How to Overcome Validation Challenges in a Single-Use World

By
Derek Pendlebury

OEM Channel Manager
Bioprocessing
CPC - Colder Products Company

Single-use systems (SUS) are changing the way end users think about validation. The complex supply chains of SUS are not always as robust as necessary. This presents both manufacturers and end users of SUS with validation challenges not present with a stainless steel equivalent. Given increased regulatory scrutiny on supply chain security and risk mitigation strategies throughout the development and manufacture of a therapeutic drug product, how can end users ensure the expected level of compliance in this new world of SUS? The secret: shared responsibility for validation with your supply chain.

WHY VALIDATION NEEDS TO BE A SHARED RESPONSIBILITY

Therapeutic drug manufacturers today face multiple challenges to produce safe and effective drugs. These include: downward cost pressures, in a highly regulated market, with a multi-tiered supply chain.

The trend away from stainless steel-based processes to single-use processes introduces a myriad of different suppliers and points of failure. Starting at the component level, suppliers use multiple raw materials in their supply chain. Some of the raw materials needed to manufacture the parts they supply to system integrators are themselves individual components with their own raw material supply chain. Many system integrators not only fabricate systems, but also manufacture some of the components used in a single-use assembly. Therefore, the system integrators also have their own raw material supply chain to manage and validate before they assemble and supply the finished system.

Validation of fixed pipe-based manufacturing systems used to be the primary responsibility of the drug manufacturer. However, that model is changing. It is not rigorous enough to ensure reliable and repeatable performance of all the products delivered from all suppliers of an SUS. In this new SUS world, validation needs to begin at the component raw material level and continue successively through all manufacturing, operational, and supply steps to the final assembly.

Many drug manufacturers understand how to validate in their own environment. But, what does a rigorous validation program look like for their component suppliers and systems integrators?

THE CHALLENGES OF COMPONENT VALIDATION

The basic building blocks of a single-use assembly are the components. Common components include connectors, filters, tubing, clamps, cable ties, ports, and bag chambers. This is where validation begins for the completed SUS. The drug manufacturer and system integrator need to ensure quality controls and robust systems are in place.

Yet, several challenges exist:

- *Lack of a standard approach* — One of the challenges for component validation is the lack of applicable standards or uniformity in the industry. This leads to several issues:
  - lack of a reliable and repeatable production process

- o inability to measure quality and performance accurately
- o inefficiency caused by training required for different components
- o inconsistencies across facilities
- o restriction of implementation of flexibility due to limited interoperability

Several industry groups such as BPSA, BPE, and BPOG are proposing uniform procedures and methods, but major challenges still remain. For example, plastic films used in the manufacture of single-use bags are currently regulated under USP<661>, which is a standard written specifically for packaging. A proposed new standard (USP<665>) specifically for polymer components and systems used in manufacturing pharmaceutical and biopharmaceutical drug products is currently out for comment, but is not yet an industry standard. However, as specific standards for single use technologies evolve, the component suppliers will start to converge.

- *Variability among suppliers* — Some suppliers have a specific focus on meeting the needs of the biopharmaceutical industry, while others enter the SUS supply chain from industries where different levels of control, documentation, validation, and cleanliness apply. Suppliers entering from other industries are challenged with limited in-house bioprocess expertise and often a lack understanding about the requirements of the system integrator, drug manufacturer, industry, and the regulatory bodies. Many suppliers are moving towards cleaner manufacturing and assembly processes, including clean room manufacturing (typically ISO Class 7), clean component molding, and clean extrusion capabilities.
- *Understanding end users' needs* — Component suppliers can be many manufacturing steps away from the drug manufacturer who is the ultimate end user of the SUS. The resulting lack of direct communication with the user makes understanding their needs a challenge. In addition, component suppliers have to not only meet the needs of end users, but also the needs of their system integrator customers. This may impose additional requirements on the component supplier. Examples of this include: batch records, quality documentation, lot traceability, and return goods processes required to support the integrators' manufacturing and supply chain specifications.

Despite these challenges, as the market matures, so do the players and their approaches to validation. The end users' expectation is a robust, scientific approach that results in a stable and dimensionally centered process.

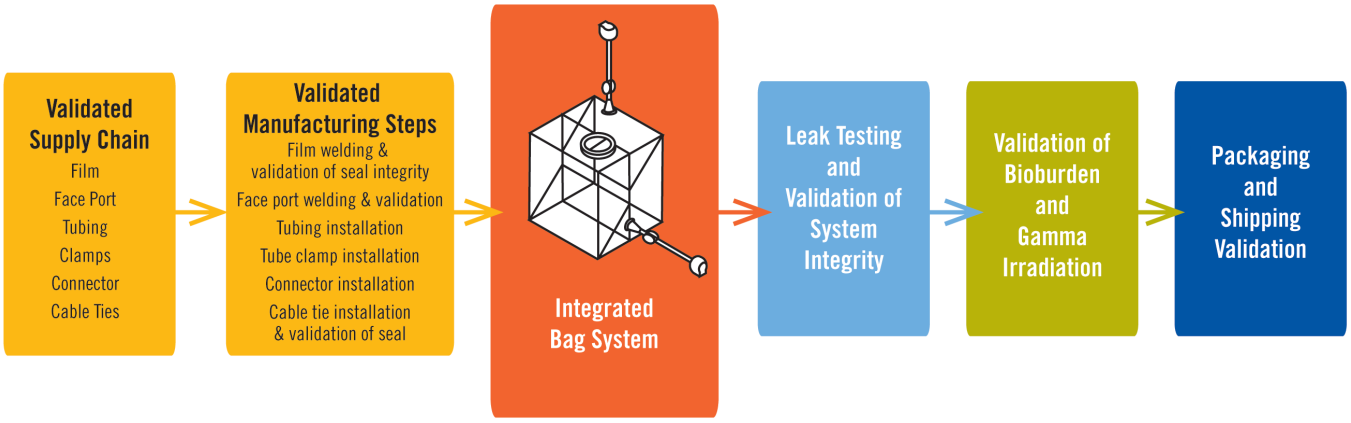
BEST PRACTICES FOR COMPONENT VALIDATION

What can component manufacturers do to produce and validate their products to help integrators and GMP manufacturers meet their regulatory needs? Component suppliers can do this primarily through validation of the product supply and design and validation of the manufacturing process.

Validation of the product supply and design

- *Material and Supplier qualification* — A robust approach starts with both raw material and supplier qualification. Ensuring raw materials meet the standards required for the finished component can be a lengthy process. Typically, most companies have industry-acceptable materials identified and they select one of these core materials of construction that meets the performance requirements. Qualifying material suppliers upfront is equally important. Some important criteria include: the ability to meet both current and future anticipated requirements, expertise and control to manufacture and supply a consistent product, and financial health.
- *Rigorous design process* — After identifying the appropriate materials of construction and defining the component of design, the supplier should perform a robust manufacturing validation process. This includes functional testing, mold validations, qualification of assembly of the component (if required), physical and chemical testing to specifications, dimensional tolerances, and establishing specification ranges. Elements

IQ	**Installation Qualification**	Verify equipment design features and ensure correct installation and calibration
OQ	**Operation Qualification**	Establish control limits for a process that produces product to meet predetermined requirements
PQ	**Performance Qualification**	Demonstrate the process consistently produces product that meets all predetermined requirements under normal operating conditions



Manufacturing validation of a simple 3-dimensional bag assembly

include installation qualifications, operations qualifications, and process qualifications (IQ, OQ, PQ), which focus on the equipment, the critical process parameters, and the stability of those processes.

Validation of the manufacturing process

- *Assembly process validation (if required)* — IQ, OQ, and PQ are undertaken to ensure that good product with reproducible performance is manufactured across the complete specification range, including the steps required to assemble the finished product.
- *Product performance validation* — The final product is validated to ensure it meets operational specifications. The PQ is performed on the nominal, the optimized position relative to the settings of a process, for an extended period of time depending on the components. Up to three lots are made during PQ to collect additional data points to confirm a controlled and consistent process. During this time, validation, technical, installation, and application documents are developed, extractables testing is performed, and biocompatibility and reliability data are developed.
- *Inspection* — One way to ensure that a product is fit for the role it is designed for, is to undertake 100% inspection and/or testing prior to final packaging and shipping. A successful final test not only proves the product is fit for purpose, but also acts to validate that the manufacturing process is producing good product. A visual inspection will detect gross flaws, but may not detect smaller flaws that could result in product failure. It may not always be feasible, or even possible, to undertake 100% product testing. If the test method is destructive, or could result in potential contamination or damage to the product then it is unsuitable as a final test. The increased focus on SUS performance and validation, coupled with recent advances in ease of use and accuracy, has allowed non-invasive test methods such as a 100% helium leak test to be easily integrated into the final testing of certain components.

An evolving requirement is the expectation that the quality systems mirror that of a GMP operation. For component suppliers, minimum expectations include:

- Compliant formalized system
- Written quality manual
- Full product traceability
- Manufacturing controls
- Ability to handle formal customer quality audits

While these are not GMP-regulated, many component manufacturers describe their goal as being "GMP-compliant."

Drug manufacturers are now auditing component suppliers to the same standards and with the same expectations as full system integrators. This approach serves to allow the drug manufacturers to both understand the whole supply chain for SUS, and also to drive the quality and validation requirements throughout the complete sourcing and manufacturing process.

THE CHALLENGES OF SYSTEMS INTEGRATOR VALIDATION

What does it take to supply a complete single-use sterile system to the biopharma market? It can be a complex process — even for a relatively simple product such as a storage bag comprised only of flexible film, face ports, tubing, clamps, connectors, and cable ties, double bagged and gamma irradiated.

Most integrators do not manufacture all of the products used in a single-use assembly. Some integrators don't manufacture any of the components. This complex supply chain can include both external and internal suppliers,

and in some cases, all suppliers will be external. The number of components, assembly steps and the actual suppliers may vary depending on the design and complexity of the final assembly.

BEST PRACTICES FOR SYSTEMS INTEGRATORS VALIDATION

Key requirements for achieving product quality at the systems integrator level include the following:

Manage the Supplier Base

Final product quality starts with selection, qualification, and validation of all raw material and component suppliers. This evaluation is the same as that undertaken by component suppliers but is critical to ensure that both parties are comfortable working together. One framework for supplier evaluation is called the 10-Cs of supplier evaluation.

Once a supplier has been selected, it must be qualified and validated. That includes validating manufacturing quality across all processes the supplier has in place: the quality program, product certification, returns process, paper and site audits, risk mitigation strategy, their supply chain security program, manufacturing controls, raw materials sourcing strategy, and corrective action process. From a risk management standpoint, do they dual source? Do they make or outsource? Do they have an active continuous improvement process and a new product development program that can support the integrator's program?

Once a supplier is chosen, validation continues on the selected supplier's ongoing processes. This includes but is not limited to quality, form, fit, and function of parts, service, delivery, and supplier score cards.

Manufacturing Considerations

From a system manufacturing perspective, customization is one of the greatest advantages of single-use technology, but also a disadvantage. Customization presents challenges for supply chain management and product validation. Recognizing that different levels of validation are needed based on the level of customization, many manufacturers have adopted a multi-tier approach to system supply.

SUPPLIER EVALUATION 10-Cs

ATTRIBUTE	EXPLANATION
Capacity	Does the supplier have adequate engine room to produce your goods? Capacity includes equipment, human resources, materials and space. Can your supplier adjust their capacity in line with your requirements?
Cash	Does your supplier have adequate financial standing and resources? This is especially important if you expect your business to grow.
Clean	Does your supplier have an appropriate sustainability policy?
Commitment	Quality is a key requirement for any business – does your supplier have the commitment to maintain suitable quality performance?
Communication	What tools will you utilize to communicate with your supplier? Another key point is who will communicate with who. For example consider how you will manage problem resolution and issue escalation.
Competency	Does your supplier have the skills to deliver the materials you require?
Consistency	Does your supplier guarantee and deliver a consistent product every time and are they on time with their deliveries?
Control	Is your supplier in control of their policies and procedures? Can they ensure that their performance can be consistent?
Cost	What is their cost of goods and do they have their own supply chain under control?
Culture	Does your supplier share the same cultural values as your organization? Does it make sense that your supplier share similar values and attributes to avoid strains in future relationships?

Ref. Ray Carter, DPSS Consultants, UK. www.supplychain-mechanic.com

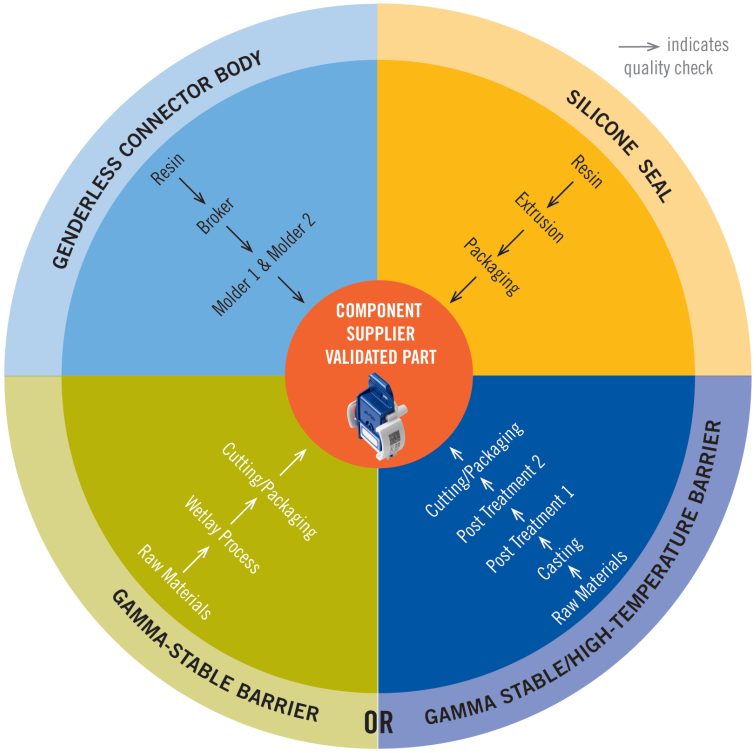
Manufacturing Validation

The focus on product quality continues through the validation of the manufacturing process, facility, equipment, and personnel who manufacture the assemblies.

- *Parts and raw materials*
  Assess whether the component

parts and raw materials meet the specifications required for quantity, cleanliness, documentation, and visual inspection, and conformance to the bill of materials (BOM) for the assembly to be built.

- *Assembly*
  The assembly process requires multiple levels of validation to answer questions that include:
  - o Are components that can only be used one way assembled in the right orientation?
  - o Are the weld temperatures and the dwell times on the welding systems correct to ensure a reliable seal?
  - o Does the seal strength meet specifications?
  - o Are all parts documented?
  - o Are the guns used to apply the cable ties validated for the correct torque?
  - o Does the final assembly conform to the BOM?
  - o Is there documentation that each of the in-process quality assurance tests are performed and passed?
- *Personnel*
  Critical considerations here include documented training and certification of the assembly and manufacturing personnel (e.g., operations, gowning, hygiene, and inspections), internal and external audits of the manufacturing processes, regular retraining and refresher training, continuous improvement programs, and six-sigma continuous improvement processes.
- *Facility*
  Important validation considerations for the facility include:
  - o Operation and performance of the manufacturing environment to the required cleanliness standards
  - o Robust preventative maintenance schedule for all manufacturing and ancillary equipment



Manufacturing validation of a critical Single-Use System component

  - o Continual monitoring of critical process parameters such as particulates, bioburden, temperature, pressure, and humidity
  - o Continual monitoring and validation of the set alarm levels that trigger alerts and actions.
- *Product*
  Finally, the finished product is validated prior to sending to the end user. This validation is designed to ensure that all of the work previously undertaken on raw materials, components and manufacturing, results in a product that meets the requirements of the end user:
  - o Is it integral, and fit for purpose?
  - o Does it conform to the design specifications for the customer?
  - o Is the packaging validated to protect the product during inventory, shipping, handling, and storage prior to use?
  - o Is the irradiation process validated and certified?
  - o Is the assembled product full traceable through batch records to allow identification of components/processes in the event of a failure?
  - o Does the product meet all appropriate industry standards?
  - o Is it certified to the level which the end user customer wants it to be?

5 CONSIDERATIONS FOR THE DRUG MANUFACTURER

Industry collaboration is still needed. As with the adoption of any new technology, there will be challenges with single-use technology until it matures. In the meantime, there are some critical areas where drug manufacturers and suppliers can work together to make the adoption of single-use technology simpler, more efficient, and less daunting for the benefit of the industry as a whole.

1. One challenge for the drug manufacturer is setting clear expectations for the suppliers. Setting expectations requires a significant amount of communication with each supplier. This is where industry standards can be of great benefit. Industry groups such as ASME, BPE, BPSA, BPOG, and ASTM are the way to reach consensus and efficiency for product standards. Industry groups enable participants to come to agreements in a non-competitive and non-confrontational setting.
2. An unmet need in the industry today is the drug manufacturers' desire for suppliers to provide more information about the useable range for components in their validation guides. End users are seeking more information about the limits of both the components and the assembled systems. Communication between end users and suppliers to identify limits, and developing a joint understanding of what's required and what's possible, will help define the operational parameters of single-use technologies.
3. Variation is a threat to validation. Validation needs to take into account that things may change, not just over time on a large scale, but maybe even from batch to batch or item to item. Trying to get a sense for the intrinsic variability of systems should be considered for validation guides. One way to do that is to increase process controls to reduce the variation of production processes, in which case validation at a point may be closer to validation in a population.
4. Change control procedures are needed. In addition, consensus is needed on what constitutes a change, and how that change should be communicated. Understanding what the original validation was, in the context of any changes that happen, helps determine what confirmatory or additional testing should be done.
5. Finally, with this great new SUS technology, the industry needs more focus on proper training for the users. People are part of the system and can be a major source of variation. Suppliers need to consider what types of training to provide with their products in order for users to achieve expected performance.

A TEAM APPROACH

Realizing the full benefits of single-use technologies requires an unprecedented level of communication and information exchange among the key players. More collaboration is needed by the drug manufacturers, integrators, component suppliers, and regulators than exists with traditional manufacturing systems. This increased collaboration must work through all aspects of the design, testing, manufacture, and validation of the single-use systems and the drug substances with which they are used for many years after approval. This creates a pathway for industry to share information and to partner at multiple levels.

Shared validation for single-use systems is only one step — but a very important step — in developing a greater understanding of the needs and constraints facing the industry and ensuring safe and effective drug products are supplied to patients in need.

About CPC

CPC (Colder Products Company), the leader in single-use connection technology, offers a wide variety of bioprocessing connection solutions. Our innovative designs offer flexibility to easily combine multiple components and systems including process containers, tubing manifolds, transfer lines, bioreactors and other bioprocess equipment. Sterile fluid connections from CPC are available in a complete range of 1/8- up to 1-inch flow configurations. For more information, visit **cpcworldwide.com/bio**

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