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The Future of Single-Use Components in Biopharmaceutical Production

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Single-use equipment has become ubiquitous in the biopharmaceutical industry, but further development in four key areas is needed to continue progress in this field.

The biopharmaceutical industry has employed single-use systems consisting of bags, tubing, filters, and other connecting elements (Figure 1) for more than 25 years. Virtually all processes have at least one aspect that can benefit from the convenience of disposable, presterilized components. Many industries have rapidly adopted single-use technologies because they offer quick turnaround times, low capital costs, and significantly lower validation costs.

New biopharmaceutical facilities are able to benefit from a single-use system upon start-up, thus avoiding the costly buildout of a fully stainless steel reusable plant. The adoption of single-use equipment and the prevalence of contract manufacturing organizations (CMOs) can reduce the timescales and up-front investment costs required to develop pharmaceuticals.

▲ **Figure 1.** Single-use equipment can include presterilized, disposable bags, tubing, fittings, and connectors. Bioreactor volumes up to 2,000 L are also available for completely single-use cell culture processes.

As single-use technologies become more commonplace, users are demanding advances and improvements in these technologies and their associated processing techniques. The BioPhorum Operations Group (BPOG) has published a set of explicit requests and roadmaps for advances in biopharmaceutical production, some of which provide feedback on single-use technologies.

Users and equipment manufacturers must work together to improve single-use systems as the industry shifts away from reusable equipment. This article addresses four areas where development is needed, and discusses how together biopharmaceutical companies and equipment manufacturers will be responsible for driving change. These four areas for potential development are:

- understanding and reporting of biocompatibility
- improving integrity assurance for single-use systems
- integrating single-use measurement and automation to support process analytical technology (PAT) efforts
- developing a resilient global supply network.

Understanding and reporting of biocompatibility

The biocompatibility of a single-use system can refer to its compatibility with cell culture, as well as its compatibility with any downstream products and process conditions. In cell culture applications, any single-use components must allow cell cultures to proceed normally. In downstream applications, biocompatibility concerns focus on ensuring protein stability and minimizing leachables (*i.e.,* substances that are expected to leach from the equipment and enter the process). Extractables (*i.e.,* substances that can be detected after contact between liquids and a solid under worst-case conditions) and leachables can migrate from plastic materials into the production stream.

Typical minimum required biocompatibility data for single-use plastics are:

- U. S. Pharmacopeia (USP) 87 and 88 compliance
- European Medicines Agency (EMA) 410/01 compliance
- a full set of data on extractables.

USP 87 and 88 are *in vitro* and *in vivo* biological reactivity tests to demonstrate that a plastic component meets USP Class VI standards. Compliance with EMA 410/01 indicates that the plastics are processed to minimize the likelihood of the transmission of prions (*i.e.,* a type of misfolded proteins) that can cause fatal neurodegenerative diseases in humans. Single-use equipment manufacturers perform extractables studies to identify substances originating in their assemblies that could end up in a drug product.

These measures of biocompatibility have become the minimum requirement for consideration of use. Manufacturers could go further than the minimum and provide more data about their products, primarily with regard to customized extractables data for a particular assembly and increased data on particulates.

The BPOG initiative has convinced most single-use assembly providers to tailor their extractables data to the format specified in the BPOG extractables guide. Harmonized extractables datasets enable biopharmaceutical companies to more easily interpret and compare extractables from single-use components under a variety of conditions. Traditionally, however, each dataset focuses on only a single type of component, such as bag films, and does not take into consideration the entire assembly. A bill-of-materials (BOM)-specific extractables profile that incorporates data for all components within an assembly represents one possible evolution of extractables datasets.

Maintaining biocompatibility data relevancy over time. Given that extractables information represents a single dataset at a single time point, equipment manufacturers should strive to ensure their biocompatibility data remains accurate over time. For example, in the case of a film used to make single-use bags, once the extractables data for the bag film is in hand, it is important to consider the relevance of this data in the context of ongoing film production.

Consider how many and what sorts of controls are in place to ensure that the data is representative of ongoing production years after the original extractables assessment. Specifications for all raw materials and understanding and control of the film production process can be key to ensuring that any data provided will remain valid in the future.

When the formulation of the plastic resins and additives used in a material are known in detail, the extractables studies can better target, quantify, and identify the profiles of the film's extractables. While this may seem obvious, gaining a view into the full formulation of all plastics used in manufacturing of equipment can be difficult, sometimes impossible.

Once all raw materials are fully characterized, controlling the film's production processes ensures that any

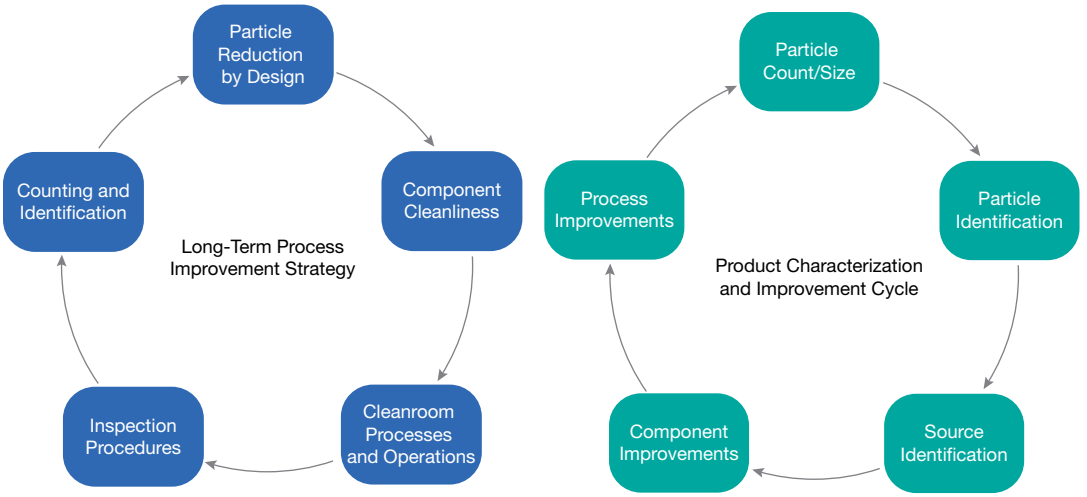


Figure 2. Continuous improvement in reducing particulate counts requires a combination of long-term strategy for process improvement and constant monitoring and identification of particulate sources.

extractables present will be consistent from lot to lot. One approach to ensure a reliable operational space is to use design-of-experiments (DOE) principles to gain a fuller understanding of the operational parameters and their effects. The control of critical process steps such as extrusion, welding, and gamma irradiation ensures the consistency of the extractables profiles across all batches. The extractables data thus remains representative and valid during the product lifecycle.

Particulates within single-use systems. Similar to compounds that can leach from single-use assemblies, particulates present in the system can also interfere with a process and are thus monitored rigorously. Single-use equipment providers work diligently to minimize particulates within their processes, but it is not possible to completely remove all particles from any product. The USP 788 protocol provides a framework for evaluating subvisible particulate loads, but it does not address visible particulates. Thus, drug makers typically aim to reduce the visible particulate load and remove as many particles as possible during manufacturing. Some guidelines have been published by industry associations, but no standards exist for visible particulates in single-use systems. Some related standards have been proposed *(1, 2)*.

Although visible particles would be removed by any downstream 0.2-µm filter, their presence is still a concern in the production of protein drugs. As single-use equipment makes its way into all areas of bioprocessing, including fill/finish applications, it is imperative that the number of visible particulates in single-use systems be reduced and better controlled. If final sterilizing-grade filtration cannot be performed for a particular drug (*e.g.,* cell therapies), the requirements for reducing the particulate load are necessarily more strict.

Manufacturers can examine and reduce inherent particulate loads in single-use systems over time by adopting a continuous-improvement workflow, such as the one shown in Figure 2. A systematic study of background particulate load accompanied by a detailed source identification procedure can provide process insight. Once the sources of particulates are understood, steps to reduce their presence can then be taken. When the new strategies are in place, the particulate load should be reassessed and the continuous improvement procedure can be repeated. The Bio-Process Systems Alliance (BPSA) has released a document entitled "Recommendations for Testing, Evaluation, and Control of Particulates from Single-Use Process Equipment" *(3)* that provides useful information.

In addition to reducing particulate sources in a process over time, there is also room for innovation when it comes to particulate detection during manufacturing. Visual inspection on light tables remains the industry standard for visible particulate detection. Improvements to this method can provide greater assurance that any visible particulates will be detected and removed or diverted from the assembly.

There is no way to eliminate all particulates within a given assembly, but adopting a continuous-improvement approach to particle reduction will improve the system if conducted appropriately. This will enable the implementation of single-use processing in the most critical areas of the process.

Improving integrity assurance

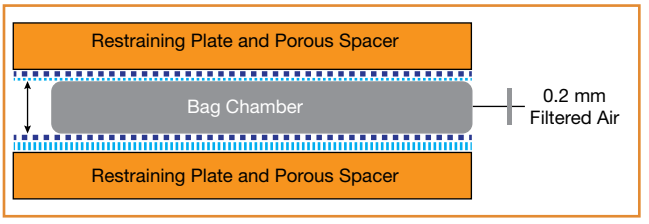
As single-use bags continue to make their way into commercial current good manufacturing practices (cGMPs) for critical steps in a process, users and regulatory agencies have been increasingly interested in reliable methods for measuring container closure integrity (CCI). Simple inspection of single-use assemblies by a technician can detect gross defects that will cause a liquid leak, but this visual inspection alone cannot catch all defects that might cause a leak or contamination.

To improve CCI, pressure decay tests using air or other gas tracers have been developed using apparatuses similar to that shown in Figure 3. Guidelines have recently been published or are being finalized to improve test method standardization and effectiveness *(4–8)*.

Bag damage during shipping and handling and the loss of valuable biopharmaceutical materials are the primary concerns reported in several user surveys on single-use equipment. Therefore, point-of-use leak tests can improve user confidence *(9, 10)*. Such testing is sufficient to detect gross defects such as a film punctured by an outside object, which is the type of defect most likely to occur during shipping and handling. Air leak tests performed on-site can detect defects as small as 10–50 µm (depending on the size of the bag), whereas puncture defects are typically 200 µm or larger.

Point-of-use leak tests can contribute to an overall CCI assurance strategy. However, point-of-use leak tests alone are not sufficient to provide complete assurance of integrity.

To increase final assembly integrity assurance beyond



▲ **Figure 3.** Air-leak tests are able to detect holes in a single-use bag as small as 10–50 µm. Leak testing equipment is based on recommendations from the American Society for Testing and Materials (ASTM) F-2095.

that of a single point-of-use air leak test, equipment manufacturers can perform a very sensitive integrity test during fabrication to ensure any manufacturing defects are detected prior to shipment. Helium leak testing of the final assembly at the manufacturing site can reliably detect defects down to 2 µm. It is important to perform a risk assessment for each type of potential application, but 2 µm is the maximum allowable leakage for single-use systems in many applications.

A sensitive gas-tracer test during manufacturing and a pressure-decay air leak test on-site can inform a reliable and advanced CCI strategy for risk mitigation in single-use system assemblies. The gas-tracer testing ensures integrity prior to the assembly's shipment, and the point-of-use test can detect any defects that occurred during the shipping process or subsequent handling.

Developing measurement and automation solutions

As biopharmaceutical manufacturers come to rely on single-use equipment in all unit operations, the need for robust and scalable inline and *in situ* process sensors has become critical. Single-use assembly manufacturers are responding to users' requests and are creating a variety of approaches to inline process analytical technologies, such as single-use sensors. Single-use sensors that can provide reliable monitoring of nearly all unit operations used in typical bioprocesses are now available. Many of these sensors are available in both flow-through and in-bag measurement setups. Table 1 lists some of the types of sensors available in a completely single-use format suitable for biomanufacturing.

The need for sensors in single-use bioreactors drove much of the initial development in this area. These same sensors, or adaptations of them, are starting to be used downstream. The first single-use bioreactors employed reusable sensors due to the lack of available single-use sensors. As the selection of single-use bioreactors has increased, completely single-use setups are now available for cell culture. Most downstream unit operations are also now supported by completely single-use assemblies and equipment.

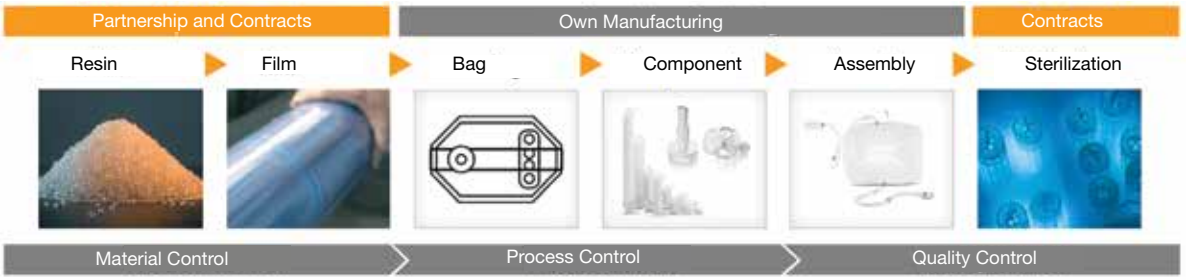
The availability of inline and *in situ* sensors for many different types of measurements has generated demand for standard single-use bioprocessing platforms that include integrated sensors. Operating platforms can help biopharmaceutical manufacturers maintain local control of the unit operation, while also easing incorporation of single-use unit operations into the larger data acquisition and process control system. These standard consumables and platforms are driving the implementation of PAT in single-use systems.

Forming a resilient global supply network

Additional, nontechnical developments will also help to advance single-use technologies. The continued expansion of the biopharmaceutical industry's global footprint necessitates the development of the single-use supply chain network for seamless production around the world. A successful manufacturing network will ensure that biopharma companies can produce equivalent products in a reasonable time frame from all facilities across the globe. In a single-use biopharmaceutical manufacturing environment, the single-use systems act as the backbone of the operation, and

Table 1. Single-use sensors can provide reliable monitoring within bioreactors, as well as in upstream and downstream processes.

Measurement Parameter	Measurement Technologies	Common Applications
Dissolved oxygen	Optical probe	Bioreactor
Viable cell concentration	Capacitance	Bioreactor
Biomass	Radio-frequency (RF) impedance	Bioreactor
pH	Optical probe, Electrochemical pH sensor	Bioreactor, Media and buffer preparation, Downstream intermediate processing
Temperature	Thermocouple, Resistance temperature detector (RTD)	Bioreactor, Media and buffer preparation, Downstream intermediate processing
Flowrate	Ultrasonic sensor	Downstream intermediate processing
Pressure	Membrane sensor	Downstream intermediate processing
Conductivity	Multielectrode conductivity sensor	Media and buffer mixing, Downstream intermediate processing
UV absorbance	UV absorbance	Protein concentration DNA concentration



▲ **Figure 4.** Suppliers must better characterize raw materials and improve controls along the entire supply chain to ensure a high-quality supply of single-use systems.

it is critical that equivalent assemblies can be delivered to every site. At the same time, vendor consolidation has left fewer providers of single-use assemblies and components. These suppliers are working to match the needs of global biopharmaceutical production.

Biopharmaceutical companies often base their research and development (R&D) and process development operations in biotech hotbeds, while their manufacturing facilities might consist of a set of CMOs or be located where the drug products are needed. It is critical for all suppliers to be able to support these process development personnel with the assurance that any single-use equipment will be available with minimal leadtime around the globe. It is thus beneficial for single-use equipment manufacturers to establish a global network to supply high-quality products around the world in a timely and consistent manner rather than from a single location.

A supply network can become more resilient by increasing the number of manufacturing nodes, as well as implementing risk management strategies relevant to the raw materials. The primary risks to the network are disruption of production at a single manufacturing site or disruptions to the supply network that all single-use equipment manufacturers rely upon. Both of these eventualities require specific strategies to ensure that any disruptions are short-lived and have minimal effects.

Four strategies for equipment manufacturers to develop a resilient global supply network are:

- establish resin specifications and process controls
- establish film-extrusion design space and process controls
- negotiate long-term supply contracts
- manufacture at multiple sites.

These methods can ensure a robust manufacturing capability, as well as assure the quality of raw material supply for single-use systems. Long-term supply contracts and quality agreements with critical suppliers help to ensure continuity in the supply of raw materials and components. It can be difficult for single-use equipment makers to obtain this type of agreement with the supplier of a plastic resin because of the relatively small quantities of material involved, but it is optimal to ensure a quality resin supply.

The next step in the manufacture of single-use items is the production of the plastic components from the resin materials. To ensure that single-use equipment can be manufactured with consistent properties and qualities, it is important to define the production space using the principles of DOE. Operating within a validated design space allows for a streamlined expansion of the supply network to additional manufacturing sites. The development represents a step forward in the production of single-use equipment and provides much greater assurance of quality supply to users around the globe.

The availability of a distributed manufacturing network enables the fast transfer of production between manufacturing sites for capacity balancing, as well as business continuity assurance in the case of supply disruption at a single site. A single-source manufacturing site will always be at a greater risk due to site-specific disruptions. Manufacturers of single-use systems continue to strengthen and expand their manufacturing networks and capabilities, because a reliable supply base is a strategic advantage when all users are seeking reliable global suppliers.

Figure 4 shows one vision of a resilient supply chain for single-use bags incorporating these strategies. This configuration keeps some activities in-house while others take place at a supplier's facility. The key is building true partnerships with the suppliers of the plastics, which establishes good raw material specifications and controls and gives the equipment manufacturer a similar degree of control over all key components whether the materials are produced in-house or externally.

Final remarks

The four strategies discussed here will be critical to the transition into a fully single-use biopharma production environment. Developments in biocompatibility and integrity assurance allow for increased use of trusted single-use systems in critical bioprocesses such as fill/finish operations. The increasing availability of sensors for single-use

applications allows for seamless integration of single-use equipment into production while meeting expectations for real-time process monitoring and control. And, the development of a truly global network for single-use supply allows biopharmaceutical manufacturers to develop processes that can be implemented globally with no risks to supply. Continued advancement in single-use technologies will remain relevant for new product niches within the biopharma space, such as cell and gene therapies and antibody drug conjugates. CEP

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