

Reliability by Design

**Custom Assemblies, Integrated
Supply, and Regulatory Readiness
in Single-Use Bioprocessing**

Technical Paper
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ABSTRACT

Single-use systems have evolved from development conveniences into the critical infrastructure of modern GMP biomanufacturing. With that transition has come a fundamental shift in expectations: assemblies must now deliver not just flexibility, but engineered reliability across fluid transfer, supply continuity, and regulatory compliance. This paper examines three interdependent pillars of reliability process-specific custom assembly design, vertically integrated manufacturing, and regulatory alignment with evolving sterility assurance requirements including EU GMP Annex 1 and the USP <665>/<1665> extractables framework. Together, these principles define a design philosophy in which performance is built in from the first engineering decision, not verified after the fact.



1. Introduction: Reliability

The adoption of single-use technology across upstream and downstream bioprocessing has been well documented. What has received less attention is the corresponding rise in performance expectations. Biomanufacturers no longer evaluate single-use assemblies as consumables; they evaluate them as process-critical components whose failure carries the same consequences as equipment failure — batch loss, regulatory investigation, and production delay.

Three converging pressures have accelerated this shift.

Process complexity. Modern biologics — monoclonal antibodies, viral vectors, mRNA vaccines, cell and gene therapies — impose more stringent requirements on fluid path design than earlier platforms. Shorter production cycles, smaller volumes, and greater sensitivity to contamination demand assemblies tailored to each specific manufacturing processes and material compatibility profile.

Supply chain fragility. The disruptions of 2020–2021 pandemic exposed the vulnerabilities of fragmented, multi-vendor sourcing. Global shortages of tubing, molded connectors, and sterilized assemblies forced production stoppages across the industry.

The response has been a structural shift toward integrated, traceable supply models. The global single-use assemblies market surpassed \$13 billion in 2024 and continues to grow at a double-digit annual rate, reflecting this reorientation toward resilience.

Regulatory evolution. The 2022 revision of EU GMP Annex 1 introduced a mandate for facility-wide contamination control strategies (CCS), formalized pre-use post-sterilization integrity testing (PUPSIT) for sterilizing-grade filters and strengthened expectations for closed-system processing. Simultaneously, the USP <665>/<1665> framework redefined how extractables and leachables are characterized and documented for polymeric single-use components. Suppliers and end-users alike must now demonstrate that reliability is designed into assemblies — not assumed.

This paper addresses each of these pressures in turn and argues that their resolution depends on a unified design philosophy in which customization, supply integration, and regulatory readiness are treated not as separate workstreams but as a single, interconnected system.

2. Custom Assembly Design: Precision Within a Validated Framework

2.1 The Standardized-Custom Paradigm

The phrase “custom assembly” carries an implied tension: customization suggests variability, while GMP manufacturing demands reproducibility. Resolving this tension requires a design approach in which process-specific configuration is achieved through the recombination of pre-validated components, rather than the introduction of novel materials or untested geometries.

This standardized-custom model begins with a qualified library of building blocks — tubing formulations, molded connectors, closures, filters, and containers all identified for extractables per USP <665>, sterilization, chemical compatibility, and mechanical performance. These components function as interchangeable elements within a validated design space. Engineers can adjust tubing length, connector type, dip-tube

orientation, or filter configuration to match a specific process without triggering component-level requalification, because the underlying materials and interfaces are already characterized.

The practical consequence is significant: assemblies developed for small-scale runs can be replicated at commercial volumes with identical documentation, qualification data, and material traceability. A buffer-preparation assembly validated at the 20-liter scale transfers directly to a 200-liter operation without requiring full revalidation. This scalability is not incidental — it is an engineered property of the design framework itself.

2.2 Closed Fluid Path Design and Contamination Risk Reduction

The transition from lab-scale flexibility to GMP reproducibility exposes a common challenge. Research-phase assemblies are often improvised: tubing lengths are adjusted manually, connectors are swapped between runs, and system geometry evolves with process understanding. These ad hoc configurations are incompatible with GMP validation, but they encode valuable information about how the process behaves.

Custom assembly design captures that process knowledge in a fixed, documented form. By mapping tubing layout, connection points, and flow paths to the specific geometry of each unit operation, closed assemblies eliminate the operator-dependent variability inherent in open or improvised systems. Pre-sterilized, double-bagged assemblies arrive ready for introduction into controlled environments without additional preparation, reducing both handling complexity and microbial ingress risk.

Ergonomic design further reduces operational error. Organized tubing layouts replace the tangled arrangements common in manually assembled setups, decreasing the likelihood of misconnection or kinking under process pressure.

2.3 Enabling Scale-Up and Modality Flexibility

Emerging therapeutic modalities — mRNA, viral vectors, cell and gene therapies — impose unusual demands on single-use assemblies. They require smaller volumes, shorter production cycles, more frequent configuration changes, and heightened sensitivity to extractables given the nature of the drug substance. Standard assemblies designed for large-scale monoclonal antibody manufacture often cannot accommodate these requirements without modification.

A validated-component design framework provides a pathway for faster and more adaptable single-use system development. Because the building blocks are already characterized, new configurations can be designed and qualified rapidly without restarting the qualification process. Standardized component libraries — including sanitary fittings, venting solutions such as Cap2V8™, and validated fluid handling platforms like PharmaTainer™ bottles and carboys — enable flexible system design while maintaining consistency across process configurations.

This modular approach allows specialized venting arrangements, inline sampling points, and custom flow path geometries to be introduced with reduced implementation risk and accelerated qualification timelines. The ability to rapidly configure assemblies using pre-characterized components is especially valuable in process development environments where configuration changes are frequent and timeline pressure is high.

Inline pressure monitoring represents a specific example of this integration. Electronics-free sensing interfaces — designed to maintain a sterile barrier while accepting standard reusable gauges or transmitters — allow real-time visibility into flow and system conditions without introducing calibration dependencies or fluid-path contamination risks. A good example of this is the aSURE Instrument Tee. As process analytical technology (PAT) becomes more prevalent across both traditional and emerging modalities, the ability to incorporate sensing elements within a validated single-use framework will define the boundary between scalable and constrained manufacturing platforms.

3.0 Vertical Integration: Engineering Supply Reliability

3.1 The Cost of Fragmentation

Multi-vendor single-use supply chains introduce variability at every interface. Tubing extruded by one supplier may have wall thickness tolerances that differ from the specifications assumed by a connector manufacturer; sterilization parameters validated by one party may not reflect the conditions applied by another. Even minor dimensional inconsistencies can produce engagement failures, pressure-decay deviations, or leachable anomalies that trigger requalification or compromise batch release.

These risks compound under time pressure. When a single component in a multi-supplier assembly is delayed or fails incoming inspection, the entire assembly is unavailable regardless of whether the other components are on hand. In media preparation, buffer hold, and product-transfer operations, where timing is tied directly to bioreactor schedules and downstream capacity, even a one-week delay cascades into lost production days and potentially abandoned batches.

Independent benchmarking of integrated versus fragmented bioprocess supply chains consistently shows that vertically consolidated suppliers reduce average schedule delays by 5–20% compared with multi-vendor networks — a margin that translates directly into higher facility utilization and more predictable regulatory filing timelines.

3.2 What Vertical Integration Delivers

End-to-end manufacturing control — encompassing resin sourcing, tubing extrusion, injection molding for fittings and containers, cleanroom assembly, and gamma sterilization within a single quality system — eliminates the principal sources of inter-vendor variability. Specifications are harmonized across all contact surfaces; dimensional tolerances are validated against the actual connector geometries they must engage; sterilization parameters are qualified against the specific polymer formulations being irradiated.

The documentation benefit is equally important. When every step from resin lot selection to finished-product release is captured within a single quality management system, the resulting Certificates of Conformance are unified rather than aggregated from separate vendor packages. Extractables data are linked directly to the specific resin, processing conditions, and sterilization cycle used for that assembly, rather than representing a generic material characterization. This traceability gives end-users clearer visibility into material compatibility and significantly simplifies the risk assessments required under ICH Q9(R1) and facility CCS frameworks.

From a procurement standpoint, internal control over the full value chain reduces administrative burden, eliminates third-party markups, and removes the coordination overhead inherent in managing multiple qualified suppliers. Lead times that once spanned months in multi-vendor configurations can shrink to weeks, directly supporting the shorter development cycles demanded by newer modalities.

3.3 Integration and Environmental Accountability

Supply chain consolidation also has a measurable environmental impact. Manufacturing and assembly within a geographically distributed but organizationally unified network — with facilities serving both the Americas and EMEA regions — reduces inter-facility transport and associated packaging waste. Consolidated production allows scrap from extrusion and molding operations to be segregated and recycled at the source, rather than dispersed across multiple facilities with inconsistent waste management practices.

These operational efficiencies support alignment with greenhouse gas accounting frameworks such as the GHG Protocol Scope 3 Standard, Science Based Targets initiative (SBTi) commitments, and emerging sustainability disclosure expectations across global pharmaceutical supply chains. Increasingly, biopharma manufacturers are requiring supply partners to provide greater visibility into Scope 3 emissions, material utilization, and lifecycle environmental impact as part of procurement and supplier qualification processes.

The same traceability infrastructure that supports quality assurance — resin lot tracking, process step documentation, material flow records — can be extended to track polymer origin and carbon footprint, providing the data increasingly requested in supplier qualification and ESG audits.

4. Regulatory Alignment: Annex 1, PUPSIT, and the USP <665> Framework

4.1 EU GMP Annex 1 and the Contamination Control Strategy

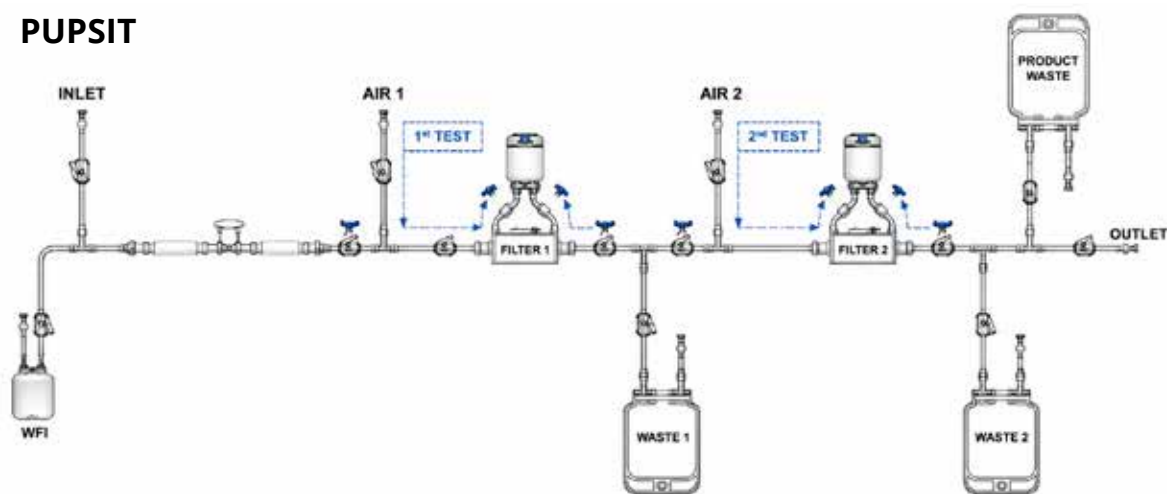
The 2022 revision of EU GMP Annex 1 fundamentally changed how regulatory authorities expect manufacturers to manage contamination risk in sterile manufacturing. The introduction of a mandatory contamination control strategy (CCS) a facility-wide, documented risk assessment covering every potential source of microbial, particulate, and pyrogen contamination — shifted the regulatory model from procedural compliance toward systemic risk management.

Within a CCS framework, single-use fluid-path assemblies occupy a central position. Every tubing connection, filter housing, sampling port, and container interface represents a potential ingress point that must be assessed, controlled, and documented. Assemblies that arrive with unified mechanical qualification data, pre-validated sterility assurance, and standardized extractables documentation integrate more naturally into CCS risk assessments than those whose performance must be reconstructed from multiple vendor sources. The ability to demonstrate that design, manufacturing, and validation are governed by a single quality framework directly reduces the documentation burden of CCS preparation and supports more defensible risk assessments during regulatory inspection.

4.2 PUPSIT: Sterile Filter Integrity as a Regulatory Requirement

Pre-use post-sterilization integrity testing (PUPSIT) is now a defined expectation under Annex 1 for sterilizing-grade filtration of sterile medicinal drugs. Its purpose is to verify filter integrity both before process fluid contacts the membrane and

PUPSIT



immediately after sterilization, ensuring that no damage has compromised the filter's ability to maintain sterility.

PUPSIT's execution depends critically on the integrity of the entire upstream fluid path. A connection defect — incomplete barb engagement, a micro-gap at a clamp fitting, stress-induced deformation at a weld point — can cause erratic pressure profiles during the integrity test, leading to failures (either false or true) that interrupt production, or worse, masking a real filter defect by creating a bypass path for microbial ingress. Connection integrity is therefore not merely a mechanical property; it is a direct input into the reliability of sterility assurance testing.

Standardized engagement testing, by single use assembly vendors, addresses this requirement systematically. Pull-force evaluations confirm mechanical retention across all molded and assembled connection points. Burst testing validates safety margins under extreme pressure conditions. Pressure-decay testing identifies micro-leaks that would compromise PUPSIT pressurization or create ingress channels during GMP operation. Together, these tests establish that the fluid path will behave predictably and consistently during integrity testing — that any PUPSIT failure reflects genuine filter performance rather than mechanical variability.

This alignment between connection qualification and PUPSIT execution is a concrete example of how assembly design choices propagate into regulatory outcomes. Manufacturers who specify assemblies with documented engagement testing data are better positioned to demonstrate CCS compliance and to defend integrity-test results during regulatory review. This allows drug sponsors to advance more rapidly toward CMC submission and approval as part of their New Drug Application (NDA).

Table 1. Engagement Testing Parameters and Their Relationship to PUPSIT Performance and Annex 1 Compliance

Test Type	Mechanical Parameter Measured	PUPSIT Failure Mode Prevented	Annex 1 / CCS Rationale
Burst Testing	Maximum pressure threshold before connection or tubing failure	Catastrophic failure under PUPSIT over-pressurization; obscures true filter integrity signal	Validates safety margin for assemblies operated at or near maximum rated process pressure
Pressure-Decay Testing	Rate of pressure loss across sealed fluid path over defined hold period	Micro-leaks that destabilize PUPSIT pressurization or create undetected microbial ingress pathways	Directly supports CCS risk assessment by confirming absence of low-level leak paths at all junctions
Dimensional Tolerance Verification	Connector OD/ID, wall thickness, and engagement depth against specification	Inconsistent fit across production lots causing variable seal performance between assemblies	Ensures batch-to-batch reproducibility required for qualified, validated single-use systems

4.3 USP <665>/<1665> and the Evolving E&L Landscape

Regulatory expectations for extractables and leachables characterization have undergone significant revision. The legacy BPOG solvent-extraction framework has largely given way to the USP <665>/<1665> approach, which defines standardized extraction conditions, analytical methods, and reporting thresholds for polymeric single-use components. ICH Q9(R1) quality risk management principles are now expected to underpin E&L evaluation during the design phase — not as a post-manufacture verification activity but as a material selection criterion.

For end-users, this shift has practical consequences. Suppliers who can provide extractables data generated under USP-aligned conditions, linked to specific resin lots and processing parameters, significantly reduce the burden of leachables risk assessment. When the same organization controls resin sourcing, extrusion, molding, and sterilization, E&L data can be presented with full traceability to the actual process conditions rather than representing a conservative generic characterization.

This specificity supports more accurate safety thresholds and reduces the likelihood of conservative assumptions driving unnecessary formulation or process changes.

Maintaining a validated extractables library for all contact materials also enables streamlined documentation when new assembly configurations are designed. Because each component in the library carries established E&L data, new configurations built from existing elements do not require full-cycle re-extraction studies — the risk assessment draws on existing characterized data, with studies triggered only when novel materials or significantly altered processing conditions are introduced.

5. Validation as Evidence of Reliability

Across all three dimensions — custom design, integrated supply, and regulatory compliance — validation is the mechanism that converts engineering intent into documented product and process performance. The standard validation suite for sterile single-use assemblies includes pressure-hold and burst testing to verify mechanical integrity under process conditions, engagement verification to confirm dimensional consistency, and particulate and endotoxin testing to confirm biopharmaceutical-grade cleanliness.

The value of this testing is amplified when all data are captured within a unified validation package. Quality teams reviewing a transfer set or bottle assembly receive a single, traceable record linking mechanical, chemical, and biological test results directly to the specific material lots, manufacturing parameters, and sterilization cycles associated with that assembly. The need to reconcile data across multiple vendors — each with its own test methods, documentation formats, and qualification scope — is eliminated.

For tech transfer and scale-up, unified documentation provides a direct operational advantage. When a development-scale configuration is replicated at GMP scale, the validation package transfers intact. Auditors and regulatory reviewers encounter a coherent evidence package rather than a compiled dossier, accelerating inspection preparation and reducing the risk of documentation gaps surfacing during review.

6. Conclusion: Toward Intelligent, Integrated Bioprocessing

Reliability in single-use bioprocessing is not an intrinsic property of any single component or technology — it is an outcome of how components are designed, manufactured, qualified, and documented in relation to each other. Custom assembly design reduces variability at the fluid-path level. Vertical integration reduces variability at the supply level. Regulatory alignment with Annex 1, PUPSIT requirements, and USP <665> reduces variability at the compliance level. Each pillar reinforces the others.

Looking forward, the integration of process analytical technology within single-use fluid paths — inline pressure, flow, and temperature monitoring that maintains sterile barrier integrity — will extend reliability into the real-time domain. As continuous manufacturing and digital process control become more prevalent across both established and emerging modalities, single-use assemblies will increasingly function not just as fluid conduits but as active data sources within manufacturing ecosystems. The design principles discussed here — validated component libraries, unified quality systems, traceable material characterization — are the foundation on which intelligent, sensor-enabled assemblies will be built.

For biomanufacturers navigating this transition, the central question is not whether to invest in single-use technology but how to ensure that investment delivers consistent, auditable, scalable performance. The answer lies in demanding that reliability be designed from the start: in the precision of the fluid path, the integrity of the supply chain, and the rigor of the validation record.

7. Addressing the Core Challenges: SaniSure's Custom Fluid Management Platform

The challenges described throughout this paper — process-specific fluid path design, supply chain fragility, and evolving regulatory requirements — do not resolve themselves through any single product or technology choice. They require a supply partner whose capabilities span design, manufacturing, qualification, and documentation within a unified framework.

SaniSure's [custom assembly and fluid management platform](#) is built around this requirement. Its validated component library — encompassing tubing formulations including TPE, silicone, Cellgyn®, and Pharma-Line™ I TPV, alongside molded connectors, PharmaTainer™ bottle systems, and filtration interfaces — provides the design flexibility to configure process-specific assemblies without sacrificing the standardization on which qualification and scale-up depend. Vertical integration of extrusion, molding, cleanroom assembly, and sterilization under a single quality system ensures that traceability, dimensional consistency, and documentation are inherent to every assembly rather than assembled after the fact from multiple vendor sources.

For manufacturers navigating Annex 1 implementation, SaniSure's PUPSIT-compatible assemblies and standardized engagement testing program provide a direct path to documented CCS compliance. For those managing emerging modalities or frequent process changes, the modular design framework accommodates rapid reconfiguration while preserving qualification continuity. And for quality and supply chain teams managing procurement risk, vertically integrated production — with geographically distributed manufacturing across the Americas and EMEA — provides the delivery reliability and audit-ready documentation that fragmented sourcing cannot.

These capabilities are documented in detail at sanisure.com/products/custom-fluid-management. Technical teams evaluating assembly configurations, regulatory documentation packages, or qualification support are encouraged to engage SaniSure's application engineering group directly.

About SaniSure®

SaniSure® is a leader in providing high-quality, innovative solutions for biopharmaceutical manufacturers. With a focus on meeting the unique needs of aseptic processing and high-pressure applications, SaniSure® combines advanced materials with rigorous testing protocols to deliver products that set the benchmark for reliability and compatibility. By continually pushing the boundaries of what is possible, SaniSure® ensures that its solutions remain aligned with the evolving demands of the biopharma industry.

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