Planning for Smooth Implementation of Single-Use Unit Operations

by Jim Furey

Potential benefits of single-use (disposable) manufacturing technology in the bioprocess industry have been well documented (**1**). The technology can be particularly useful in clinical phases of development, when a company may handle a variety of drugs each year with limited quantities required (Figure 1). The burden of conducting necessary changeovers and associated validation studies when using stainless steel equipment reduces available production time in a multiproduct facility.

When considering single-use technology — and to assure the benefits of using that technology — it is important to have a methodology in place to minimize risk and facilitate a smooth implementation without delays that could affect time to clinic or to market, especially for breakthrough treatments.

Numerous unit operations in a biological production process can take advantage of single-use technology: production (bioreactors), mixing, product transfer, connection/disconnection, filtration, chromatography, centrifugation, storage, sampling, and filling. One unit operation may involve a single technology or several, and each technology typically offers more than one choice. And there is always the option of product customization.

Planning Ahead

Figure 2 shows one possible implementation approach for disposables in a unit operation.

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Defining **user requirements** is important to ensuring that technology with the correct functionality is designed and delivered. Such requirements may include the following:

- Process parameters (volume, pressure, flow rate, process time, storage time, temperature, pH, adsorption limit)
- Application requirements (filtration, possibly with integrity testing required; sampling; process monitoring; integration with specific hardware; and inlet/outlet connections requirements such as sterile, aseptic, quick connect, transfer port, steamable, and tri-clamp conformation)
- Cleanliness requirements (USP Class VI; extractables/leachables; particles, pyrogens, and freedom from animal-derived components)
- Microbiological requirements (sanitized, sterile, or sterile fluid path only).

Functional specifications should define which types of materials best meet user requirements as well as detail the types of process components and dimensions. It also must specify processing and packaging to meet microbiological and handling requirements. Also at this stage, specialized hardware components needed to meet user requirements should be identified and a plan for their delivery decided upon. If the hardware includes automation, industry-accepted GAMP methodology (Figure 3) can be adopted to manage the project and the system development life cycle (**2**).

The next step in Figure 2 is working with vendors to develop a **design specification** based on either off-the-shelf or customizable components to meet the functional specification. The design specification should include necessary drawings, a bill of materials (BOM), a requirement of lot traceability, and performance specifications on critical components. Any required vendor qualifications/audits should be scheduled at this time. If there is more than one design option, economic analysis can compare the choices based on pricing and considering factors such as fixed cost, variable costs, capital costs, and productivity.

Qualification Testing

As a process migrates from fixed-capital stainless product contact surfaces, with their requirement for steam compatibility, to single-use technology, a **preliminary**

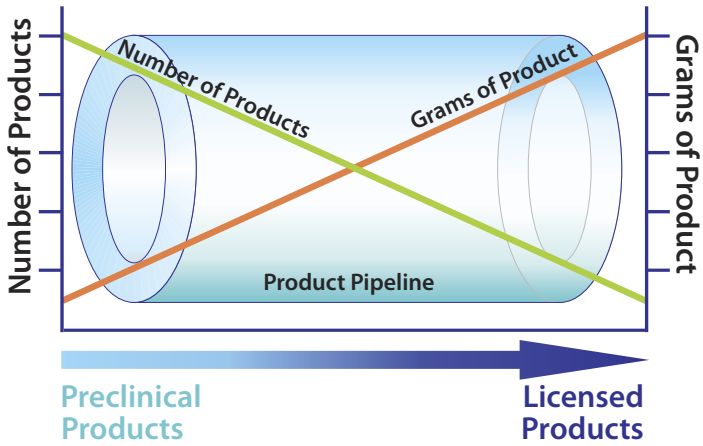
qualification testing step is possible. Unlike stainless steel components (with lengthy lead times and frequent need for welding that is not easily reengineered), single-use products can be quickly reengineered or reconfigured with readily available components. In this step, a design review and risk analysis can be conducted to account for performance data not supplied from vendors (pressure limits on an assembly, for example, and performance effects of post-gamma aging) and to ensure safety by identifying potential failure conditions (e.g., leaking, ruptures, and overpressurization).

Extractables data may be previously available on certain components involving similar solvent streams (as with the film used to make containers), but an approach must be decided to consider all components. The depth and breadth of extractables testing may be determined by risk analysis, depending on whether the process is making clinical product (less in-depth analysis, limited patient dosage) or a licensed product that may be administered in routine dosages (more risk to patients).

Different approaches are outlined by Bennan et al. (3) and Green (4). Preliminary qualification also requires a representative hardware interface. If the final hardware is not yet finished/available (per the system build, installation qualification, operation qualification process as outlined in GAMP4), then representative hardware components can be used to test the single-use components.

For example, a pump integrated into a hardware system that will fill disposable process containers to a user-defined weight is designed to run at a certain rpm for a certain amount time (delivering the required flow rate to generate a specified process pressure). The same pump model planned for use on the system could be used for testing. At this stage, the design can be modified if necessary to meet functional specifications with a margin of safety. Tubing secured to the disposable process container might leak or slip off with the initial design, for example, and replacement of the tie wrap with a BarbLock connector (www.barblock.com) would minimize this process risk.

Figure 1: Drug production requirements (©PENDOTECH 2005)



Different risk analysis methods are used to examine processes at the prequalification testing stage, including the different approaches outlined by Vesper (5). A method such as FMEA (failure mode effects analysis) is rather exhaustive. With or without testing, it could necessitate hardware modifications to account for risk conditions (particularly safety) that cannot be minimized solely by single-use component redesign. For instance, if a biohazardous substance will be filled into a disposable process container, an automated proximity or pressure switch with a strategically placed liquid detector might be integrated into the hardware as an automatic pump shut-off to prevent operator exposure to the substance.

The preliminary qualification testing step helps minimize failures or setbacks in the final qualification process. With this testing in mind, the system build step of the GAMP methodology should not begin until risk analysis and preliminary qualification of single-use components is complete. This allows for modifying the functional and design specifications, which is easier than making changes in the system build stage or IQ–OQ. Use of a requirements traceability matrix as described in GAMP4 facilitates the efficient incorporation of such changes (2).

A process with stainless steel product-contact surfaces and the need for steam compatibility — in contrast with one using single-use components — changes hardware requirements and engineering capability. Single-use technology may require instead a simple, stand-alone automated system with an embedded controller for process efficiency and safety (e.g., to shut off a pump when the disposable process container reaches a predefined weight). However, as single-use technologies become more accepted and the associated benefits materialize, more sophisticated integration with hardware will be necessary to meet user requirements for process efficiency.

A single-use process can benefit from the automation of its stainless steel counterpart. An example would be implementation of large-scale, single-use, stirred-tank bioreactor technology into a GMP clinical production facility (technology currently in the late product development stage). A company might have a large amount of capital invested and a strong knowledge base surrounding

Figure 2: Single-use technology implementation approach

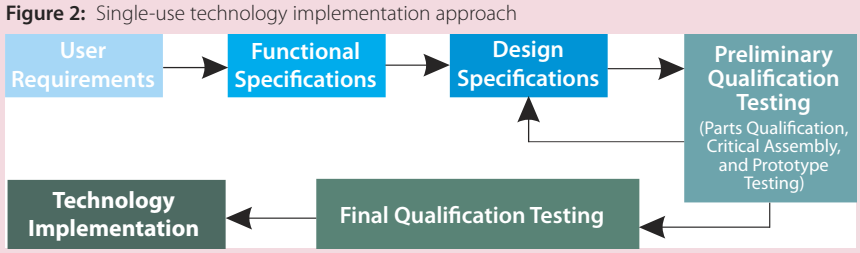
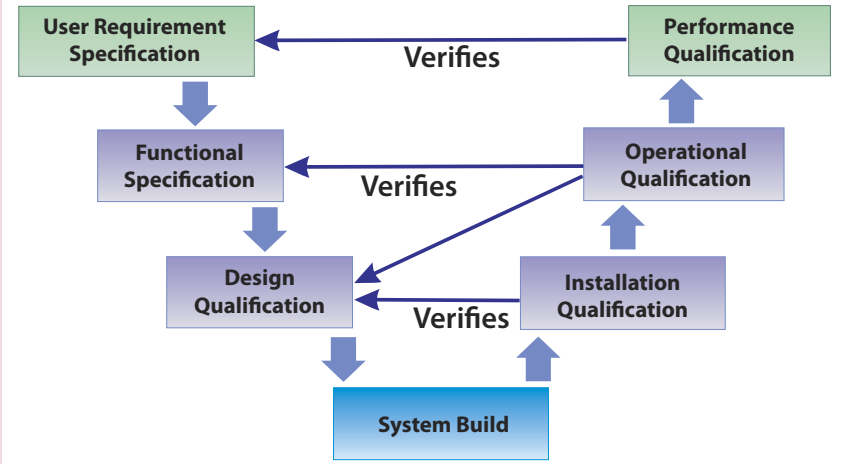


Figure 3: A basic framework for specification and qualification (**1**)



a certain process control platform along with a great deal of capability it does not want to abandon in migrating to single-use technology. The control system might be a highly integrated and validated, Part-11–compliant SCADA (supervisory control and data acquisition) system that could even be integrated into the company-wide enterprise resource planning (ERP) system. The control system might include batch recipe management and incorporate paperless batch records. If it can control multiple bioreactors, incorporation of single-use bioreactor technology into the bioreactor process train at such a development or clinical manufacturing facility can provide tremendous facility productivity enhancements. For instance, stainless steel vessels of 40-L, 200-L, and 1000-L sizes would be installed with CIP and SIP (clean- and steam-in-place) capability. Even with more than one bioreactor of each size, the capability is fixed and not readily changeable.

Single-use bioreactor technology offers flexibility regarding the size of bioreactors that can be operated as demands on the facility change (they may vary from month to month or year to year). For example, if a large number of 200-L runs became necessary, single-use bioreactors could be set up and connected to the existing process control system. Many components used by such a system would be similar for either a stainless steel or single-use reactor: e.g., the pH and DO inputs and the mixing speed and pump control outputs. Certain components of the control system may need to be configured for using different size vessels (e.g., mass flow meters with range to cover different gas flow requirements to different size reactors based on process measurements). Either barcode or RFID (radio-frequency identification) technology could be included on bioreactors and scanned by the control system to ensure that it is configured correctly for each and to provide certain information to the batch record (e.g., catalog number traceable to the entire BOM, including hydrophobic and hydrophilic filters delivered as part of the bioreactor assembly that may need to be integrity tested).

Planning for integration of single-use projects would be much simpler than for stainless steel, particularly bioreactors. If using GAMP4 or a similar methodology, the user requirements specification and subsequent functional specification would be simplified by elimination of the requirements for CIP and SIP and associated software, piping, instrumentation, and other capital requirements.

Finalization

The final steps outlined in Figure 2 are *Final Qualification Testing* and *Implementation*. The detailed steps for final qualification testing will vary depending on the type of project. Basically, final products should be tested to ensure that all functional specifications and user requirements have been met. Training and standard operating procedures (SOPs) should be addressed, along with commercial issues such as purchase specification finalization, usage forecast, and supply chain planning. Product contact process components now must be handled similar to raw materials, shifting some burden of quality and on-time delivery to the vendor.

For implementation, points to consider include change control (making sure there is a vendor notification plan in place), back-up supplier considerations, incoming inspections, product life-cycle management (including plans for potential discontinuation of components), and waste management. As use of disposables technology grows — eliminating steam production and post-use handling of water for steam and CIP as well as associated chemicals — solutions should evolve to assist in handling the solid waste. It took several years (since the early 1990s) for an infrastructure to evolve for handling the increasing amount of household waste generated as the convenience of single-use packaging of consumer products took hold. For the bioprocess industry, some incremental steps have occurred, and more are on the horizon.

References

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