

Single-Use Bioreactors

A Brief Review of Current Technology

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Say “disposable bioreactor,” and whoever you’re talking to is most likely going to picture a plastic bag on a rocking platform. In fact, I remember back in late 1999, as associate editor for another magazine, when I copyedited one of the early papers that described the Wave bioreactor (1). Even that early in my career as a technical editor, when my understanding of the industry was over six years younger than it is now, I recognized the thing for what it was: a potential revolution in biopharmaceutical production.

Since then, it has become an established and accepted addition to the biotechnological toolbox, having proven itself in published studies from Chiron Corporation, IDEC Pharmaceuticals, Introgen Therapeutics Inc., Lonza Biologics, the Massachusetts Institute of Technology, Merck Research Laboratories, Novartis, and Schering-Plough Research Institute, among others (2). However, although it may have been the first name in disposable bioproduction, the Wave bioreactor is far from the last word in this growing field.

Several single-use options have been introduced for 21st-century bioproduction, including disposable flasks and spinner bottles, hollow-fiber bioreactors, and specialty devices including bag-based systems such as the Wave technology (3). Each has its pros and cons, with scalability often presenting the greatest limitation. Some equipment is better suited to



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small research-level applications; other equipment is intended for use in industrial settings. The advantages of single-use technology in general don’t need to be reiterated here; by now they are well known. But in a 2006 D&MD report, the authors identified scaling-up as the major limitation of most disposable bioreactors while also mentioning potential contamination issues and operational difficulties as other limitations (3). Regulatory unfamiliarity may also present challenges.

Seed Train: Production of biotherapeutics begins with a cell line, whether microbial or animal in origin. Bioengineered cells are stored frozen — currently in small plastic tubes, but the near future will see disposable bags storing larger amounts (a 20-mL bag instead of 20 1-mL tubes) so processes can begin with bigger inocula. That saves time in scaling up the seed train to full production scale — a process ideal for the smaller-scale

disposable bioreactors. This is one area where they made their first inroads.

Media Development: In parallel with that scale-up of the working cell bank, culture media are mixed and optimized using plastic bags and special mixing technologies. Hynetics products involve a special plastic mixing disk. LevTech uses superconducting technology for a levitated impeller that works inside bags up to 500 L in volume. And ILC Dover offers an accordion-style bellows-based diaphragm mixer for large-scale mixing up to 10,000 L.

IT’S IN THE BAG

Flexible plastic containers supported by rigid containment made single-use bioproduction possible — which suggests that stainless steel won’t disappear completely from bioprocessing in the near future. Because of the fragility of living cells, mixing becomes a more delicate issue

when it comes to single-use bioreactors. For years, the only disposable option was the Wave-style rocking bioreactor, essentially a bag on a platform that oscillates back and forth to create waves in the solution contained within. That works quite well up to the 100-L scale, and a 500-L version is available. Larger production volumes are then accomplished through redundancy. But there are other options.

Stedim/Sartorius: When you talk about plastic bags for bioprocessing, you may well be talking about the French company known as Stedim SA (www.stedim.com). For years, many companies have been using plastic bags from Stedim to make their own integrated systems (4). And until recently, the company focused almost exclusively on its core competency: plastics.

In 2004, Stedim acquired Integrated Biosystems, makers of Celsius controlled freeze-thaw systems, and Isolateur Dénominateur Commun, known for its expertise in aseptic transfer. In 2006, those were united with Stedim's single-use bag products under the common marketing name of Stedim Biosystems. And early in 2007, the company announced its pending merger with Germany's Sartorius AG to create "a globally leading technology provider for the biopharmaceutical industry."

About the merger, which should be complete in summer 2007, Bernard Lemaître, Stedim's chairman, said that "once combined, Sartorius Biotechnology and Stedim Biosystems have the realistic ambition of forming the worldwide market leader for single-use technologies over the next five years." The companies' technologies are certainly compatible, with Sartorius focusing on filtration, chromatography, and analytical devices as well as small-scale flask- and spinner-based bioreactors (see "Old School, New School," below) while Stedim fills out the bioprocess spectrum with container bags and integrated systems based on them.

An example of Stedim's leadership in single-use technology is the AppliFlex bioreactor, which came about as the result of an alliance between that company and Applikon

Biotechnology (www.applikon-bio.com). Its design is strongly reminiscent of the Wave machine, and Applikon touts the accuracy of its control system and disposable sensors for measuring important parameters such as pH, temperature, and dissolved oxygen. The combination of the bioreactor with sensors and control system offers great opportunities for CGMP applications. The AppliFlex Rocker can be applied to a range of reactor volumes.

Cellexus Biosystems: Another bag-based bioreactor system is the 1-L to 50-L CellMaker from Cellexus Biosystems (www.cellexusbiosystems.com) (4). Incorporating a unique bag geometry, this system is designed to provide gentle but effective mixing and oxygenation without mechanical shaking or stirring. The aeration process itself mixes the culture. "Growing cells in a culture bag is not new," says the company website. "What is new is the shape of the bag and how its shape is directed by the enclosure that supports it when filled with the cell culture medium. What is also new is the three-fold way in which the culture is aerated. This includes the option to pressurize the space above the culture, a unique feature in a disposable cell culture system."

HyClone: Plastic bioprocess containers (BPCs) have formed the basis of HyClone's movement into disposables. Once known mainly for its leadership in media, sera, and other culture supplements, the company introduced BPCs around the turn of the century. Since then, it has used them in developing single-use mixing systems through collaboration with Alfa Laval Biokinetics under the Hynetics brand name, as well as a much-touted stirred-tank bioreactor (SUB) introduced in 2006. The company became a subsidiary of Thermo Fisher Scientific in the same year.

The SUB is intended as a retrofit product to replace stainless steel vessels for animal cell culture in existing systems, and it comes in 50-L and 250-L sizes, with a 1,000-L version in development. The system comprises a reusable stainless steel outer support

container holding a BPC bag, filters, and impellers, with ports for sampling and transfer of gas and fluids. As a direct, disposable answer to stirred-tank bioreactors, it is establishing itself quickly on the market.

SAFC Biosciences: Another maker of plastic bags, SAFC Biosciences sells large-scale (up to 1,000 L) polyethylene and small-scale (up to 20 L) ethyl vinyl acetate versions of them under the BIOEAZE brand name. They're good for things like media preparation and intermediate holding, and the company also supplies connectors, tubing, drums, and tank liners to go with them. It can assemble bioprocessing systems based on customer designs or create custom systems according to client needs. But no standard, integrated bioreactor system is yet available.

Xcellerex is known more as a contract manufacturer than maker of single-use components or systems. But the company does sell turnkey skid-based systems. Its XDR disposable bioreactors are scalable stirred-tank reactors that use disposable bag liners (3). These portable systems scale from 50-L through 100-L, 200-L, 500-L, and 1,000-L to 2,000-L working volumes. Single-use components include

the reactor bag liner, agitation impeller, dissolved oxygen and pH probes, discharge tubing, media feed tubing, acid and base feed tubing, vent tubing and filter element, and all other sample and tubing arrangements required for bioreactor operation. Tubing connections are made by tubing welders or by discreet aseptic connectors. Process control and batch automation start with the installation of sensors on the disposable surfaces, matched through optical and electronic detection and measurement analyzers. (3)

Wave Biotech: Researchers using the baculovirus insect-cell transient transfection expression system were among the first to adopt the early small-scale version of the wave-mixed bioreactor in the late 1990s. They found it to be a practical and economical system for laboratory-scale production of recombinant proteins. Vijay Singh, president of Wave

Biotech, says his company has since managed to take disposable bioreactors “from a laboratory curiosity to mainstream GMP manufacturing of biologics” (4). And that certainly seems to be the case.

There are four Wave systems available: a 0.1-L to 5.0-L version for laboratory research, 1-L to 25-L and 10–100-L versions for scale-up, and a 100-L to 500-L version for commercial-level bioproduction. Cellbags are also sold separately for custom arrangements. The company has an agreement with ILC Dover for the use of its FlexMixer accordion-style mixing bag. It also sells Wave-style mixers and warmers for thawing frozen material. And Wave has gotten into tube-welding and sealing as well.

Variation on a Theme: The Tsunami bioreactor was developed by fans of wave-style mixing who were looking for more linear upscaling, smaller footprints, and lower capital investment requirements than were possible with other types of systems (5). CatchMabs (www.catchmabs.com) and Mega Partners International (www.megainternational.com.hk) worked together to develop this alternative, which they presented to the world in 2005. Disposable bags (made in China) of up to 40-L volumes rock on four platforms that are stacked up inside a vertically oriented machine. For scale-up, the depth and height of each culture bag remains constant for all volumes from 5 L to 160 L, which provides the same hydrodynamics for wave agitation throughout.

OLD SCHOOL, NEW SCHOOL

Flasks, spinners, and roller-bottles have long been a staple of biotechnology, mainly for small-scale cell culture. It was easy to convert these concepts to fit the single-use paradigm: disposable plastic containers rather than washable glass ones pretty much did the trick. An article in our January 2006 issue described a similar approach using 20-L and 50-L disposable vessels on a shaking machine (6).

Famous for its transparent glass bioreactors of varying size, New Brunswick Scientific (www.nbsc.com) recently introduced a relatively small-

scale disposable bioreactor system based on Fibracel disks, a solid-support matrix for high-yield attachment-dependent cell cultures. Fibrastage uses plastic bottles that are alternately compressed and expanded for movement of media and air.

A different small-scale concept called TubeSpin has been developed by ExcellGene (www.excellgene.com) with the assistance of TPP (www.tpp.ch) and the renowned Swiss scientist Florian Wurm (4). These small plastic bioreactor tubes are used as a high-throughput scale-down system with high equivalency to large-scale suspension bioreactors. Hundreds can be run simultaneously, with cell culture volumes of 5–35 mL each, which is good for process development and media optimization studies as well as small-scale protein production. An industry study using them was presented by Genentech scientists at the AIChE annual meeting in November 2006 (7).

Synthecon: Another unique small-scale bioreactor system is the rotary cell culture system (RCCS) from Synthecon (www.synthecon.com). Distantly related to the familiar roller-bottle system of old, the RCCS was originally designed by NASA to carry cells into space on the space shuttle. They grow inside small (10 mL to 50 mL) disposable vessels attached to a reusable vertical rotor that spins them around. Gravitational, centrifugal, and Coriolis forces induce a slow sedimentation of cells as the vessel turns, minimizing damaging shear forces and allowing cells to form three-dimensional, tissue-like aggregates.

A variation on this theme is available from Cellon SA (www.cellon.lu) in Luxembourg. Cellon's RollerCell automates all stages of tissue culture based on roller bottles: from cell inoculation through incubation, media change, and trypsinisation to final harvest. A single unit can process the equivalent of 200 standard roller bottles simultaneously. Traditionally, roller-bottle culture in has been divided into two distinct phases, incubation (carried out in incubators or hot rooms using conventional roller apparatus)

and bottle processing (carried out manually by skilled operators or robotic processors in laminar flow conditions). The RollerCell replaces the traditional roller apparatus and performs all related tasks.

Integra Biosciences' Cellroll cell cultivation systems are quite similar to the RollerCell unit. Cellroll systems are programmable, modular roller systems that accommodate roller bottles with culture volumes from 300 to 400 mL. (3)

Hollow-Fiber Bioreactors: “In its simplest form,” write the authors of a recent D&MD report, “two-compartment cultivation occurs when cells grow inside dialysis tubing placed in a culture bottle filled with medium.” Semipermeable tubing allows nutrients to diffuse to cultured cells and removes toxic waste products. With these protective solid supports, cells can safely grow to high densities. That's the basis of hollow-fiber bioreactors (HFBs), which use bundles of slender tubes embedded into disposable plastic cartridges.

HFBs require specific equipment consisting of a pump to maintain medium flow and provide gas exchange. HFBs are still used for higher-scale applications, but small-scale HFBs have been displaced by membrane-based two-compartment systems, which have proven to be more cost-effective and simpler to use. Currently two systems are available: the two-compartment roller bottle miniPERM (designed by the German-based In Vitro Systems and Services GmbH) and the static flask CELLLine (Integra Biosciences AG, Switzerland). (3)

FiberCell Systems (www.fibercellsystems.com) is a Maryland-based company that describes its hollow-fiber bioreactor as “the most in-vivo like manner to grow cells,” for up to 100 times greater productivity over traditional stirred-tank bioreactors. Its disposable perfusion cartridges come in small (75 cm² surface area for 10⁸ cells), medium (2,100 m², 10⁹ cells), large (1.2 cm², 5 × 10¹⁰ cells), and extra large (2.5 m², 10¹¹ cells) sizes.

Cesco Bioengineering (www.cescobio.com.tw), a Taiwanese company, developed its milliliter-scale BelloCell system based on an artificial lung design that gently and continuously supplies oxygen to cultured cells. Cells can be grown at high densities (up to 6×10^9 cells per plastic bottle). The company also offers TideCell in 5-L and 25-L sizes, which uses two concentric chambers for culturing attachment-dependent cells. Its inner chamber is packed with carrier disks and interconnected with an exterior chamber. Adjustment of air pressure allows liquid medium to move between the chambers like ocean tides, exposing cells transiently to the air for maximum oxygen transfer. Both types of device provide foam-free conditions and very low shear stress on fragile cells. Cesco sells the plastic carrier disks as well as pumps, controllers, and glucose monitors for its unique bioreactors. A Pfizer study using the BelloCell was published in 2004 (8).

Nunc: A June 2006 article introduced BPI readers to Nunc's (www.nuncbrand.com) Nunclon Cell Factory system, which uses stacked culture trays with an active gassing system (9). Each plastic tray has a 200-mL working volume, and the company sells units for one, two, four, 10, and 40 trays for up to 8-L scale operations. Scale-up is straightforward and as in many disposable bioreactor systems involves adding more individual, identical culture units. Nunc also offers tubes and flasks for more traditional cell culture operations, as well as the Opticell system, which uses parallel gas-permeable polystyrene membranes attached to a standard microplate-sized frame for small-scale growing, monitoring, freezing, thawing, imaging, and transporting of cells.

Fluorometrix: For small-scale "high-throughput" cell culture, the CellStation from Fluorometrix (www.fluorometrix.com) offers noninvasive sensing and optional control of critical bioprocess parameters such as pH, dissolved oxygen, optical density, and temperature in a multireactor form with multisensor architecture (3).

Twelve disposable, miniature bioreactor vessels (up to 35 mL each) attach to a horizontal rotor that spins them at 10–1,000 RPM. Because they're made of glass, the small vessels are both reusable and disposable. The company is most proud of its noninvasive sensor technology, which involves a special chemically treated luminescent patch located inside the vessel that's read by light-based technology.

Corning: Cellcube from Corning Life Sciences (www.corning.com) integrates disposable culture modules into a programmable system that includes a controller and oxygenator with circulation and media pumps (3). A wide range of scales are possible, from 8,500 cm² to 340,000 cm² of cell growth surface with the same controller package.

In research conducted by Introgen Therapeutics, adenovirus vectors grown in INT 293 cells were cultivated in the CellCube system. To support CellCube production process validation, extensive process characterization activities were performed to identify critical process parameters. . . . The CellCube production process is currently used for the production of adenoviral vectors for Phase 3 clinical trials. (3)

KBI Biopharma: Along with the increasing product titers that are coming out of improvements in cell-line engineering, KBI Biopharma's development of a centrifugal bioreactor (CBR) for high-density cell cultures could help make scale-up less of a concern than it has been in the past. The technology applies fluidized-bed methodology in perfusion mode, with cells immobilized at very high densities (2×10^8 mammalian cells/mL) without membranes or other solid supports. Microbial cells can be maintained at densities that are several orders of magnitude higher than usual. The company claims productivity improvements as well, based on proof-of-principle studies. CBR technology is said to facilitate linear process scale-up, which could present a regulatory advantage over stirred-tank systems. It may also incorporate high-resolution

separations as part of the bioreactor rotor.

NOT THE LAST WORD

The FDA's process analytical technology (PAT) initiative emphasizes bioreactor monitoring and control, and single-use products can help here as well. Disposable heat-exchange technologies are finding their way from biomedical into biotechnological applications. Polestar Technologies and other companies offer single-use probes for monitoring dissolved oxygen, a key parameter in the health of cultured cells. Digiflow Systems is one vendor of single-use flowmeters, NovAseptic provides disposable sampling systems, and PendoTech makes single-use pressure sensors and pressure control kits. The future will see temperature control with disposable thermometers, lab-on-a-chip biosensors, and optical analysis, as technologies created for biodefense and "homeland security" find application in biotherapeutics development and production.

With any type of "disposable" product, environmental issues are sure to be raised. Depending on the application, some single-use products need sterilization (e.g., with gamma irradiation or aqueous ClO₂) before they can be disposed of. Some are shredded and chemically treated, and others are incinerated at facilities certified to handle medical waste. The products are made of organic polymers, and users want to be sure no animal products are used in their manufacture. Over time, raw materials and disposal standards will be developed and should be enforced.

In this brief format, I couldn't hope to cover all the bioreactor options that are either available or in development. Just since the turn of the century, we've seen an explosion of disposable bioproduction technology — and a consequent dance of companies that rather resembles bubbles in a lava lamp. New ones appear, partner or merge with others, swallow up smaller ones, and give birth to other new ones. But none of that should be new to anyone who's worked in biotechnology for a while.

We've also seen great advances in cell-line engineering over the past few years (10). What was once considered a good showing titer-wise (a gram of product per liter of culture) has become the baseline. We're seeing animal cell culture titers of 5–10 g/L these days. And a tenfold increase in titer per liter could translate to a tenfold decrease in culture volume needed to produce the same amount of recombinant protein. So what once required a 1,000-L bioreactor may well be made using a 100-L Wave Cellbag system. As I've shown in this review of the current state of the art, scale is still the biggest challenge when it comes to disposable bioreactor technology. A decade ago, people were talking about transgenic animals as a way to solve the problems of manufacturing capacity for high-demand biopharmaceuticals. Cell-line engineers responded to that challenge by kicking up the producing power of our familiar cell lines. In doing so, they may have also unintentionally paved the way for single-use technology.

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