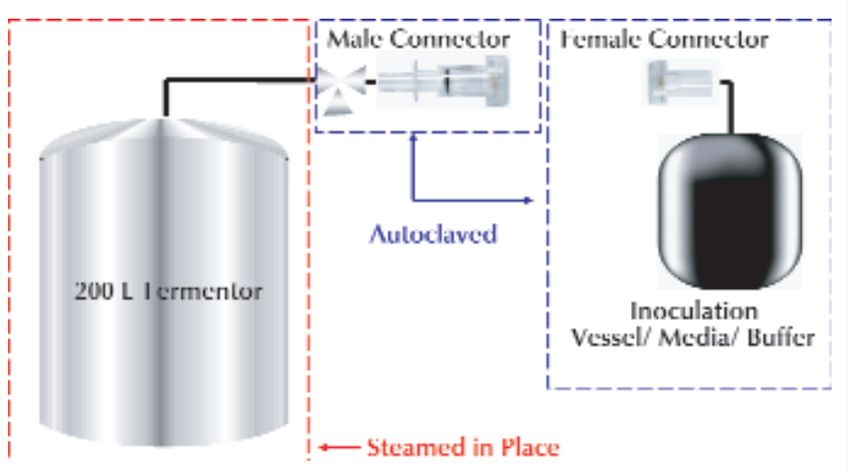
Disposable Systems

One More Manufacturing Option

by Hazel Aranha

Figure 1: Inoculation of a steamed-in-place fermentor with a seed culture; connection made with a disposable KleenPak connector (COURTESY OF PALL CORPORATION)



Intense pressure on pharmaceutical companies to increase productivity and profitability requires them to entertain all available options in an effort to achieve optimal operational modality. Contract operations at all stages — from drug development research to validation activities and contract manufacturing — are now accepted alternate operational modes. The emphasis today is on engaging in-house personnel in strategic activities while outsourcing or assigning tactical tasks to contractors. The sequential-mode project management paradigm (design–build–validate) of the past century is today nothing short of suicidal. Multipurpose/multiproduct plant design is the norm; the "greenfield" plant dedicated to a single product is a relic from the past.

Fueled by a need for faster processing times and increased productivity, but tempered by a regulatory environment that emphasizes product consistency and culpability for noncompliance, the transition to automated manufacturing and disposable processing is not surprising. The concept of a completely disposable manufacturing process, which would have been considered utopian a few years ago, is today just another shift in the manufacturing paradigm.

SYSTEM DESIGN AND COMPONENTS

The design requirements for a disposable unit are dictated by its application. Factors to consider include the size of the production unit (volume and capacity requirements), the number of manufacturing campaigns per year, operating conditions (temperature, pressure, operation period), and overall compatibility of the system materials with the product. Elements of traditional and disposable systems are compared in the sidebar.

Disposable components meeting pharmaceutical specifications have been available for some time, essentially as system components. For example, plastic tubing (typically platinum-cured silicone) serves as a replacement for steel pipes and plumbing; expandable bags substitute for stainless steel vessels; and pinch or side clamps are swapped for valves. Vendors have revisited mature unit operations (e.g., filtration and chromatography) and made disposable products for them. Synergistic alliances have formed (and continue to do so) between filter and bag manufacturers (among others) to make assembled modular systems, good for both users and suppliers. Users purchase prevalidated systems, decreasing (but not eliminating) the onus of validation on them. Suppliers can sell such systems at a premium. Currently, most systems are customized to account for varying types of connections used. As disposables become more common, it may be possible to order specific standardized components.

Minimally, a fully disposable production system would include disposable containers (bags) for the input (feed) along with a reaction container (bioreactor) and its

output for bulk product connected by tubing equipped with pinch or side clamps that can be used to isolate certain sections of the system as required. According to process requirements, additional bags containing process fluids or serving as collection receptacles may also be included along with disposable capsule filters and monitoring equipment. Table 2 describes the basic components of a disposable system. Depending on the application and its market, compatibility of all system components to applicable standards (e.g., ISO and the international pharmacopoeias) may need to be demonstrated.

Bags: Single-use containers, commonly called bags, provide an alternative to capital-intensive stainless steel containers. Among the many advantages of using flexible bags are decreased requirements for floor space and dedicated drums. Bioprocess bags typically come in the form of "two-dimensional" pillow type for small volumes (50 mL to 50 L) and "three-dimensional" bags for large-volume (100–2500 L) applications. Made of flexible polymeric materials, these bags must be supported when they are filled with fluid. The smaller ones can be supported in trays, whereas the larger ones are supported by rack and frame systems or used to line stainless steel or aluminum tanks (eliminating the need for cleaning those tanks between uses).

Most commercially available disposable bags are of either single-web or multiweb film construction, with 2-D or 3-D geometry as described above. The films use either polyethylene (PE) or ethylene-vinyl acetate (EVA) for solution contact; all contain ethylene-vinyl alcohol (EVOH) as a barrier resin. The plastic films also contain additives that aid in processing, add strength, optimize performance, and/or prolong polymer shelf life.

As with any component or raw material used in pharmaceutical manufacturing, bags must be manufactured in an appropriate environment (cleanroom classification) under controlled conditions, i.e., statistical process control (SPC). Most polymers contain extensively processed stearates and other bovine-derived additives at very low percentages, unlikely to serve as vehicles for BSE transmission. However, many pharmaceutical bag users require vendors to document appropriate sourcing of bovine constituents — from BSE-free countries as classified by the Office International des Epizooties (OIE) — and confirm that stringent steps with demonstrated efficacy to inactivate prions are used in the manufacture of the polymers that make up the bags.

For any polymer to be used in therapeutics manufacture, a basic requirement is chemical inertness. In general, most biotechnology products are aqueous based; however, high/low-pH buffers or other corrosive salts may be used in downstream purification. Biological compatibility must be determined and may include tests to evaluate biological reactivity of the polymeric materials (**1**) and biological reactivity to polymeric materials in mammalian cell cultures (**2**), physicochemical tests on plastics and their extracts (**3**), bacterial endotoxin tests (**4**), and hemolysis tests (**5**).

Additionally, the physical attributes of the polymer (e.g., tensile strength, elongation at break, and puncture resistance) are important to ensuring a system's potential resistance to damage during shipping and handling as well as storage and use. The glass transition temperature (T_g) indicates the mechanical capabilities of a polymer at various temperatures: Materials with a low T_g have superior mechanical capabilities at lower temperatures and are more resistant to flex cracking.

Physical haze measures the clarity of a polymer: The higher the clarity, the better a user's ability to see container contents. Multiweb systems, in general, have reduced clarity (higher haze than single-web systems). Polymer translucence facilitates early detection of potential problems and timely troubleshooting during manufacture by allowing operators to observe fluid levels and detect fluid discoloration and air pockets during manufacture. Translucent containers also help maximize product volume removal from bags during harvest, eliminating the need for "chasing" the product with buffer — which is a common practice with high-premium products produced in stainless steel bioreactors.

Barrier properties (e.g., gas and vapor permeability) are important, especially for equipment with high surface-area-to-volume ratios. Diffusion rates may affect product pH, stability, and concentrations. The significance of pH stability depends on the system in use (type of solution, buffering capacity, storage, and end use). In general, EVOH is used as a gas barrier material.

Capsule Filters: Disposable capsule filters have been available for over three decades; however, it is only in the past several years that manifolded disposable filtration systems have become popular. Such systems can include a series of prefilters along with the final filter (which is, in general, more expensive), that prolong the life of the final filter, improving process economics. Additionally, if the process requires filtration to be completed within a specified time, either due to product lability or manufacturing shift time constraints, filters of the same pore size rating can be manifolded to increase total filter area. The kind of filter used and the filtration area necessary are dictated by the application and process requirements.

Currently, small-scale filtration devices and process-scale capsules are made of the same materials of construction (MOC), including filter membrane and associated hardware. This is a significant advantage that streamlines scale-up

Comparing Traditional and Disposable Systems

Figures quoted here come from Sandstrom CE. The Economics of Storing Process Solutions. *Chem. Engin.,* April 2003: 36–45.

Traditional Bioreactors

Capital Expenditure: significant upfront investment for equipment and hard piping associated with these bioreactors and utilities required for operations

Cost Distribution: 67% upfront for capital equipment and installation; 22% process use; 11% cleaning and validation

Lifetime Operating Costs: influenced by manufacturing scale (20-L scale US$40,000/year, 200-L scale $62,000/year)

Materials of Construction (MOC): stainless steel

Extractables Issues: chemically compatible with a wide range of organic solvents and aqueous solutions used in bioprocess operations

Validation Issues: significant — all critical operations need validation (equipment, systems, sterilization, cleaning) and documentation

Product Security: risk of cross contamination

Environmental Impact: extent of cleaning chemicals and utilities used depends on manufacturing issues (scale, frequency)

Space Requirements: large footprint

Flexibility for System Upgrades: limited due to capital investment and extensive retrofitting required

Portable Bioreactors

Capital Expenditure: intermediate upfront costs

Cost Distribution: 33% upfront capital outlay; 33% process use (including set-up and disassembly); 22% cleaning and validation

Lifetime Operating Costs: In general, portable vessels are more expensive to operate than fixed vessels. They have both the high costs associated with fixed systems and the labor requirements (for staging of manufacturing) associated with disposable bags — 20-L scale $40,000/year, 200-L scale $80,000/year.

Materials of Construction (MOC): stainless steel

Extractables Issues: similar to fixed vessels

Validation Issues: similar to fixed vessels

Product Security: same as fixed vessels

Environmental Impact: same as fixed vessels

Space Requirements: large footprint (not dedicated, however; requires more space than fixed equipment due to need for staging space and access corridors for equipment transport)

Flexibility for System Upgrades: same as fixed vessels

Single-Use Systems

Capital Expenditure: several orders of magnitude less than traditional bioreactors

Cost Distribution: 33% for initial and consumables cost; 50% process use; 17% handling and storage

Lifetime Operating Costs: influenced by manufacturing scale (20-L scale $20,000/year, 200-L scale $21,000/year)

Materials of Construction (MOC): polymers supplemented with additives to aid in performance and/or prolong shelf life (potential for for product/polymer interaction)

Extractables Issues: a significant concern; however, manufacturers of these systems follow USP guidelines and document that products meet compliance requirements

Validation Issues: many validation issues are eliminated (presterilized systems eliminate the need for sterilization validation); no cleaning validation; decreased documentation requirements

Product Security: minimal risk

Environmental Impact: costs associated with disposal of single-use plastics

Space Requirements: smaller footprint than traditional systems

Flexibility for System Upgrades: more flexible modular approach

processes and assists in regulatory compliance.

Slide or pinch clamps allow temporary isolation of certain sections of a system. For example, it may be necessary to isolate the presterilized sections of an assembly from upstream nonsterile operations. Another case is preuse wetting/flush of a filter with sterile water/buffer to decrease filter extractables and minimize protein adsorption. For aseptic processing applications, postuse filter integrity must be established with a bacterial retention–correlated integrity test.

Tubing: In many biopharmaceutical operations, platinum-cured silicone tubing is preferred because it has fewer leachables than other types such as peroxide-cured silicone tubing. In addition, platinum-cured tubing tends to have smoother internal surfaces, minimizing protein loss due to adhesion.

Tubing Adaptors: Straight runs of tubing may be inappropriate for disposable systems that include in-process sampling or additional manipulations. T- and Y-style connectors add flexibility and can be used to create branched systems. To accommodate differences in tubing diameters, step-down tubing and adaptors provide additional flexibility in tubing sizes.

Connections: Disposable systems often comprise modular units that require connection. For example, a gamma-sterilized component may need to be connected to another part of the system that has been sterilized by steam. The most critical connections are aseptic connections between two sterilized components, and such connections are often performed in a laminar-flow, HEPA-filtered air hood. Quick-connects, tubing welders, and aseptic connectors may be used and are discussed elsewhere (6).

Applicability and Advantages

Disposable technology applications can be broadly classified into three categories: storage applications, blend/formulation applications, and reactor applications. For fluid storage containers, the transition to disposable systems should be relatively straightforward, although it requires demonstrating the compatibility of each stored fluid

under the storage conditions (temperature and time). Single-use storage systems are used for growth media, buffers, reagents, bulk harvest fluid, and intermediate/final products.

Another application becoming increasingly important is pre- or in-process blend/formulation. As the scale of manufacturing increases, transport of liquid growth media from suppliers to users becomes cumbersome. Reconstitution of dehydrated media at point-of-use is becoming more common. Such media require less storage space, too.

Reactor applications are more challenging and can range from scale-up of inoculum for a fixed-vessel fermentation process to carrying out the entire product conversion in a disposable bag. These applications require process control and monitoring. To ensure appropriate conditions, a suitable mixing/stirring mechanism and adequate temperature control will need to be included with process monitoring devices such as probes for pH, dissolved oxygen (DO), and carbon dioxide (CO_2). Although availability of single-use probes is limited, manufacturers of such equipment are starting to make low-cost, disposable monitoring probes.

Aggressive agitation is undesirable when working with protein-containing solutions, especially during cultivation of anchorage-dependent mammalian cells. Manufacturers such as HyClone address the mixing issue with innovative approaches, such as a mixing disk internal to the bag but driven by an outside motor for blending/formulation applications. Specific equipment such as the Wave bioreactor rocking platform were designed to provide oxygenation and mixing with minimal shear forces.

Speed to market is important in any industry, but in the pharmaceutical industry it is critical. A disposable manufacturing option could offer time savings of as much as six months within a 30-month validation process (7).

When a product launch is delayed, revenue losses are compounded by the additional resources expended as well as by lost revenue opportunity. A case scenario provided by Kenley (8) illustrates this point. Assuming that the operating expense (or burn rate), for a start-up company is US$5 million per month, and its product postapproval would bring in $120 million revenue in the first year, a three-month delay in completing product development translates to a loss of $15 million incurred by the additional burn rate as well as a lost revenue opportunity of $30 million, a total incremental cost of $45 million.

Capital Investment: Equipment and facilities costs are significant, especially at start-up of any operation. The benefits are clear for any approach that defers a portion of the capital costs until the product is being commercially manufactured. This is especially important in the case of small/virtual biotech companies that rely on venture capital. The venture capital pipeline

for biotechnology-derived products is not as robust as it once was, so any strategy that can defer investments provides the user significant returns.

Safety Considerations: Disposable bags and components are recommended for the safety of both products and operators. Product cross-contamination is eliminated by the single-use nature of these systems. Product security makes sense not just for contract manufacturers that process a range of products but also for companies that manufacture multiple products in-house. Additionally, the decreased assembly and handling demands of the system make it less dependent on operator intervention and decrease the potential for microbial contamination.

Customized therapies that require administration of cytotoxic products/drugs or radiolabeled chemicals are best served by single-use systems. Elimination of clean-in-place (CIP) operations serves to decrease operator handling of corrosive chemicals. Concern is increasing over occupational exposure and health of operators in pharmaceutical plants, so from this standpoint, disposable systems are in the best interest of manufacturing personnel.

Quality and Compliance: Quality is absolutely essential to any therapeutics development program, both for cost-effectiveness and regulatory compliance. Pharmaceutical companies are willing to accommodate extra costs because yield losses and manufacturing delays are more expensive in the long run. Adherence to compliance may appear to conflict with business and market needs, but it is the cost of doing business in this industry, and drug companies have moved from a reactive and superficial approach to a system-based approach to regulatory compliance.

Disposable systems aid in compliance on several fronts. Among the GMP deficiencies for which drug manufacturers are commonly cited are inadequate validation and incomplete batch records and documentation. Using disposable systems may not be the panacea for all compliance ills; however, they do decrease requirements for certain types of validation (e.g., CIP/SIP) and in-process documentation (batch records documenting cleaning and sterilization). Failure to execute specified standard operating procedures (SOPs) for cleaning and sterilization are noncompliances. For each disposable component, there is one less cGMP record to keep and one less engineering drawing/batch record to track.

Recent amendments to EU directive 91/256/EEC require GMP compliance for investigational medicinal products (**10**). This has provided an added impetus for the use of disposables. Although FDA documents state that the GMP regulations apply to the production of clinical supplies, no formal document spells out the requirements.

Aseptic processing depends on validation, not release testing. Sterilizing-grade filters commonly used for filter sterilization are subjected to a postfiltration integrity test specified by the manufacturer and correlated to bacterial retention. Operator handling and reverse pressurization during steaming are reportedly common causes of filter integrity test failure. The cost of one such failure is significant not only in terms of time lost and supplies wasted, but in production schedule interruption and delay. Reprocessing may also require additional product testing and long-term stability studies.

Process scalability from bench to manufacturing scale is essential for both downstream purification (e.g., chromatography and filtration) and upstream operations (e.g., bioreactor inoculation). Spinners and roller bottles, once the staple of early fermentation processes, are becoming obsolete. Currently, stringent requirements exist for cultivation and scale-up of seed inocula. A carefully controlled inoculum scale-up process facilitates consistency and repeatability in operation while reducing operating costs by decreasing compliance burdens (Figure 1).

Labor and Time Allocations: Disposable systems can provide significant savings at all stages of drug development and manufacturing. At the early stages of drug development, in-house personnel can be allocated to strategic tasks rather than the scores of validation activities required by traditional facilities and equipment. Multitasking and parallel processing of drug development activities by streamlining/eliminating certain operations can advance development timelines significantly.

During manufacturing, labor and time savings are realized because disposable assemblies are often purchased presterilized, eliminating the need for equipment cleaning, sterilization, and/or assembly between campaigns. Equipment support and routine inspections and preventative maintenance require labor, money, time, and effort. In-process labor and time savings are realized by decreasing operator dependence, freeing up operators and other resources for other tasks. Equipment turnaround time is rapid when no CIP/SIP is needed.

Utilities will always be needed, but use of disposables decreases some requirements. Presterilized single-use systems eliminate steam sterilization, reducing or eliminating the requirement for clean plant steam. In general, large volumes of water for injection (WFI) are used during multiple stages of biopharmaceutical processing, from preparation of fermentation media and purification buffers to making equipment cleaning solutions. Reportedly, every liter of WFI used in a process requires 5–10 times that volume in downstream operations (**11**). These large volume requirements for WFI present a bottleneck during pharmaceutical manufacturing (**12**).

Space Considerations: Glass bottles and carboys take up counter space

and require storage; empty single-use systems store in smaller spaces. For facilities with limited space, single-use systems can help maximize what's available.

Environmental Impact: Not addressing environmental issues during process development can lead to serious problems during process commercialization because it is costly and time-consuming to make process changes after a process is approved by regulatory agencies. Computer simulation commonly used to evaluate and optimize integrated biochemical processes (**13**, **14**) should include environmental impact studies. Material balances calculated for projected large-scale manufacturing can reveal environmental hot spots: process steps that require solvents or regulated materials with high disposal costs.

At first glance, it would appear that adoption of disposables would increase a plant's adverse environmental impact. This may not necessarily be the case. Using discrete event modeling, Sinclair and Monge (**15**) compared disposable and fixed-vessel submodels. The disposal submodel required about 100 plastic bags with associated tubing per batch, amounting to ~200 kg of plastic waste. The fixed-vessel submodel used an additional 141 tons of WFI generated from 204 tons of purified water. Additionally, it required 4.2 tons of dilute CIP chemicals (equivalent to about 100 L of 40% caustics and 5 L of 80% phosphoric acid). Those materials require treatment before discharge. The increased consumption of plastic was reportedly offset by large reductions in water and CIP operations.

Purchasing/Procurement: The numerous pieces of a whole stainless steel system must often be ordered from different suppliers. Stainless steel filter housings and tanks use parts that require routine replacement (e.g., O rings). Each disposable component means one less O ring to track and one less part number in the procurement system.

Risk–Benefit Analysis

Understanding the risk associated with any decision is the first step in managing that risk. The pharmaceutical industry is subject to the vagaries of scientific, clinical, and regulatory processes. Disposables can be a risk-management strategy allowing drug manufacturers to defer some large capital investments in manufacturing facilities until the product risk is reduced.

Levin refers to designing efficient manufacturing facilities as an exercise in "reality-based creativity" (**16**). An efficient manufacturing plant accommodates growth (increase in sales), different products (multiuse or even multiple technologies), and different phases in product development. Timelines for construction of a brick-and-mortar biopharmaceutical facility are estimated optimistically at 30–48 months from project initiation to production of drug substance. Considering the progression of a typical clinical development pipeline, the decision to construct a commercial production facility to support the launch of a new biopharmaceutical product should be made around the time a product is in phase 2 clinical trials (**17**). Based on average success rates, the probability of a successful launch is only 26% at that point; if a company decides to build, it faces about a 74% chance that the facility will not be needed by the time it is completed. Any technology or strategy that can defer capital commitments until risk is reduced (past phase 2) will have significant value.

Risk–Benefit Considerations: The risks associated with making a right-fit manufacturing decision must be balanced against the benefits of the disposables option. The net benefit accrued by using disposable systems depends on what is limiting production. In many bioprocess facilities, problem areas include floor space and insufficient CIP and utility capacities. In such cases, use of disposable bags can increase production throughput; the exact increase would depend on individual circumstances.

Manufacturing Issues: Biopharmaceutical companies have begun to view manufacturing decisions as strategic because of their long-term organizational and financial implications. Increasing capacity is difficult in fixed facilities, and multiproduct facilities are not always a feasible option.

Manufacturing (of which capital costs of equipment are but a part) constitutes 18–20% of a pharmaceutical company's operating costs. When evaluating cost-of-goods, it is necessary to evaluate not just materials, utilities, and labor but lifecycle operation and disposal costs as well. As the size of a particular processing line increases, bags become more cost-effective. At the 20-L scale, for example, Sandstrom (**18**) projects a disposable-bag system to cost about $20,000/yr (per solution) compared with $40,000/yr for portable and fixed vessels. At the 200-L scale, the disposable system costs do not increase significantly (roughly estimated at $21,000/yr), but portable and fixed systems run about $62,000/yr and $80,000/yr, respectively. However, disposable applications have a maximum size beyond which concerns related to mechanical strength and physical properties of the bags preclude their use.

Sustainable Competitive Advantages (SCA)

Streamline operations, especially in the early stages of drug development when resources (time and labor) are at a premium.

Defer a percentage of the upfront capital costs and implement a better risk management strategy until there is a higher probability of clinical and commercial success compared with a traditional stainless steel infrastructure.

Decrease validation requirements when certain manufacturing steps are eliminated (e.g., CIP, SIP).

Decrease in-process documentation requirements.

Facilitate regulatory compliance.

Reduce manufacturing time, and facilitate faster equipment turnaround.

Maintain product integrity, especially in multiproduct and contract facilities.

Ensure operator safety when exposure to cytotoxic and corrosive chemicals (such as those used in cleaning operations) is reduced by eliminating certain steps.

Respond to the vagaries of scientific, clinical, and regulatory processes.

Optimize available space.

Productivity and Profitability Issues: A survey conducted by the American Society for Microbiology's venture arm, ASM Resources, found that biopharmaceutical manufacturers' two biggest challenges were increasing productivity (46%) and complying with FDA regulations (45%). Approaches to increased productivity and profitability include enhancing biological expression systems (providing higher product yields) and maximizing productivity by decreasing yield loss during downstream processing. A 1% loss is not uncommon in biotechnology, so with products valued at thousands of dollars per microgram, even cutting that loss in half would significantly improve on the cost-of-goods. In general, the greater the number of steps in any process, the greater its potential for product losses. With increased regulatory requirements (e.g., introduction of viral clearance steps into an existing process), redundant processes often continue to remain part of manufacturing operations. So it is essential to examine existing systems, question the utility of each step, and evaluate its impact on process productivity and efficiency.

Validation of Disposable Systems

Extractables Issues: In general, extractables associated with a disposable system may be inherently present in the material or secondarily derived as a result of its processing, use, and/or sterilization. Possible sources of leachable compounds include the base polymers and associated contaminants; primary and secondary additives; polymerization and processing residuals; and impurities and/or decomposition products of additives, adhesives, and noncontact sources such as secondary packaging (**18**).

The kinds of interactions that could potentially occur between a bag's polymer and contents include leaching of chemicals from the contact surface, reaction of the contents with the bag polymer, and uptake of product components by the plastic. Intrusion of gases or other contaminants through the polymer material and into the bag contents is another possibility. Additionally, the polymer must be stable to the sterilization method used. Gamma irradiation often used for bag sterilization can modify/degrade some polymeric materials, leading to increased extractables or even destruction of the polymers.

Drug products may contain strong-solvating additives (solubilizing agents, stabilizers, cosolvents). Such additives and other material-related compounds may migrate from the plastic into process solutions. Factors affecting leachability include

- intrinsic solubility (e.g., leachable levels associated with certain compounds accumulate in the parts per billion range consistent with their aqueous solubility)
- available pool of the chemical (that for a component of the primary plasticizer would be several times greater than for a contaminant associated with that primary plasticizer)
- conditions of use.

When used for solution storage, bags are used under static conditions. In a dynamic contact application (e.g., a bioreactor), the total dose of extractables delivered includes the pool, solubility, and migration constraints.

Extractables Testing: Disposable systems manufacturers conduct tests to validate their systems, but system users must generate their own data demonstrating that extractables will not adversely affect a drug product or in any way change its composition. Controlled extraction tests in a model solvent that simulates worst-case exposure is a common approach. The model solvent and test conditions are based on rational models derived from known behavior of various solvent groups, chemical similarity of its constituents to the product being modeled, or characteristics of the product that may affect compatibility with the disposable system (**19**). These worst-case scenario tests help estimate the maximum amount of extractable material that can reasonably be expected.

Extractables testing must be done not just with the disposable bags (with their high surface area to volume ratios) but with an entire disposables assembly: bag + tubing + other ancillary appendages such as filters, aseptic connectors, and so on. In general, such testing should be conducted under actual conditions during storage (temperature, humidity, and so on). If during storage a bag is sprayed periodically with a sanitizing agent, that also should be included in the study.

Samples collected from a disposable system at time zero and

periodically thereafter are subjected to tests such as determination of total organic carbon (TOC), pH, conductivity, endotoxin, and bioburden to ensure that the fluids meet basic requirements. Detailed analysis (quantification and identification) of extractables may be achieved using tools such as solvent extraction by gas chromatography with a flame ionization detector (GC-FID) and mass spectrometry (GC-MS). Commonly leached compounds are further quantified and identified using GC-MS and electron ionization mass spectrometry (EIMS).

Many Voices, One Topic

In an industry vulnerable to the vagaries of scientific, clinical, and regulatory processes, disposables technologies offer a novel manufacturing option and potential risk-management strategy. Flexibility is essential when speed-to-market demands are paramount alongside the stringent requirements of regulatory compliance and process control. Maximizing productivity from manufacturing assets to maintain a sustainable competitive advantage (SCA) is critical in the biopharmaceutical industry, as described in the "SCA" box. Ultimately, the feasibility of the disposables option must be considered from a number of perspectives including manufacturing scale, technology requirements, and the availability of an appropriate infrastructure.

This supplement provides a cornucopia of related topics. Regulatory, qualification, and validation considerations are covered along with specialized applications (e.g., disposable systems for filtration of bovine serum and freeze–thaw applications). The selection offered to satisfy your intellectual appetite is diverse. Enjoy!

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