can build any device needed - as long as the validated parts are used.

The toolbox provides various types of tubing, filters, connectors and other parts necessary to create an assembly. It is similar to customized, but with a reduced number of choices. The materials used meet the quality profile with the right supporting documentation prior to being included in any design.

This requires controls regarding how something is designed, built and tested. The controls should ultimately lead to the development of the design space from which assemblies are built.

Design space eliminates availability issues, offers faster implementation, improved control, documentation of components and reduced workloads. With the design space, the SUT supplier is responsible for assembly design and ensuring the product fit not only from a performance and regulatory point of view but also ensuring it can be manufactured robustly and consistently.

Using the design space concept for a configured solution offers significant speed benefits. Table 1 illustrates the speed gained with using the design space. The drawing and prices would be available within 72 hours, with further revisions taking another 72 hours. Samples could be provided within a week. Finished products would be available in about eight weeks. The design space concept takes 10 weeks in total and results in significant time savings compared to a customized solution.

	Current Industry Experience	Configured Within Design Space
Stage 1: Drawing	14+ days	72 hours
Stage 2: Samples	2+ weeks	<1 week
Stage 3: Finished Product	12-20 weeks	8 weeks
Total Time to Implement*	20-28+ weeks	10-11 weeks

Table 1: Speed gained from using a single-use design space concept compared to current industry experience

* Total time allows for two drawing revisions

Configurable Car Design Analogy

A good analogy of a configured design space is from the automotive industry. If you go online to design a new car, there are many options available.

The options are defined by the car manufacturer. The car manufacturer offers choices and the customer feels like they are customizing their car to their specifications.

The customer chooses a steering wheel, but in reality, there are only four models of steering wheels and not a whole universe of steering wheels. The customer can also choose a paint colour from 12 options - again a limited number.

What differentiates configuration from standard is the customer specified the design. Parker's bioprocessing design space in Birtley, UK is similar.

A tool box of validated parts has been tested for quality and performance. Specifications are

known. The supply is backed-up and extra parts are in stock. Having a design space not only saves lead time, but improves quality, performance, and the reliability of the supply chain.

The automotive industry analogy illustrates that hundreds of different cars are built on the same production line based on a standard, configurable package.

The resulting car can be operated by many different people, and the people building it have the right skills, but they are not specialists. The process to build and maintain a car requires some training but it is not at a specialist level requiring years of experience.

A customized product would have much more complexity such as

requiring specialist training for the operator and the people building it.

As an industry, one way to simplify is to move away from customized solutions to configured solutions based around a validated design space.

Making the compromise of choosing from a limited toolbox offers the benefits of time, performance and quality.

Responsibilities of the Vendor and End User

Defining roles when using the design space is also helpful. End users own their process and product and are responsible for the optimization of those. Vendors have industry-wide experience and expertise with building assemblies.

Vendor expertise, such as knowledge about how liquids flow through tubes and how to create assemblies is a different skill set than what customers typically have. End users who are accustomed to designing assemblies can gain time and expertise by deferring to their vendor for assembly design.

It is easy for the end user to fall into the habit of wanting to design the assembly. But if vendors and end users each stick to their areas of expertise, time and results can be optimized. It also requires that special measures are put in place in the testing laboratory to ensure containment and prevent cross-contamination and environmental contamination which can lead to false positive results.

How Can Standardization be Achieved?

While a substantial amount of work is still needed across the industry to standardize materials, connectivity and testing, the design space is one way to achieve some benefits of standardization now.

Customized assemblies are commonly used, but rarely needed. Configuring assemblies within a design space is a solution with many benefits, especially the six weeks gained in speed to market.

What does a design space actually look like? It is, in effect, a large spreadsheet containing all the potential components. The number of components can appear daunting. For perspective, a design space could offer over sixty different tubing options alone. Yet, there would not be 60 different tubing materials, perhaps only four - but including different inner and outer diameter (ID/OD) dimensions, the options multiply.

The design space is dynamic but controlled. Before something can be added to the design space, documentation to support both product specifications and regulatory requirements is

needed. If an item is not being used in assemblies, it is taken out of the design space to maintain focus on ensuring the quality and supply chain reliability for the materials in use.

The design space offers a number of benefits in addition to the speed to market. The supply chain is robust and reliable. The vendor audits the supply chain. Supply agreements are in place, including change control, to ensure long term availability and quality of parts. The vendor has performance data available and knows how the part can be used in manufacturing.

Having such a process allows vendors to design, test, and supply assemblies to customers quickly and efficiently, while offering process flexibility. It also means the end user can stay focused on producing biopharmaceuticals.

Conclusion

In summary, after 20 years, single-use technology is here to stay. It is the key enabling technology for biopharmaceutical production today. A dynamic design space, with its rapid design, testing, and manufacturing of configured solutions can improve the efficiency of single-use technology in bioprocessing.

As the industry matures, standardization of systems, components, and designs, plus manufacturing and testing methods, is necessary to support continued growth. Standardization frees up the end user to concentrate on process development and production, rather than having to focus on being a design engineer for SUT systems.

Figure 1: Example of a Parker single-use filtration manifold



Q&A:

Standardization of Single-Use Technology

Answered by Guy Matthews

Market development manager

Q: How would you define standard, configurable, and customized in the context of single-use technology?

Matthews: Standard means we have it on a shelf somewhere. One example is 50 centimeter lengths of tubing with the appropriate connectors on them. These are ready to ship today.

Configurable means the customer comes to you and says "I accept your standard tubing, but it needs to be 60 centimeters in length." It's the same material, but configured to the customer's requirement. For configurable devices, the vendor's design space is used - the vendor has predefined lengths of tubing, filters, connectors, etc. Configurable pieces will take six to eight weeks.

Customized is where the customer says "This is what I want, and you can't deviate from that." A customized piece can take months to provide.

Q: Can you describe the concept of design space, and give an example of how this is used in bioprocessing?

Matthews: With the design space concept, Parker has a toolbox of validated parts. Customers can build anything as long as the validated parts are used. Within the toolbox are standardized types of tubing, filters, and connectors, for example.

To give an example from the bioprocessing industry, let's

consider a customer with a 1,000 L vessel who wants its contents split into 10 different parts. A solution is to take the 1000 L vessel and attach ten 100 L bags. For a different process, there might be a 1000 L vessel and the customer requests for it to be split into four parts. The solution is to use four 250 L bags.

The next week, the customer has an 800 L vessel, and still wants to split that into 100 L parts. In the past, the customer may have a manifold of eight bags or a manifold of six bags, and be storing different combinations in their warehouse waiting for them to be used.

A far more sensible approach is to create a crosspiece that enables you to attach bags of the right size and quantity to a spine that can come off. That way, if there is a 600 L batch that you want to split into 100 L bags, the solution is to attach six bags - as opposed to having a manifold of six or eight or whatever it might be. The creation of a manifold device is a good example of where you can simplify.

Let's look at another example. When putting filters in-line, the filter size is based on the batch size and the properties of the material to be filtered.

Instead of integrating the filter directly into every customized assembly, the correctly sized filter can be attached to a bag via

a manifold. Being able to choose the appropriate filter and the appropriate bag size, the need to stock many different combinations of filters, bags, and tubes is eliminated.

Q: When does customization make sense?

Matthews: Customization makes sense when your process absolutely demands it. It makes sense if, during process development, there is no other way to run the process. An example is the use of specific needles during a fill finish process.

Not all processes need customized solutions. The end user should work with the vendor and tap into their experience of designing systems before moving forward with a custom solution. Often, solutions can be created in standard assemblies.

Customized should only be considered when everything else has been tried and nothing else works. There will be a case for customization, but it should be driven by the process development people, rather than someone who wants a customized part because it can be made, when it may be judicious to go with the configured alternative.

Have more questions about single-use bioprocessing?

Reach our experts at bioscience@parker.com

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