BioProcess International SPECIAL REPORT

Managing Risk in Single-Use Systems Design and Implementation

A Shared Responsibility

PALL Biotech

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Hélène Pora

Drug production is a risk-filled process. From research phases to commercial launch, the development of a successful drug product can take a decade or more and requires large investments. Throughout clinical trials and into commercial manufacturing, there is a risk of failure. Because of the level of risk involved in manufacturing drug products, work is done in phases and evaluated along the way. Throughout a process, the risk profile will shift but will always exist, and it will require a clear and effective approach to planning for and overcoming risk.

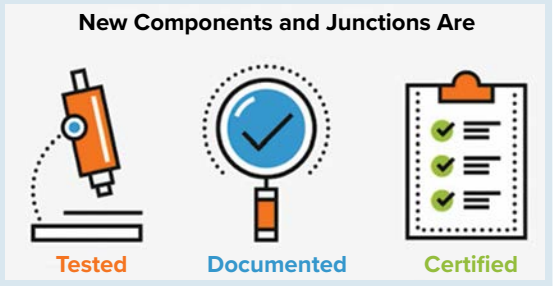
Today's market demands more targeted drugs to be produced rapidly and at a lower cost, yet risk remains. Biopharmaceutical manufacturing is tightly regulated. Although total removal of risk is impossible, the goal is to create success based on a complete understanding and mitigation of risks. In addition to local regulatory requirements — which can vary by country — there are a handful of generally accepted regulations.

Current good manufacturing practices (CGMPs) are supported by the World Health Organization (WHO) and generally are accepted. Established in 1968, CGMP guidance focuses on critical quality attributes (CQAs) for products and addresses the legal implications for all classes of drug production. Risk assessment and risk management are included as critical components of the drug-making process.

Guidelines from the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) were launched in 1990 in Belgium. This set of guidelines is based on input and consensus from worldwide regulatory authorities and is continually evaluated and updated. In 2006, ICH Q9 was introduced to cover quality risk management (QRM) expectations for the practice of evaluating and implementing processes and tools that protect the integrity of the drug production process.

Quality by design (QbD) is a concept introduced by the US Food and Drug Administration (FDA) and is applied across the drug-making industry, regardless of the type of drug product or location of manufacturing. QbD focuses on process understanding and design space to create controlled and consistent processes that result in high-quality, efficacious products.

Figure 1: To become preferred, components and junctions are tested, documented, and certified for application in single-use assemblies.



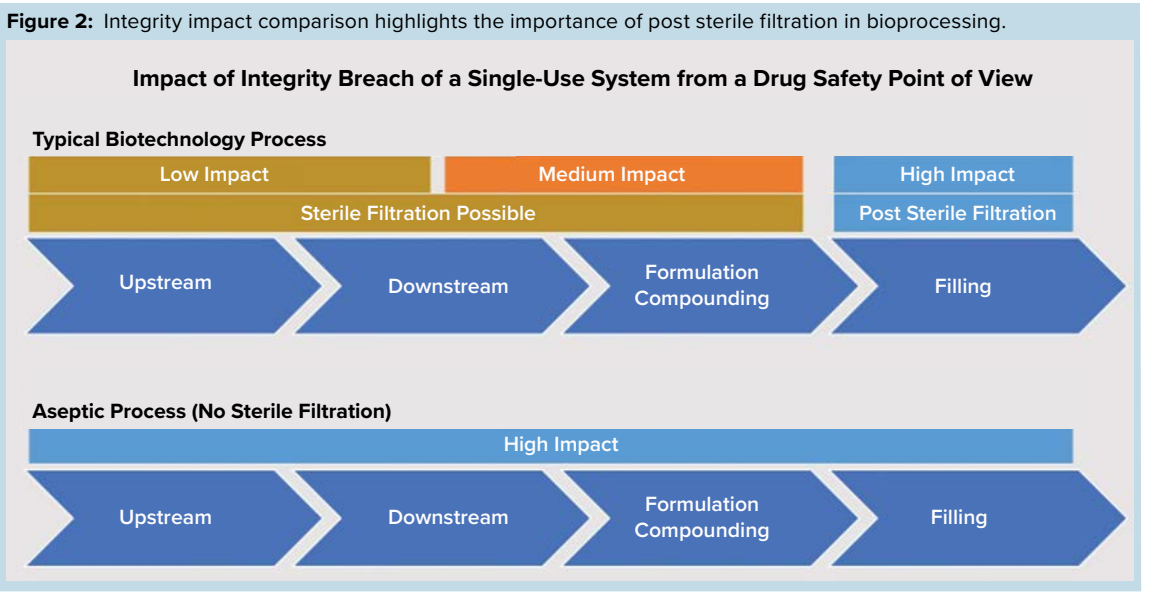
Single-Use Solutions and Challenges

Single-use technologies (SUTs) for commercial bioprocessing first started to gain interest in the biopharmaceutical industry about two decades ago. Buffer storage solutions were adopted early on, and over time SUT adoption has expanded across a number of bioprocessing steps.

The popularity of SUTs comes from the unique and significant benefits the technologies deliver in terms of cost, time, and cross-contamination risk reduction. SUTs offer a level of flexibility and interchangeability that traditional stainless-steel systems cannot match. SUTs have a smaller footprint and can be moved easily within a facility. SUTs also eliminate the need for laborious and costly cleaning, changeover, and validation processes, which reduces required processing time. And as hybrid and modular approaches to bioproduction continue to gain interest and uptake in the industry, the value of SUTs is undeniable.

Demand for single-use systems (SUS) that take advantage of SUTs and components is on the rise. Although all SUS contain consumable components

Figure 2: Integrity impact comparison highlights the importance of post sterile filtration in bioprocessing.



such as bags, tubes, filters, and sensors, supplier variations in design and materials of construction can make selection and validation a challenge. System integrity must be ensured, especially when multiple supplier components are combined in a single-use system or when different systems are used at different sites across a company. It is important to choose fit-for-purpose SUS to manage risk and improve the life of a process.

For most of today's processes, scale-up is the most critical need, but as the industry advances and treatments become more personalized, **SCALE-DOWN** also is important.

Shared Responsibility

Ultimate responsibility for drug processes and products always will remain with manufacturers. However, implementation of SUS can shift responsibilities to SUT suppliers within key areas, including design and sterilization methods that must be controlled and validated. Suppliers such as Pall Biotech know that smart design and automation, data collection, validation, and support services can ensure everyone's success.

Within the industry, experts are calling for a harmonization of SUS best practices to enhance users' experiences, mitigate risk, and advance innovation. Organizations such as the Bio-Process Systems Alliance (BPSA) have worked with the BioPhorum Operations Group (BPOG) to develop the single-use user requirement (SUUR) template, the supply chain memo, and the technical diligence document, all of which are tools designed to support communication. End users and suppliers also are aligning through BPOG to create frameworks for suppliers to work from.

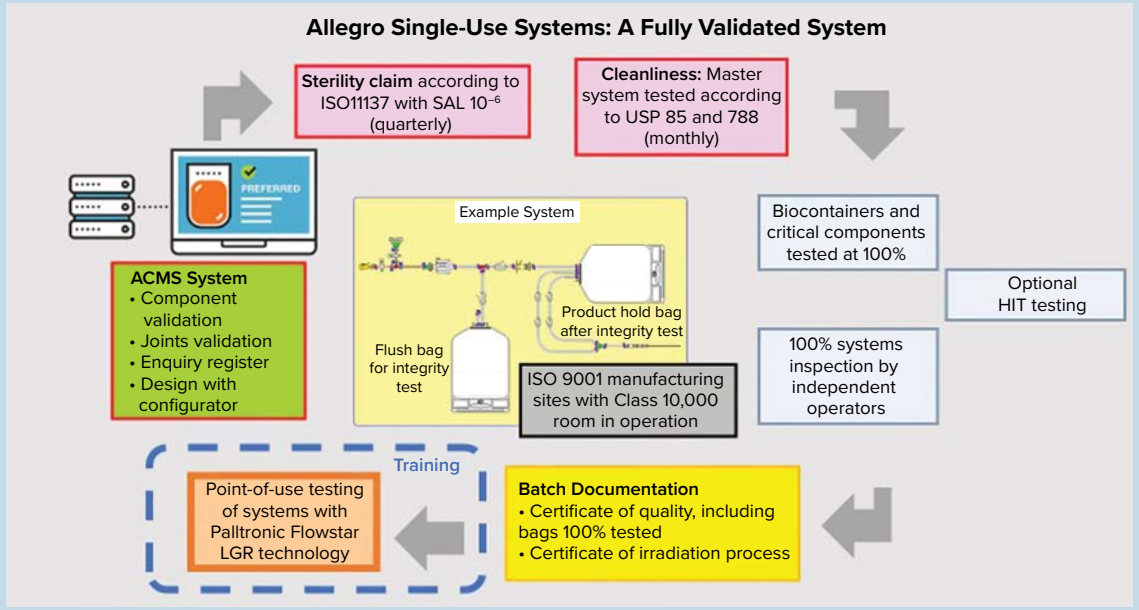
When implementing SUS, it is important to ensure compatibility of equipment and components. From the design and manufacturing of components, to their assembly, packaging, gamma irradiation, and transport between the point of manufacture and point of use, all steps should be validated to ensure integrity. Suppliers should offer clear documentation. They also should work to align with customers to make all modifications needed or include additional controls to mitigate risks in processes and to smooth point-of-use implementation.

During the process development phase, scalability always should be kept in mind. For most of today's processes, scale-up is the most critical need, but as the industry advances and treatments become more personalized, scale-down also is important. A good supplier will have all the tools to help manufacturers reach the appropriate scalability for their processes.

Data-Driven SUS Component Selection

Each SUS component brings in an element of risk. A clearly defined process built with the core fundamentals of QbD helps to ensure that SUS design decisions are made for that process and that the necessary quality, regulatory documentation, and performance validation data are available.

Figure 3: SUS component selection and process flow with optional HIT testing for successful risk management



A **CLEARLY DEFINED** process built with the core fundamentals of QbD helps to ensure that SUS design decisions are made for that process and that the necessary quality, regulatory documentation, and performance validation data are available.

When SUS adoption first started advancing in the biopharmaceutical industry, component selection was manual, and information was captured and tracked in vast spreadsheets. That quickly became overwhelming and insufficient, particularly because SUS assemblies often can have 50 or more components.

The Pall Biotech team created a system to house component data and validation information that would help biomanufacturers with SUS selection and assembly. Because no software program was on the market that could meet the team's needs, Pall worked to develop a proprietary solution called the ACMS. Every standard and customized single-use system project that Pall Biotech works on is detailed within the ACMS, thus creating a data archive that is both powerful and invaluable.

Component Categorization

The ACMS houses complex component information, including validation of SUS junctions. Component selection is based on process needs and is fully documented from the start of an inquiry to the process design phase of a project.

The ACMS classifies SUS components into three categories: preferred, nonpreferred, and restricted.

Preferred components are held in stock to expedite lead times, have been subjected to extensive evaluation, and include comprehensive validation packages. Many junctions in those components also have been tested and validated, which accelerates final design lead times. Working with preferred components provides a more streamlined experience and manages risk from the start (Figure 1).

Nonpreferred components are not held in stock, which corresponds to longer lead times. However, these components have validation packages that satisfy regulatory and customer requirements, though not as exhaustively as those for preferred components.

Restricted components are specialized components for custom assemblies and are addressed on a case-by-case basis, drawing on system data.

Qualifying Extractables and Leachables Data

The construction materials of SUS contact layers contain chemical compounds that are susceptible to migration in process fluid. Such materials are referred to as *extractables and leachables* (E&L) and

are critical to review and document for process integrity. Robust validation studies must be carried out to ensure that components are safe for use. Data obtained during E&L validation studies will be used to provide guidance and assurance to biopharmaceutical manufacturers when selecting a SUS supplier, or when transferring to a different technology because of existing site resources.

In the qualification phase, it is important to remember the following:

• Extractables tests are performed using a model solvent, whereas leachables studies use actual drug products or process fluids.

• Extractables tests are conducted under exaggerated or aggressive conditions, but leachables tests use normal process conditions.

Numerous Pall Biotech components are subjected to extractables testing, and technical reports are generated in accordance with BPOG recommendations. All data are captured in the ACMS, including a descriptive summary (with major results, extraction parameters, and analytical and quantification methods) and detailed results for all compounds observed. Results from elemental impurities analyses are collected and documented according to the ICH Q3D guideline.

Configuring Systems for Integrity

Every project begins with a customer inquiry, which is documented in the ACMS in a customer inquiry module that uses URS documentation to house information about the customer. The module will document desired systems, project specifications, and operating conditions (e.g., upstream, downstream, fluids, and process parameters). Other project details such as delivery times, testing requirements, and prototype needs also will be included.

When all customer data are acquired and verified, they will be summarized into a document located in the ACMS that details how an assembly will be used through its lifetime. That information is critical for determining the feasibility of a project based on a component search.

The information in the ACMS inquiry module plays a key role in guiding transparent discussions with customers about their goals and process parameters and how best to meet them. With powerful search features built in, the ACMS facilitates efficient SUS design and creates drawings of potential configurations as solutions based on individual customer needs.

Particularly if there is a request for a specific or specialized component, the ACMS can offer solutions (or alternatives, if needed) that meet process parameters while keeping quality, time, and cost in mind. If a design is already in use at an end-user site, or if a standard system can be leveraged, project timelines can be reduced significantly.

Every standard and customized single-use system project that Pall Biotech works on is detailed within the ACMS, thus creating a data archive that is both POWERFUL and INVALUABLE.

Leveraging Data for Safety

Numerous automatic checks and workflows are in place to ensure that projects will not be moved forward unless all requirements and specifications are met. The ACMS allows the use of only components that fit the operation parameters set (e.g., temperature and pressure). Junction testing also is included automatically in a process parameters check.

In the design phase, a bill of materials (BoM) is created. Designs are sent to customers for review and can be approved using electronic signatures for further business efficiency.

It is important to note that drawings can be finalized and sent for customer review only if all components and junction tests meet the specifications of process parameters. Prototypes will be built to help customers understand how a final solution will look and operate, and those prototypes can be tested and augmented as needed for compliance to process parameters.

Most important, all information is kept in one place for traceability and accessibility. As a project moves forward, the ACMS tracks every component used throughout the technical and manufacturing design as well as the review process to create a historical reference.

Streamlined SUS Assembly and Point-of-Use Implementation

Once a design is drawn, prototyped, tested, validated, and approved for compliance with GMP standards and process parameters, the SUS assembly can be put into production. Compliance reports are issued with a letter from the quality department that is always up-to-date and accessible.

For very critical applications, Pall's HIT technology is a helium integrity test that ensures component

Figure 4: The Palltronic Flowstar LGR test instrument

Table 1: Comparing nondestructive test methods: pressure-based and tracer gas

Consideration	Pressure-Based Test (Pressure or Flow Measurement)	Tracer Gas (Helium) Test in Vacuum Chamber
Sensitivity	>10 µm	>2 µm
Impact of environmental conditions (e.g., temperature) on sensitivity	Medium	Low
Impact of volume of SUS on sensitivity	Medium to high	Low to medium
Impact of materials of SUS on sensitivity	Low to medium	Low*
Handling	Simple to medium	Complex
Test time	Medium to long	Short, cycle time is much longer than test time
Cost of equipment	Low to medium	High
True point-of-use test	Possible	Not possible

* Provided that adequate parameters are selected

security and reliability. This testing method is suitable for SUS because it offers the highest level of sterility assurance by measuring trace leakage of helium from a single-use assembly. Tests are conducted inside a rigid container connected to a helium source. When air is evacuated, helium is injected into a single-use component. Helium detected in the chamber can be correlated to the defect size with a detection limit of ≥2 µm — the most sensitive available on the market (Figures 2 and 3).

Assurance of Integrity of Single-Use Systems

Currently, no formal regulatory requirements have been issued on performing integrity testing of SUS. However, drug manufacturers are expected to conduct risk assessments on the use of SUS in their applications and to define appropriate risk-mitigation strategies. Integrity testing of SUS can be part of that risk mitigation.

The most commonly used nondestructive test methods for checking a single-use system for integrity are pressure decay, flow measurement, and gas tracer methods.

Pressure Decay: SUS are inflated with gas at a given pressure, and the drop in pressure is measured after a specified time.

Flow Measurement: SUS are inflated with gas at a given pressure. The flow required to keep this pressure constant is measured over time.

Gas Tracer Method: SUS are placed into a vacuum chamber and connected to a gas tracer line (typically helium for SUS). The gas leaking out of the SUS is detected and quantified.

Table 1 is a summary comparison between two key nondestructive test methods (routine industrial parameter setting) applied on a single-use system.

As a project moves forward, the ACMS TRACKS every component used throughout the technical and manufacturing design as well as the review process to create a historical reference.

Training for GMP Compliance and Reliable Use of Single-Use Assemblies

Appropriate levels of operator training are both critical to the successful implementation of equipment and required for compliance with GMP guidelines. When a single-use system is implemented at a customer site, the supplier should support the user with single-use experts that can impart knowledge and best practices to operators. Operators will require training for unpacking, handling, and installing a single-use system, in addition to operating the assembly effectively.

Initially, suppliers and manufacturers can work together in person to instruct operators on how to operate the SUS, make improvements if needed in standard operating procedures (SOPs) and ensure that best practice is established and maintained. Through the life of a process, training also can be carried forward with e-learning and virtual/mixed reality modules to facilitate ongoing and/or on-demand transfer of critical knowledge.

Point-of-Use Leak Testing of SUS Assemblies

Point-of-use leak testing helps manufacturers to mitigate unforeseen risks from system leaks that can result in deviations or lost batches/products. A risk assessment might require that the absence of leaks be confirmed with a reliable point-of-use leak test. Such a test can verify that an assembly was not damaged during its installation, use, or storage at the end-user manufacturing site.

The Palltronic Flowstar LGR test instrument enables point-of-use leak testing within a small footprint and is easy to use.

Designing Integrity into a Process

Unfortunately, risk is a reality in the biopharmaceutical industry. It is not going away and must be respected always. Pall Biotech takes a combination approach to managing risk and continuously improves bioprocesses for customers through transparent communication, efficient support services, and optimized technologies. From the first inquiry through to configuration, implementation, and use at manufacturing sites, design and data play critical roles in ensuring success.

The creation of the ACMS for SUS is one way that the Pall Biotech team helps to manage risk with its customers while delivering total solutions throughout the lives of their processes. Doing the critical work of identifying risks and then documenting, testing, and validating integrity of a process, customers can find more rapid and reliable success in their bioprocessing journey.

Additional Resources

ASTM Subcommittee E55.04 on General Biopharmaceutical Standards. ASTM International: West Conshohocken, PA; https://www.astm.org/COMMIT/SUBCOMMIT/E5504.htm.

ASTM WK64337 Best Practices: Integrity Assurance and Testing of Single-Use Systems. ASTM International: West Conshohocken, PA; https://www.astm.org/DATABASE.CART/WORKITEMS/WK64337.htm.

ASTM WK64975 Testing Method: Microbial Ingress Testing on Single-Use Systems. ASTM International: ASTM International: West Conshohocken, PA; https://www.astm.org/DATABASE.CART/WORKITEMS/WK64975.htm.

BioPhorum Operations Group (BPOG) and Bio-Process Systems Alliance (BPSA). *Single-Use User Requirements (SUUR) Toolkit;* https://www.biophorum.com/resource/single-use-user-requirements/.

BPSA Technical Guide: Design, Control, and Monitoring of Single-Use Systems for Integrity Assurance. Bio-Process Systems Alliance, July 2017; http://bpsalliance.org/technical-guides.

Bio-Process Systems Alliance. Recommended Practices for Assuring Integrity of Single-Use Systems. *BioProcess Int*. 17(3) 2019; https://bioprocessintl.com/manufacturing/single-use/recommended-practices-for-assuring-integrity-ofsingle-use-systems.

Masy C. *Ensure Integrity of Single-Use Systems for Vaccines Sterile Processing.* Pall Corp.: Port Washington, New York; https://biotech.pall.com/en/webinars/ensuring-integrity-single-use-systems-sterile-processing.html.

Pall Biotech Regulatory Portal; https://biotech.pall.com/en/regulatory.html

USP ‹1207›: Sterile Product Packaging: Integrity Evaluation. *USP–NF.* United States Pharmacopeial Convention; Rockville, MD, May 2018.

Hélène Pora, *PhD, is vice president of technical communication and regulatory strategy at Pall, where she leads technical training and regulatory support improvements. She has been instrumental in the development of Pall single-use technologies for the past 20 years while heavily involved in manufacturing, quality, and regulatory aspects. Pora has over 30 years of experience working for the biopharmaceutical industry, the past 29 years within Pall Corporation. She speaks regularly at conferences about single-use technology with a strong focus on validation and overall process integration aspects. Pora is involved in different industry groups, with a strong focus on the BioPhorum Operations Group (BPOG), and she sits on the board of the Bio-Process Systems Alliance (BPSA).*

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With single-use technology adoption, quality ownership involves shared responsibilities between suppliers and the end user. Join us as we present existing good practices to ensure critical quality attributes (CQAs) of single-use-systems (SUS) throughout their life cycle.

Participants will learn:

- How to implement and validate SUS using Quality Risk Management (QRM)
- Define a reliable integrity strategy for SUS
- Recommendations for Pre Use Post Sterilization Integrity Testing (PUPSIT) for filters in SUS
- How to simplify validation and toxicological assessment using standardized extractable data sets

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