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<table>
<thead>
<tr>
<th>Feature</th>
</tr>
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<tbody>
<tr>
<td>&gt; Intuitive CLICK-PULL-TWIST connection</td>
</tr>
<tr>
<td>&gt; One-step disconnection</td>
</tr>
<tr>
<td>&gt; No need for clamps, fixtures or tube welders</td>
</tr>
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Cover images are courtesy of Arkema, GE, and Therapeutic Proteins.
A Brief History of Single-Use Manufacturing

Jerold Martin

Single-use manufacturing may seem like a new trend, but it has actually been around for almost 30 years, beginning in the early 1980s when filter manufacturers began to make small process-scale plastic filter capsules to replace “junior” size stainless-filter housing assemblies. Small laboratory syringe filters were already being supplied presterilized by gamma radiation, but originally, disposable filter capsules for pharmaceutical production were only available in nonsterile format for autoclaving by the user. Higher area filter capsules for even larger volumes did not become available until the late 1980s to early 1990s, eventually including the large scale 10-inch modular capsule filter assemblies available today. Around the same time, the smaller production-scale filter capsules presterilized by gamma irradiation began to be offered.

On a parallel track, the mid-1980s also brought developments in disposable biocontainers. Bioprocessors began to use plastic film bags originally developed for large volume parenterals or food storage for serum and culture media containment as well as for buffers. Similar to the large-scale filter capsule developments, the late 1980s and early 1990s brought the introduction of large-scale single-use processing with 2D bags in volumes from 50 to 1600 L and by mid to late 1990s, 3D bags for process volumes up to 3000 L, along with the first generation of totes to contain them.

As larger-scale capsules and biocontainers became more available, bioprocessors began to request that suppliers assemble early systems with pre-connected tubing, and by the mid-1990s, bag suppliers had begun offering single-use systems with filter capsules that were pre-attached to biocontainers, and filter manufacturers began offering filter capsules with tubing and bags pre-connected. Gamma-irradiated systems followed shortly thereafter, and by the mid 2000s, they were being validated as sterile systems. In addition, more advanced totes and biocontainer designs offered reduced leakage risks.

continued on next page
Single-use manufacturing was further facilitated in the early 2000s by the introduction of large-scale tube welders and sterile connectors that enabled the connection of two sterilized fluid pathways/systems while maintaining the sterility of both. Availability of larger biocontainers by the early 2000s brought with them the innovative development of the disposable rocking-bag bioreactor, and by the late 2000s, stirred tankliner bioreactors and mixers came to market, with the larger filter capsule formats enabling the development of membrane chromatography units for trace-contaminant polishing.

The mid-late 2000s also brought the industry disposable depth-filtration capsule systems and a new generation of disposable sensors. During that time, the Bio-Process Systems Alliance (BPSA) was established. BPSA has been instrumental in promoting best practices for implementation of single-use technologies. The most recent developments in the 2010s have been sterile disconnectors and single-use tangential-flow filtration systems.

**Single-use technology applications can be found in manufacturing processes for licensed drug and vaccine products around the world.**

Today, the term “single-use technology” encompasses a broad range of primarily plastic disposable technologies that are suitable for a wide variety of scales and applications, from upscale bioprocessing to final formulation and filling. They can be found in manufacturing processes for licensed drug and vaccine products around the world.

This primer explores these various uses with articles on moving from a fixed system to a single-use system, working with flexible manufacturing facilities, determining carbon footprints, and more.

**Acknowledgment:** The author wishes to acknowledge Paul Priebe of Sartorius-Stedim Biotech for his input. **BP**
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Bioprocessing Methods

New technology is designed to improve production efficiency by taking advantage of the properties of single-use bags.

Sarfaraz K. Niazi

Single-use technology for bioreactors has come a long way during the past 25 years, yet some of its capabilities remain to be exploited. Equipment manufacturers have adopted the technology as if it were an evolutionary step, but it is, in fact, revolutionary. Current offerings in single-use technologies often are not presented this way, however.

Single-use bioreactors currently follow one of two general formats. In one of these, the single-use components are used as linings for stainless-steel tanks. In a second model, a flexible bag is affixed to a rocker system that helps aerate and mix components inside the bag (1–3). Both of these models limit the value of single-use systems, however.

Equipment manufacturers conduct extensive exercises to chart the future of bioprocessing methods, but the real judge of what is needed is the consumer. The development of large-scale bioreactors for the manufacture of commercial quantities of monoclonal antibodies and vaccines at an affordable cost and with a short development time would fill an unmet need. Therapeutic Proteins is looking at ways to meet this demand by incorporating a comprehensive bioprocessing unit capable of upstream and downstream processing inside a single bag without any moving parts. The company has filed or received dozens of US and worldwide patents for these inventions. In this way, the company hopes to spur the further evolution of single-use technologies.

In this new unit, mixing is achieved by gentle pressing on the bag to create a wave. Figure 1 shows a bioreactor with a flapper that pushes down on the bag to create a wave motion inside the bag. The bag itself lies flat and does not move. The Navier–Stokes equations describe the motion of fluid substances, such as liquids and gases (4). These equations state that changes in the momentum (i.e., force) of fluid particles depend only on the external pressure and internal viscous forces (which are similar to friction) acting on the fluid. The equations also describe the balance of forces acting

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at any given region of the fluid. A force applied to any portion of a fluid would thus be transferred to the rest of the fluid (4). A flexible bag never needs to be shaken or rocked. All that is needed is to apply a minimal force, a pressure on any part of the bag, to start the motion of liquid. Rocking and shaking technologies generally fail to account for the physical constraints on the amount of stress that can be applied to the bag. Bags used in the rocking model cannot hold more than 500-L of media because the bag would break when rocked at a larger size.

Air-septum mixing is another efficient method employed by the new system. Figure 2 shows a model of an air septum that pushes air from the bottom of the bioreactor to create mixing throughout the bag. The bag design incorporates three layers of polyethylene. The middle polyethylene layer has fine holes and is joined to the bottom layer at various points to create an upper chamber and a lower chamber. Gas is passed through the bottom chamber to create a sparging system that extends to the entire base of the bag. This system allows extensive mixing, thus removing the need for moving parts in the bioreactor.

Aeration is provided either by a ceramic sparging rod or by a perforated septum. (see Figures 2 and 3). Aeration levels of 6 vvm are easily reached, thus allowing every type of cell and organism to grow in flexible bags. The KLa values are comparable with or higher than those achieved in stainless-steel bioreactors. Until now, it was not possible to manufacture bacterial products in flexible bags. The new invention, combining a sparging system with a proprietary exhaust system, broadens the uses of this technology. The GE WAVE system uses surface aeration, which limits it to cell-culture work. Other products use traditional mixing systems that add substantial cost to the design and almost inevitably limit the size of the bioreactor.

The size of the new bioreactor is less limited because the bag remains stationary, which eliminates stress on the seam. Because the mixing and aeration systems in the new invention are part of the bag, a flexible bag can take any size, from a few liters to thousands of liters. The flappers are arranged along the longer edge of the flexible bag, and, in the case of the air-septum design, mixing and aeration are fully integrated. In addition, because the bag is not pressurized or bloated, the volume of nutrient medium can be as much as 70–80% of the bag volume. This feature further reduces the cost of manufacturing.

Batch size is varied by a gravity-driven system that mixes the contents of multiple bags to meet the 21 CFR definition

**Figure 1:** A 400-L bioreactor for bacterial fermentation used by Therapeutic Proteins to manufacture filgrastim.
of a batch without the need for transferring the nutrient media to a larger container. This design eliminates the need for validating multiple batch sizes. This invention, though not unique to the new bioreactor, confirms the idea that it is not necessary to validate large bioreactors. Instead, manufacturers can save costs by validating a single size and making a daisy chain of bioreactors to produce large batches. The gravity system (see Figure 4) reduces stress on the biological culture and requires no equipment other than a moving platform. The collection bag has no moving parts for mixing, which is achieved through a venturi effect as the media enters the bag.

Perfusion of culture is made possible by installing a ceramic filter. An air-scrubbing method prevents the filter from clogging. (see Figure 4). The nutrient media is drawn through filters that are continuously scrubbed by a constant stream of fine air bubbles. This filter can be used in many other stages of bioprocessing that require the concentration of nutrient media, thus making cross-flow filtration redundant. No equipment currently available can perform the function of this filter. It can be positioned inside the bag and used indefinitely.

A single-use bioreactor that takes advantage of gravity can reduce stress on the biological culture and requires no equipment other than a moving platform.

Secreted proteins can be harvested by binding them to a resin in the bioreactor, thus eliminating the need for cell separation and cross-flow filtration. The resin is added to the bag after the completion of the upstream cycle in the upper chamber of the air-septum bioreactor (see Figure 3). Once the binding is complete, the nutrient medium and cell culture are drained out. The protein–resin complex can be eluted or packed into columns for further purification. This method works on the principle that it is unnecessary to...
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remove the cells and reduce the volume of nutrient media if the purpose is to separate a protein. The binding resin can be a specific resin, such as protein A, that can be reused hundreds of times, or a mixture of inexpensive resins, including hydrophobic and ion-exchange resins. The nutrient media’s properties can be adjusted to maximize the binding.

This invention is intended to reduce the time and cost of drug manufacturing. Two major steps, both requiring expensive equipment and substantial time to achieve the same goal, are eliminated. It is anticipated that in the manufacturing of monoclonal antibodies, this new unit saves a process time of approximately 50 h for a 2000-L batch. In addition, the limited handling of proteins can improve the final yield substantially, sometimes as much as 20–30% (5).

Proteins can be purified in the bag by using it as a chromatography column. Although the idea of using a flexible bag as a chromatography column appears alien, nothing prevents a process from being developed by taking into account the geometry and the physical state of resin suspension in the bag. The elution may include a step elution, a gradient elution, or a programmed elution. An example is washing the bound resin to remove cells, and then equilibrating the protein–resin conjugate in a buffer to elute the target drug. A buffer that would break down the binding can be used to collect a highly

**Figure 3:** A separative bioreactor, including (1) liquid inlet–outlet, (2) exhaust, (3) media sample, (4) flexible 2D bag, (5) polyethylene perforated septum, (6) heating–cooling element, (7) gas sterilizing filter, (8) gas flow valve, (9) source of gas, (10) drain, (11) drain control valve, (12) lower chamber, (13) upper chamber, (14) nutrient media or chromatography media, (15) support stand, (16) support base, (17) septum tufting point, (18) buffer inlet, and (19) mixing plenum.
Figure 4: A gravity-driven mixing system, including (1) vertical moving stand, (2) bioreactors, (3) drain tube, (4) support base, (5) transitory vessel, (6) and venture mixing vent.

purified solution of the target protein. Even if this process of purification does not achieve the quality that traditional methods do, the possibility of eliminating a few steps in downstream processing would have a great effect on the cost of purification because no equipment needs to be installed for large volumes to be fed through the purification column. An AKTA Pilot liquid-chromatography system (GE Healthcare) might do the job of an AKTA Processor (GE Healthcare), for example.

Other uses of the new bioreactors include media and buffer preparation and sterile transfer to final containers. The unit also may be used as a pressure vessel in pharmaceutical manufacturing. The air-septum bioreactor is suited to performing many functions. As a complete system with no moving parts and the ability to be pressurized, this invention fulfills the bioprocessing industry’s needs for manufacturing recombinant proteins, monoclonal antibodies, and vaccines.

Other uses of the perfusion filter include concentration of slurries, reduction of volume of a bacterial nutrient media, water purification, and sterile liquid transfers. The filter can be made in several shapes and combinations to fulfill the need for a particular flow rate from a specific mixture. Using air to scrub a filter and keep the pores open enables new filtration methods. This filter system requires a solid base to keep the filter from collapsing. The base can be layered with fine membranes, such as a 0.22-μm filter, to separate bacteria and sterilize a solution. The filter system can be sterilized in situ and placed inside a bag for an unlimited time of operation.

The new technology described above is designed to take advantage of the properties of a flexible bag. By incorporating a bioreactor inside the bag, the technology offers a transportable system that does not require extensive validation when manufacturing sites are changed. Because users can link the units together to produce batches of practically any size,
SINGLE USE BIOREACTORS

Figure 5: Air-scubbed filtration system for nutrient media perfusion, cell removal and volume reduction.

The technology could expand the adoption of single-use systems for the commercial production of biological drugs.

A significant advantage of the new technology developed is its low capital and operational costs. The flexible bags are placed on a heating or cooling platform (see Figure 1). The system monitors the nutrient media for dissolved oxygen, pH, and glucose levels either by remote sensors or by direct sampling. Although other methods, such as fluorescence-based monitoring, are available, Therapeutic Proteins believes that, in the long-term, the wired sensors inside the bags are the most appropriate tools.

The systems described above are routinely used at Therapeutic Proteins’s cGMP compliant facility to manufacture large-scale cytokine and monoclonal-antibody production batches. Although the technology requires substantial modification and validation of the process, the systems operate smoothly once these efforts have been completed because they contain few components.

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The Evolution from Fixed to Single-use Systems

An overview of applications for disposable components and important property considerations.

Gary M. Dennis, Charles Weidner, and Saeid Zerafati

For many years, “blockbuster” drugs have made fixed systems the most pragmatic choice for manufacturing high volumes to meet high demand. Fixed systems rely heavily on stainless steel for piping, valves, tanks, and fittings because the parts needed are rigid and fixed in nature. Steel components can be manufactured with a variety of surface finishes, are sterilizable using most sanitizing medium, and can withstand high temperature. Production runs in fixed systems tend to be long with infrequent changeover. For the above reasons, and because of the risk-adverse culture that is synonymous with drug manufacturing and engineering, stainless steel has been the predominant material in biopharmaceutical manufacturing.

This thinking began to evolve with the advent of single-use systems (SUS), most commonly referred to as “disposables.” A new mindset and technical platform was introduced to meet the changing industry needs presented by “personalized” large-molecule drugs. Initial SUS processes were deployed by manuf-

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Image courtesy of the authors
turers in response to the need for the low-volume production of vaccines in high concentration (Merck) and to meet hormone medication commercialization (Amgen) in a relatively short period of time (1). Fixed stainless-steel systems require extensive downtime because the process needs to be revalidated and sterilized after each use. Disposable process technology, on the other hand, utilizes fewer parts and eliminates the costly need to revalidate; the system can be used once before the prevalidated components are replaced for a fast change-over to a new vaccine or drug.

Factors favoring the fundamental shift to SUS are:

- Reduced R&D costs compared with using a high volume fixed system as part of the research line.

Compared with stainless-steel systems, disposable process technology utilizes fewer parts and eliminates the costly need to revalidate.

- Decreased time to market for a specific medicine, which can be tailored for smaller volume use.
- Rapid setup and regional deployment to meet drug needs worldwide.
- Ability to manufacture many products in the same facility with no risk of cross-contamination.
- Minimal expansion cost through drug development and scale up.
- Lower utility costs in cleaning and system revalidation.

### Table I: Chemical, brand name, and application of common plastics.

<table>
<thead>
<tr>
<th>Chemical name</th>
<th>Brand name examples</th>
<th>Applications</th>
</tr>
</thead>
<tbody>
<tr>
<td>Polytetrafluoroethylene</td>
<td>Teflon</td>
<td>Filters, tubing</td>
</tr>
<tr>
<td>Polyvinylidene fluoride</td>
<td>Kynar, Kynar Flex</td>
<td>Filters, fittings, tubing, bags</td>
</tr>
<tr>
<td>Polycarbonate</td>
<td>Lexan</td>
<td>Fittings</td>
</tr>
<tr>
<td>Polypropylene</td>
<td>Moplex, Profax</td>
<td>Filters, housing, piping</td>
</tr>
<tr>
<td>Polyethylene</td>
<td>Dowlex, Engage</td>
<td>Bags</td>
</tr>
<tr>
<td>Polyamide</td>
<td>Nylon, Rilsan 11&amp; 12</td>
<td>Films, filters</td>
</tr>
<tr>
<td>Polyvinylchloride</td>
<td>Lacovil</td>
<td>Pipes, films, tubes</td>
</tr>
<tr>
<td>Silicone</td>
<td></td>
<td>Tubings, fitting</td>
</tr>
<tr>
<td>Poly ether block amide</td>
<td>Pebax</td>
<td>Tubing</td>
</tr>
<tr>
<td>Ethylene vinyl acetate copolymers</td>
<td>Evatane, Elvax</td>
<td>Bags</td>
</tr>
<tr>
<td>Compounds (blends of multiple polymers)</td>
<td>C-Flex, Santoprene</td>
<td>Tubing, fittings</td>
</tr>
</tbody>
</table>
Table II: Properties of PVDF fluoropolymer (Kynar) before and after gamma sterilization at 50 kgy.

<table>
<thead>
<tr>
<th>Injection molded type</th>
<th>Stress at yield (psi)</th>
<th>Strain at yield (%)</th>
<th>Stress at break (psi)</th>
<th>Flexural modulus (psi)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kynar RX Homopolymer</td>
<td>7210</td>
<td>5.9</td>
<td>4600</td>
<td>199000</td>
</tr>
<tr>
<td>Kynar RX Homopolymer Gamma Irradiated</td>
<td>7440</td>
<td>5.5</td>
<td>4400</td>
<td>207000</td>
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<tr>
<td>Kynar RX Copolymer</td>
<td>3570</td>
<td>10.6</td>
<td>4300</td>
<td>57800</td>
</tr>
<tr>
<td>Kynar RX Copolymer Gamma Irradiated</td>
<td>3670</td>
<td>9.6</td>
<td>4700</td>
<td>60400</td>
</tr>
</tbody>
</table>

PLASTIC COMPONENTS AND SINGLE-USE SYSTEM RESEARCH

Many questions were raised over initial plastic designs. These issues were exacerbated by the general lack of polymer knowledge after years of metal use.

The list of candidate plastics for single-use pharmaceutical processing includes those currently used in industry designs (see Table I). One of the strengths of these plastic components is the diversity of properties and designs presented. However, this also represents one of the main challenges as biopharm engineers struggled with how to incorporate a number of material components into a system and industry designed to minimize risk.

Membrane and filtration

The longest running polymer components used in biopharmaceutical applications are filter membranes and cartridges. These components have been used in fixed systems for many years. Membrane filtering applications have primarily used polytetrafluoroethylene (PTFE), polyvinylidene fluoride (PVDF), polypropylene (PP), and polyethersulfone (PES) (2). PVDF has been the resin of choice for over 20 years in protein synthesis and separation for biopharm applications. The large surface to volume ratios required in filter membranes exceeds that of other common components including tubing and containers. Therefore, this fluoropolymer resin has been long vetted and provides biopharmaceutical process engineers with a track record and history of successful performance in industry processes.

Piping

Polymer materials, especially PP and PVDF, have experienced success supplanting stainless steel in some fixed industry piping designs as the materials could be used in various water service criteria, including United States Pharmacopeia (USP) purified water for both plastic resins. Additionally, PVDF piping lends itself to use in ultra high purity water, laboratory reagent grade water...
Type 1, as well as Semiconductor UHPW ASTM Type 1 service criteria. One advantage of polymer components to stainless steel is the latter’s capacity to rust or rouge in high-purity water causing system contamination. Chemical passivation is frequently required to remove free ions from the surface and restore the oxide film that gives stainless steel its corrosion resistance (4).

**These bags must be strong and tough, possess barrier properties and have the ability to melt bond effectively in multilayer structures.**

**Tubing and fittings**

Tubing is the most highly utilized component within a disposable system because large fluid transfer is required with the single-use system design. Multiple materials have been used ranging from silicone, EVA, TPE compounds, low density PE, PTFE, and PVDF copolymers.

Molded fittings are required to attach or weld to other process componetry including bags and containers. Therefore, welding and processability becomes an important design criteria. The most common industry fitting materials are PE, PP, polycarbonate (PC), silicone, and PVDF.

**Bags**

Film bags and containers pose possibly the most significant challenge as they are needed in numerous disposables functions starting with reaction vessels and progressing to transfer, storage and media preparation. Long dwell times are the norm, which makes purity concerns paramount despite being only one of a host of factors that affect their maximum utilization. These bags must be strong and tough, possess barrier properties and have the ability to melt bond effectively in multilayer structures. Purity, melt processability and bonding, as well as the contact layers ability to be sterilized while providing a significant barrier or permeation properties is a tall task. Common bag layers include EVA, PE, and PVDF.

**FLUOROPOREYLMERS MOVE TO THE FOREFRONT**

As previously stated, one of the original concerns with plastics was the many varieties to meet multiple design characteristics. Biopharm engineers desired a more universal option. In other words, a polymer alternative to stainless steel. The industry hit on the idea of a more defined and singular “contact layer” to meet the diversity required in SUS. This search for a common contact material instinctively led its way to PVDF fluoropolymers (e.g., Kynar) for many reasons, as noted below (5).

**Processability**

PVDF is completely melt processable on conventional equipment allowing for its ability to be found in the complete range of component forms required. This melt processability attribute extends itself to not only rigid parts (pipe, filter housings and membranes, pumps) which use PVDF homopolymers, but also to parts favoring added flexibility (tubing, fittings, and film). Copolymer PVDF resin helps at-
Stainless steel continues to lead the way for mass-production drugs, but disposables equipment has moved into the biotechnology–pharmaceutical mainstream.

tain the more flexible part designs while maintaining the purity and processability aspects. Most importantly, the ease of melt processability allows for welding by various industry methods (6).

**High purity**
No processing aids or additives are required in PVDF fluoropolymer resin manufacturing, allowing for its compliance with USP Classification VI. There are no animal derivatives in Kynar resins.

**Cholesterol binding**
Fluoropolymers have low surface tension properties and as such do not have the propensity to attach to organic matter such as proteins and lipids. This promotes increased manufacturing efficiencies as proteins do not stick to the bags or vessel walls.

**Sterilizable**
PVDF is unique among polymer materials as it is compatible to the various sterilization methods including gamma, autoclave (steam), and chemical (EtO) (7). Gamma radiation is commonly used in disposables practices. Common industry gamma sterilization levels are 25-30 KGY. Table II contains data that shows no change in properties even after doses twice the industry level (50 KGY).

**Multilayer adhesion technology**
The ability to make multilayer film (bags) and tube structures was a final obstacle to overcome. As PVDF fluoropolymers have the advantage of low surface tension, this same property can make it more difficult to adhere to complementing resins when appropriate. This can often be the case in bag manufacturing. Multilayer bag structures and technology utilizing PVDF fluoropolymers as the contact layer are now readily available due to the development of new extrusion designs. Such designs allow plastics with additional barrier properties, such as EVOH, and lower cost softer resins, such as PE and copolyamides, to be incorporated in outside layers.

**Chemical resistance**
The appropriate selection of polymers can offer long term advantages to metals in areas where cleaning agents are used. Plastic materials are available that fully resist a broad range of chemicals and rusting or rouge is never a concern. PVDF can handle steam, chlorinated disinfectants, oxidants and acidic chemicals at varied concentrations. PVDF belongs to the fluoropolymer family of resins which contains the carbon-fluorine bond which is one of the strongest bonds in chemistry. The high energy that is required to break this bond creates its unique chemical resistance across a broad range of pH values. PVDF components are commonly used in applications where bleach, chlorine dioxide, chlorinated water, brominated water, ozone, peroxide, peracetic acid, HCl, and alcohols are used in cleaning and bacterial control processes.
CONCLUSION
Stainless steel continues to lead the way for mass-production drugs and fixed-system approaches. Disposables equipment has moved into the biotechnology-pharmaceutical mainstream. Only 3% of biopharmaceutical manufacturers use no disposables today, according to the Third Annual Report on Biopharmaceutical Manufacturing Capacity and Production, issued in June 2005 by BioPlan. Additionally, the Biopharm Miram Murge Study estimated capital costs reduction of 40% by single use systems. This trend is expected to continue as the industry evolves into a more pragmatic approach to regionalized and smaller-dose drugs. The need for lighter and more efficient components and systems will become increasingly important as quick changeover and low costs move to the forefront. The PVDF fluoropolymer alternative has continued to gain acceptance as a single fluid contact surface as it offers biopharm engineers the advantage of reduced risk and a universal polymer-system approach.

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Upcoming special issues of BioPharm International will focus on outsourcing, expression systems, and biopharmaceutical trends. To contribute, contact the senior managing editor Angie Drakulich at adrakulich@advanstar.com.
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Approaches for Flexible Manufacturing Facilities in Vaccine Production

With careful analysis to mitigate risk, disposable technology and process closure can enable adaptable designs and reduced costs.

Kim L. Nelson

According to the US Centers for Disease Control and Prevention’s (CDC) vaccine price list, US vaccine manufacturers receive a wholesale price of between $9 and $109 per dose for pediatric and adult vaccines (1). For influenza vaccines, the wholesale price paid to manufacturers ranges from $5 to $9 per dose (2). Doses that reach the market early in the season command a higher than average price, and prices decline throughout the season. Any excess inventory is destroyed at the end of the influenza season. Small batch sizes, the high cost of labor involved in egg or cell culture based production, and the cost of filling results in a profit margin that is quite low relative to that of the rest of the biopharmaceutical industry. Such low profit margins affect manufacturers’ willingness to invest capital in a commodity business such as influenza or other vaccines. This consideration is particularly true when providing vaccines to developing countries, where the price for vaccines per dose are a fraction of those in the US. Table I provides average reimbursement prices paid by UNICEF in 2010 and vaccine prices in high income countries are represented by the CDC vaccine price list for 2011 (1, 3).

The pressure to reduce facility-investment costs and the cost of goods manufactured is a primary driver in the paradigm shift occurring in the industry’s approach to facility design. The objective is to be more competitive, reduce risk, and provide higher value for investments. Production facilities must be flexible, cost effective, and provide more rapid construction and start-up. In addition, for pandemic influenza vaccines, a surge capacity is crucial to produce the maximum number of vaccine doses in the shortest time. Cell-culture influenza vaccine processes being developed offer many advantages in scalability, but traditional manufacturing facilities may not be available or adaptable to produce such vaccines thus presenting a bottleneck to their commercialization.

Applicable to both clinical and full-scale manufacturing, single-use systems have become a mainstay of flexible and adaptable process and facility design. Although disposables provide opportunities, they also introduce challenges for biopharmaceutical manufacturing. This article discusses facility and process-design issues that should be examined when considering or implementing single-use technology.

**THE EFFECT OF THE ROOM ENVIRONMENT**

To evaluate the potential risk of contamination or adulteration involved in a production process, one must first examine the potential sources, which include carryover between batches, cross-contamination between prod-
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**Table I:** Cost for single and combination vaccines in low- and high-income countries.

<table>
<thead>
<tr>
<th>Disease</th>
<th>Average vaccine cost per dose</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Low-income countries (2)</td>
</tr>
<tr>
<td>Measles</td>
<td>mono</td>
</tr>
<tr>
<td>Diphtheria, tetanus, and pertussis (DTP)</td>
<td>whole cell</td>
</tr>
<tr>
<td>Tuberculosis</td>
<td>Bacillus Calmette-Guérin</td>
</tr>
<tr>
<td>Hepatitis B</td>
<td>mono and in combo with DTP</td>
</tr>
<tr>
<td>Hemophilus influenza Type B</td>
<td>in combo with DTP</td>
</tr>
<tr>
<td>Polio</td>
<td>oral polio vaccine</td>
</tr>
<tr>
<td>Influenza</td>
<td>N/A</td>
</tr>
<tr>
<td></td>
<td>High-income companies (1)</td>
</tr>
<tr>
<td>Measles, mumps, and rubella</td>
<td>$0.24</td>
</tr>
<tr>
<td>DTP</td>
<td>$0.25</td>
</tr>
<tr>
<td>none</td>
<td>$0.07</td>
</tr>
<tr>
<td>in combo</td>
<td>$0.27</td>
</tr>
<tr>
<td>flu vaccines (various)</td>
<td>$0.10</td>
</tr>
<tr>
<td>N/A</td>
<td>$3.20</td>
</tr>
<tr>
<td>in combo</td>
<td>$8.25</td>
</tr>
<tr>
<td>N/A</td>
<td>$21.38</td>
</tr>
</tbody>
</table>

**Figure 1:** Distinction of open, closed and rendered closed processes in classified and controlled nonclassified (CNC) spaces.

...and the introduction of contaminants from the environment, raw materials, or from inadequate cleaning.

In the US, FDA recognizes the cleanroom standards of the International Organization for Standardization, specifically ISO 14644-1 (4). European standards go further in distinguishing between static conditions at rest and dynamic conditions in operation (5). Controlled nonclassified (CNC) is a classification often used in noncritical areas in GMP manufacturing facilities. CNC areas are designed to provide a consistently controlled environment, but are not monitored to the same levels as ISO or Grade classified areas. The International Society of Pharmaceutical Engineering (ISPE) has
similarly defined CNC as a nonclassified room environment where closed processes and their immediate support systems may be located. CNC spaces are cleanable, have access control, and are served with filtered HVAC air, but do not have the rigid procedural controls and personal gowning requirements of classified areas.

Room classifications and the heavy burden they carry were considered in a recent article prepared by biopharmaceutical industry representatives that examined environmental controls in the context of current manufacturing technology (6). The authors discussed the rational for breaking the cleanroom paradigm and lowering room classifications using risk-based approaches to reduce capital and operating costs.

**SYSTEM CLOSURE—AN ENABLING TECHNOLOGY**

Closed processes or systems use process equipment that does not expose the product to the immediate room environment and therefore prevent entry of contaminants (7). In the case of biocontainment, the system must also prevent escape of organisms or products. Closure is usually achieved through aseptic connections or by using filtration in the system as a means
of rendering it closed. Additions to or withdrawals from the system must be done in a manner that ensures the integrity of system closure. It is important to note that it is the manufacturer’s responsibility to both define system closure, and to prove closure for each process step. Importantly, the loss of a closed state due to routine or infrequent activities (e.g., maintenance and cleaning) does not negate the need for the use of closure as a key aspect of the facility’s design. In such cases, validated procedures for re instituted the closed state should be part of the standard operating procedures for manufacturing. Newberger and Melton discuss brief exposure in the context of API production facility design, and it is an important concept that should also be incorporated into risk-based approaches to system closure (7).

It can be difficult or impractical to fully close some processes, for example inoculum preparation, where robotics or isolators are impractical because of high cost or operator resistance respectively. In such situations, open processing is acceptable, providing that it is protected by a suitable, monitored room environment.

In closed-system processing, the room environment becomes secondary to the integrity of the closed systems and any connections made to introduce, remove, sample, or analyze the contents. In an open operation, which is not subsequently filtered, the cleanroom environment is relied upon to reduce the probability of contamination from room air. If the process is rendered closed (e.g., by filtration into a closed tank or bag), the room environment does not affect the integrity of the system. With a closed process that is never exposed to the room, the environment does not affect the system at all.

**CLOSURE ANALYSIS**

Closure analysis is a systematic evaluation of the risk in each process step, based on the process control level required and the closure level used for particular connections. At its simplest, closure analysis examines critical unit operations and each connection into or out of the closed-
Figure 4: Schedule showing how shorter project times compared with those of a traditional stainless-steel facility can allow for improved time to market; or for added time for process development, clinical result generation, and business planning before committing to major capital investments.

- Identify the system boundary and all penetrations of the unit operation’s closed-system boundary.
- Evaluate each particular unit operation according to its bioburden control specification (e.g., controlled bioburden, low bioburden, and aseptic).
- Evaluate each connection according to agreed closure definitions (e.g., open, briefly exposed, cleaned, closed, or unexposed).
- Calculate a risk ranking based on the product of the bioburden control ranking and the closure ranking for the particular connections being evaluated.
- Evaluate connections with unacceptable risk ranking using a closure fault tree (see Figure 2). Modify the closure system, or upgrade the environment for points having unacceptable risk, or ensure that downstream steps mitigate the risk acceptably (e.g., by filtration).

All of the connections’ risk rankings can be tabulated to give a snapshot of the system, and a frequency histogram can show the number of connections considered to be higher risk; the objective is then to evaluate ways to move these to lower risk rankings. Connections that are inconsistent with bioburden control; identified for redesign, increased environmental or downstream controls; or connections that are not clearly defined in documentation will all require further attention.

FUTURE FACILITY CONCEPTS

By leveraging closed systems and maximizing the use of single-use systems, it is possible to design a facility that allows work areas to be combined and room classifications to be lowered. Such a facility offers many benefits; in studies done by CRB for a number of biopharmaceutical clients where the FutureFacility concepts were utilized and the corresponding facility costs, utility costs, and cost of goods were examined, advantages included:

- Reduced manufacturing area (by 15–30%).
- Reduced HVAC (resulting in reductions in room classifications, gowning, cleanroom areas, air changes per hour, fan power de-
mand, number of air handling units, and maintenance).

- Reduced utilities (single-use systems can reduce clean steam and water-for-injection requirements by up to 80–90%, chilled water and steam demands are reduced by up to 60%, and wastewater is also reduced.
- Reduced construction and start-up schedule (by 30–50%)
- Possible reduced cost of goods.

In the FutureFacility concept (see Figure 3) for a vaccine manufacturing plant, a contained zone is provided for the virus work, while the nonviral support functions, as well as the post inactivation steps are combined into a single room. Such an approach reduces the circulation areas of corridors and airlocks, maximizes the efficiency of labor, and offers the maximum in flexibility for changing processes. Each unit operation is connected to utility plates in the ceiling and can be readily relocated to accommodate various processes. Even the containment area can be demounted and removed, should biocontainment no longer be necessary, for example if a monoclonal antibody operation is inserted into the facility. Inoculum preparation operations in the FutureFacility utilize isolators with integrated incubators and directly adjacent seed bioreactors. Cell buildup for the viral process is outside of the containment zone, and transfer into the production bioreactors at the final stage.

The design and construction schedule for this sort of facility is significantly shorter than a traditional stainless steel facility. Time spent on design and construction is reduced because of lower system and building complexity and reduced piping requirements, and procurement of single-use systems avoids the long lead times associated with stainless steel equipment. Time saved on design and construction can be used to improve time-to-market, or if the project initiation is delayed, it can be used to allow additional process development time, or to have more certainty in clinical results before committing to major capital investments in a facility (see Figure 4).

**CONCLUSION**

Process closure provides superior product protection and permits lower room classifications. A risk-based approach must be used to review the state of process system closure and to identify all connection points, evaluating their suitability with regard to the process and quality requirements. Manufacturing facilities that use these closed-system processes in combination with single-use technologies offer process flexibility; adaptable and expandable design; shortened construction, start-up, and validation schedules; as well as decreased utility costs, all of which have the potential to reduce the cost of vaccines.

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An Environmental Life-Cycle Assessment Comparing Single-Use and Conventional Process Technology

The authors compare the environmental impact of monoclonal antibody production using fixed-in-place processing and single-use systems.

Matthew Pietrzykowski, William Flanagan, Vincent Pizzi, Andrew Brown, Andrew Sinclair, and Miriam Monge

Many biopharmaceutical companies have replaced or are planning to replace traditional multi-use process equipment (fixed-in-place stainless-steel fermenters, tanks, downstream processing equipment, and associated piping) with single-use systems to improve flexibility, productivity, and cost (1–3). The use of disposable components reduces or eliminates the need for extensive cleaning and steam sterilization between batches. However, single-use process technologies can also have negative environmental impacts because they involve the use and disposal of consumable materials.

Several previous studies have looked at environmental impacts of single use biopharmaceutical manufacturing technologies (4–7). To further understand the balance of environmental impacts, GE Healthcare in collaboration with GE’s Ecoassessment Center of Excellence has completed an extensive study of the life-cycle environmental impacts of the full process train required to produce monoclonal antibodies (mAbs). The study compares the use of single-use versus traditional durable process technologies at 100-L, 500-L, and 2000-L scales. The scales were chosen to reflect the clinical phase, the scale-up phase, and the final production phase. Process data were derived in collaboration with BioPharm Services, developer of BioSolve, an industry-standard bioprocess model that can be used to build any process including those for manufacture of mAbs, vac-
**Figure 1:** Process diagram of full process train for the production of monoclonal antibodies (mAbs). For this study, the process train was categorized into 14 unit operations and a 15th category, “Support CIP/SIP System,” that included the clean-in-place/steam-in-place infrastructure and common support activities, such as process water and HVAC requirements. IEX is ion-exchange chromatography, UF/DF is ultrafiltration/diafiltration.

This comprehensive environmental study of single-use process technology is the first to offer a comprehensive examination of environmental impacts across the full process train using life cycle assessment (LCA). LCA is an internationally recognized discipline that can be used to examine products and processes from an environmental perspective across the full lifecycle of a product or process, from raw-material extraction and refining through manufacturing, use, and end-of-life disposal or recycling. The methods involve analyzing material and energy flows from cradle-to-grave to calculate potential environmental impacts. This study was performed in accordance with the International Standards Organization ISO 14040 and ISO 14044 (8, 9).

The details and quality of the study were evaluated by a third-party critical review panel as per ISO 14044 because the study involved comparative assertions. The critical review panel consisted of an independent LCA expert and two domain experts from the biopharmaceutical manufacturing industry (10).

The results reported here focus on global warming potential (i.e., greenhouse gas emissions), cumulative energy demand (i.e., embodied energy), and water usage. The study also examined a range of additional environmental impact categories, such as ozone depletion, acidification, eutrophication, resource depletion, particulate matter formation, photochemical oxidant formation, as well as others. A companion article describing the results of the more comprehensive set of environ-
The goal of this study was to compare the potential environmental impacts associated with the production of mAbs using either single-use or traditional durable process technologies. The full process trains were evaluated at 100-L, 500-L, and 2000-L scales. Calculations were based on a 10-batch campaign assuming 6 g/L titres. The study did not account for any potential difference in product yield resulting from choice of process technology. Any such issues are product- or process-specific and beyond the scope of this study.

The results of this LCA will be used to communicate potential environmental impacts to interested stakeholders and to identify key areas for potential improvement in terms of supply chain, product design, manufacturing, or end-of-life as appropriate.

**Scope**

The scope of this study included both upstream and downstream processes involved in the production of mAbs. Figure 1 shows a process schematic of the full process train categorized into fourteen unit operations. A 15th category included the clean-in-place/steam-in-place (CIP/SIP) infrastructure and common support activities, such as process water and HVAC requirements (collectively termed “Support CIP/SIP System”).

The potential for a smaller production facility enabled by the choice of single-use technology was not specifically included in the scope of this study. However, the floor space used per HVAC class for each technology was scaled to the required facility footprint. This approach assumed that a traditional technology facility is in place and single-use technol-
Figure 3: Cumulative energy demand (CED) and global warming potential (GWP) for the production of a monoclonal antibody in a full process train at 2000-L scale with assumed mAb titre of 6 g/L. Impacts displayed by unit operation.

A variety of single-use technology from different manufacturers is available. This study systematically used GE technology (i.e., WAVE Bioreactor system and ReadyToProcess components) wherever appropriate due to the greater availability of internal data, and to support an effort to identify opportunities for environmentally conscious product design.

This study did not address any potential differences in labor requirements.

**Life-cycle inventory analysis**

The main body of data used in this study was derived in collaboration with BioPharm Services and can be considered industry average based on a combination of primary and secondary sources. Data on production of single-use components were obtained primarily from GE Healthcare. Data on transportation, packaging, and end-of-life were gathered through a combination of supplier data (GE Healthcare) and expert interviews. Additional secondary data were obtained from the ecoinvent 2.2 life-cycle inventory database (11).

The life-cycle assessment models were developed in SimaPro Analyst version 7.2.4 life-cycle assessment software (12). The inventory data were analyzed using several impact assessment methodologies. Cumulative energy demand (CED)
was calculated using the Cumulative Energy Demand v1.07 method and includes the total life cycle energy requirements including production and distribution of energy that is consumed across the life cycle, reported in units of megajoule-equivalents (MJ-eq). Lifecycle global warming potential (GWP) was calculated using the IPCC 2007 100a method and is reported as CO$_2$-equivalents (CO$_2$-eq), including all greenhouse gases specified in the Kyoto Protocol using 100-year time horizon global warming potentials from the Intergovernmental Panel on Climate Change 4th Assessment Report (13). Water usage (withdrawal) is reported in kilograms (kg) and was calculated using a custom impact assessment method that evaluates the withdrawal of freshwater (and saltwater, if any) across the life cycle of the system being studied.

**Key assumptions**

To maintain sterility, traditional durable equipment must be cleaned and steamed in place (CIP/SIP) between each batch. This requires a large amount of process water, water for injection (WFI), acids, and bases. The energy and supporting equipment required are all considered in this analysis. Single-use components that contact media do not require rigorous cleaning and sterilization, but instead are pre-sterilized by off-site Cobalt-60 irradiation. The transport of single-use components to and from the facility is included as well as the facility’s operating energy, the Co-60 source, and the concrete required for the irradiation cell. These impacts are allocated to each irradiated component as a mass fraction of irradiation facility throughput.

The traditional durable equipment is
Figure 5: Water usage for the production of a monoclonal antibody in a full process train at 2000-L scale with assumed mAb titre of 6 g/L. Impacts displayed by unit operation.

nominally assumed to have 10-year lifetimes, after which 25% of the equipment is re-used while the remainder is either recycled (90%) or landfilled (10%).
The single-use process trains contain components that are designed to be used once and then discarded. The exceptions are the replacement of single-use chromatography columns, which are typically reused for several batches depending on the number of cycles per batch. In this case, a recommended usable life for a ReadyToProcess Capto S 2.5 chromatography column is 20–50 cycles. The LCA model assumed 7 cycles per batch for Protein A and 5 cycles per batch for ion exchange chromatography (at 2000-L scale). The number of cycles for traditional chromatography is assumed to be two cycles per batch for both Protein A and ion exchange chromatography.

Several assumptions were made regarding treatment at end-of-life. For single-use components such as cellbags, filters, and connectors, disposal was assumed to occur by hazardous waste incineration without waste heat recovery. Non-hazardous waste was sent to landfill or wastewater treatment. Process water was assumed to be used once without recovery.

Use-phase electricity was assumed to be from an average US grid mix. Selection of an average European electricity grid mix exhibits lower environmental impacts but does not lead to any discernable shift of relative magnitudes between single-use and traditional process technology.

The fuel mix for generation of WFI was composed of different ratios of fuel oil, natural gas and electricity. The default mixture was equally weighted for fuel oil and natural gas at 45% each while electricity was weighted at 10%.

**Sensitivity and uncertainty analyses**
The sensitivity of the LCA results to variations in key assumptions was extensively analyzed using a Plackett-Burman experimental design. Lifetime of durable equipment was varied from 5–25 years. Chromatography column lifetimes were varied from 10–100 cycles. Transportation distances were varied from 5–25 miles (local), 1000–5000 miles (domestic), and 1500–7500 miles (international). Different ratios of WFI fuel mixes were examined. Equipment reuse was varied from 0–25%. Equipment recycling was varied from 50–100%. Co-60 irradiation facility parameters were varied as well. None of the variations in key assumptions had a significant effect on the study conclusions. The detailed results of the sensitivity and uncertainty analyses will be reported in a subsequent publication.

**RESULTS AND DISCUSSION**
Figure 2 shows the cumulative energy demand (CED) and global warming potential (GWP) for single-use versus traditional durable process technology for the full process train with a 2000-L working volume. The results are categorized by life-cycle stage. The supply chain phase includes materials and manufacturing of all process equipment and consumables required to support a 10-batch mAb production campaign. The use phase includes all impacts that occur during mAb production, including cleaning and sterilization of traditional durable equipment between batches. The end-of-life phase includes the disposal of consumables and the disposal, re-use, or recycling of allocated portions of durable components.

A substantial majority of the life cycle environmental impacts occur during the
use phase. Note that the comparative CED and GWP results are very similar because almost all of the GWP is related to energy production and consumption. The single-use process train exhibits 38% lower GWP during use phase (and 34% lower GWP across all life-cycle stages) compared to a traditional durable process train. The corresponding reduction in CED is 38% during use phase and 32% across all life-cycle stages. Supply chain GWP and CED impacts are slightly higher for single-use compared with traditional process technology due to the increased manufacturing required to provide the consumable components used in a single-use approach. However, supply-chain impacts represent <11% of the life-cycle CED impact and <5% of the life GWP impact. Environmental impacts from the end-of-life stage represent <1% of overall life cycle impacts.

Figure 3 shows the CED and GWP impacts for single-use vs. traditional process technology categorized by unit operation. The most substantial impacts (38–40% of both GWP and CED) are related to the support CIP/SIP system, which includes the CIP/SIP infrastructure and common support activities such as process water and HVAC requirements (the main difference between process approaches in this category is the amount of energy required to generate WFI and steam). The use of single-use process technology exhibits lower CED and GWP impacts compared to traditional durable technology in all unit operations except Protein A and ion-exchange chromatography, which are higher for single-use since several single-use columns must be used in parallel to reach this scale.

Figure 4 shows water usage categorized by life cycle stage. Substantial water savings are realized during the use phase for single-use process technology due to the reduction or elimination of cleaning and sterilization between batches. Figure 5 shows water usage categorized by unit operation. As expected, water usage is dominated by activities related to the support CIP/SIP system. Single-use process technology exhibits lower water usage in all unit operations except Protein A and ion exchange chromatography, again due to the need for parallel chromatography columns at this scale. Note also that the majority of water usage in the UP 03 Bioreactor is for media, so the primary water usage savings of single-use process technology is due to the shift from steam heating to electrical heating. The negative water usage during the end-of-life stage reflects credit related to the re-use and recycling of durable components.

The results in Figures 2–5 focus on the 2000-L working volume scale. Similar results were obtained at 100-L and 500-L scales, and the process technology comparisons discussed in this section apply to all three scales.

CONCLUSIONS AND RECOMMENDATIONS

The study has shown that a shift from traditional durable process technology to single-use process technology can result in substantial reductions in cumulative energy demand, global warming potential, and water usage for the production of monoclonal antibodies, in addition to improving flexibility and productivity. Although single-use process technology introduces a need for
the production, distribution, and disposal of single-use components, this approach also reduces or eliminates the need for large quantities of steam, process water, and water for injection. The LCA model developed for this study is dynamic and offers the potential for further exploration of different bioprocess conditions and “what if” scenarios. The detailed insights gained in this comprehensive study offer the potential for further improvements in environmentally conscious product and process development for biopharmaceutical manufacturing.

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