The New Disposable Evolution

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Single-use systems have advanced from a limited product line to several new products for a wider range of unit operations. As these technologies evolve, new size, cost, and regulatory needs continue to fuel industry growth.

Companies in all areas of biologics manufacturing — for example, recombinant proteins, antibodies, vaccines — can benefit from the implementation of disposables in at least some areas of their manufacturing processes,” says Lisa Crossley, CEO of Natrix Separations (natrixseparations.com), a manufacturer of high-performance disposable chromatography products for the biopharmaceutical industry.

Many factors need to be considered in making the decision to implement disposables versus reusable technologies, she explains. “The number of batches over which the cost of a reusable product will be amortized has a tremendous impact on the economics of transitioning from reusable to disposable products. The rule of thumb we use in the industry right now is that any product that is manufactured over fewer than 50 batches per year is a good candidate for implementation of disposables. Beyond that frequency, the economics are generally more favorable for reusable technologies.”

Scale is also a key consideration. Disposable products are widely available for pilot through early clinical manufacturing processes, but at the larger scales (e.g., >2,000 L for disposable bioreactors, >3,000 L for disposable buffer bags), the volumes can exceed what the current state of the art in disposables is able to support. Crossley suggests that companies need to examine the key drivers for using disposables (e.g., risk management, economics, flexibility, regulatory compliance) and perform a risk-benefit analysis of the adoption of disposables in the context of their own unique business models, products and processes.

There is no one-size-fits-all solution, adds Uwe Gottschalk, group vice president of purification technologies at Sartorius Stedim Biotech (Aubagne, France; sartorius-stedim.com), a supplier of process technology covering the whole process chain in biopharmaceutical processes. “Biomanufacturing is fixed-cost driven, as most costs are coming from the expensive infrastructure. Small companies, especially, cannot afford the significant investment in a stainless steel facility given the high risk that their product is not going to make it to the market. For those companies, a disposable-based facility for the production of clinical material is a flexible and less-risky alternative.”

Pall Life Sciences (East Hills, NY; pall.com) designs, manufactures and validates single-use disposable systems for pharmaceutical manufacturing. System designs range.

Disposable post-bioreactor depth filters are used for large-scale removal of cells and cell debris. Photo courtesy of Sartorius Stedim Biotech.
from complex hybrid (stainless steel and disposables) systems for mixing and tangential flow filtration (TFF), to tubing sets with sterile filtration and sterile connectors.

Christopher J. Mach, global product and marketing manager at Pall, explains that companies should know where implementing a single-use system will add benefit to their process — cost, speed, ease of use, and/or elimination of cleaning, bottlenecks, or human errors. “It may be true that not all areas of their process will work using a disposable format,” he says.

According to Daniella Kranjac, senior strategic marketing leader at GE Healthcare Life Sciences (GEHC; Piscataway, NJ; gelifesciences.com), implementation of disposables has ranged from restricted use in seed train operations, to expanded use for the entire cell-cultivation platform, including the final product vessel. She notes that disposables abound from a filtration perspective, and chromatography systems are also now on the market.

Kranjac, a chemical engineer, co-founded Wave Biotech, LLC (now a part of GE), where she spent most of the last decade commercializing and marketing the WAVE Bioreactor — a system that consists of a presterile, disposable chamber on a special rocking platform that induces waves in the cell culture fluid and provides mixing and oxygen transfer, creating an ideal environment for cell growth. The bioreactor and other disposable options have enabled small and large biotech companies alike to speed their products to market, while minimizing capital expenses, she reports.

“Disposables are ideal for contract manufacturing organizations and other multiproduct facilities, since they afford the end user an almost immediate turnaround of process equipment. For cell cultivation, this can mean several hours, days, or even weeks saved if a sterility challenge is required,” Kranjac explains.

“Small and start-up biotech organizations find disposables to be particularly useful to produce material for pre-clinical and clinical trials. Disposables allow such groups to get operational quickly, with shorter delivery times than traditional equipment, and typically with a lower price tag and lower operational costs as well — generally saving 50–60% over stainless steel stirred tanks. This lower capital cost removes the investment hurdles to producing clinical material for drug candidates that may or may not be successful. Most organizations involved in developing seasonal vaccines and vaccines for pandemic response are also migrating toward the use of disposables in their operations,” she says.

John Boehm, bioprocessing business unit manager at Colder Products Co. (St. Paul, MN; colder.com), a supplier of single-use connections used in disposable systems for the bioprocessing market, agrees. “Large pharmaceutical and biologics manufacturers have been moving toward disposable systems throughout their unit operations, to expanded use for the entire cell-cultivation platform, including the final product vessel. She notes that disposables abound from a filtration perspective, and chromatography systems are also now on the market.

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Disposables today

Disposables were very much in their infancy in the early 2000s. The range of available products was limited — primarily to filters, buffer bags, tubing and some connectors — as was scale — typically to pilot-scale and below. End users had yet to embrace the technology or recognize the advantages associated with implementing disposables, explains Crossley of Natrix Separations.

“Disposables have since proven their worth as a means of affording flexibility to biologics manufacturers with multiproduct facilities. They reduce turnaround times between batches and start-up times in general, and provide small biotech companies with the ability to manufacture pre-clinical through clinical material without making a significant capital investment. They also reduce cleaning, storage and validation requirements, thereby facilitating regulatory compliance, reducing cross-contamination, and ensuring sterility,” she says. “A wide range of disposable products now exists, such that a fully disposable manufacturing process is genuinely possible.” The most popular disposable products remain filters, buffer bags, tubing and connectors, but disposable sensors, bioreactors, depth filters, chromatography systems, and other complementary single-use products are now commercially available and their use is steadily increasing.

Today, many more companies, including several start-up firms, are working to develop better ways to design disposable systems for both upstream (e.g., media and buffer preparation), bioprocessing (e.g., fermentation and cell culture), and downstream (e.g., separation and purification) applications.

According to Rusty Warren, president of the products division of Polestar Technologies (Needham Heights, MA; polestar-tech.com), there is also much greater acceptance of disposable technology as a less-expensive and easier-to-use alternative to conventional steel tank processing. “We are now in a phase of consolidation as biopharmaceutical companies decide which technologies to adopt and what suppliers to partner with,” he says. Polestar develops optical sensors for measuring pH, O₂ and CO₂ that disposable bag manufacturers, systems integrators, and global pharmaceutical companies can easily incorporate into disposable bioprocessing systems.

Colder Products’ Boehm adds, “There has also been a major increase in the number of manufacturers implementing disposable systems in their unit operations. Single-use technology has moved from being primarily focused on media and buffer preparation and fermentation into the downstream processes of filtration/purification and filling operations.”

Kenneth L. Bibbo, vice president of operations at HyNetics Corp. (Warminster, PA; hynetics.com) as well as a chief inventor and designer who oversees all technical and manufacturing of the company’s production-scale single-use/disposable mixing systems, explains that the most popular single-use products (ranked in order based on total dollars spent) are for: storage and transport, filtration and purification, bioreaction, fermentation, mixing, sensing, and flow.

“We developed single-use processing for the biotech and pharmaceutical industrial sector back in 2000 and launched the product in 2003 at Interphex. Then, there were only a few players. The concept has since grown into a major business segment involving some major companies. Five to seven years ago, they were dabbling with the concepts, developing products, and feeling out the market. Now, this is a serious business,” Bibbo says.

HyNetics remains an industry leader in installed and validated systems up to and including 10,000 L. According to Bibbo, competitors’ systems range from a few liters to 2,000 L, and seem to have hit a technology and cost plateau. Scaling has always been an issue. HyNetics took a different approach by starting at 10,000 L and scaling down rather than starting at 100 L and struggling to scale up.

“As for complexity, we have moved from simple liquid-liquid mixing to liquid-solid mixing to solid-solid blending to fermentation and bioreactions. By far, the most growth and focus has been on single-use/disposable bioreactors,” he says.

The biggest change is the strategic thinking among the end users of process equipment, says Kevin Ott, executive director of the SPI Bio-Process System Alliance (BPSA; Washington, DC; bpsalliance.org), a trade association that operates as an industry group of the Society of the Plastics Industry (SPI). BPSA represents companies with interests in the disposable sector of bioprocessing. Most of the members are component and systems suppliers to the biopharma and biotech industry.

“There is a lot of stainless steel in place to serve the bio-
therapeutic industry. As we move to personalized medicine, smaller batch sizes and faster campaign turn-around times, plastic (i.e., disposable) systems will be looked at increasingly as a low-cost, flexible solution to the needs of biopharma processing,” Ott notes. “This trend has already begun. We see the growth rate for plastic components in bioprocessing on an upswing in the range of 3% to 5% growth per year.”

GEHC’s Kranjac agrees and adds that general market acceptance has grown dramatically over the past five years, as validation packages supplied by vendors have improved and more-adaptable solutions for biopharma, including well-instrumented disposable systems, have become available. Improvements in films, optical sensors (pH and dissolved oxygen), and even more-sophisticated motion-control systems, have hastened the adoption of disposable bioreactors. Applications include production of monoclonal antibodies, vaccine production, plant cell cultivation, and even patient-specific cell therapies.

Current limitations
While the disposables industry has grown, the technology still has some limitations. Ott explains that four basic areas need to be investigated when considering single-use technologies:

1. What is the application (product and process)? What stage or unit operation in the process does it represent?
2. How much capital is available to invest in initial start-up and/or technology conversion costs?
3. What data are available from the suppliers to help answer questions from the U.S. Food and Drug Administration (FDA) when validating the product and process?
4. How can the risk associated with the product or process be reduced?

Currently, single-use technology can be utilized in various stages and unit operations in bioprocessing. However, some operations and process scales are limited by the existing installed capital and the lack of technologies available in disposable formats, Ott says. Historically, media and buffer preparation were some of the first unit operations to employ single-use devices. As technologies have evolved, disposables have become available for more unit operations, such as cell culture, mixing, purification, formulation and filling, and at larger scales. As the single-use industry continues to evolve and the bioprocessing industry realizes the benefits, further investments will be required by the suppliers to develop even larger scales and newer technologies.

Polestar’s Warren explains further. “Integration is a big challenge. Companies are working to integrate upstream and downstream systems and to integrate monitoring and control capabilities for automatic management of bioprocessing.”

Another limitation, he notes, is the absence of standards. “There has been a proliferation of designs, processes and technologies in recent years. As certain of these become widely accepted, that will drive down costs and increase the acceptance of disposable technology,” he says.

John Stover, director of new business development at NewAge Industries/AdvantaPure (Southampton, PA; advantanpure.com), a manufacturer of sanitary tubing, hose, and hose assemblies, explains that there are batch size limitations relating to the volume of fluid a system can handle at one time. Larger media bags are being developed to meet the needs of larger-volume batch requirements.

In addition, he agrees with Warren that standards and regulation need to be developed. More regulation of disposable component manufacturing would require suppliers to provide complete validation testing on components to minimize any chance of contaminating or altering a high-purity fluid stream, Stover explains.

“The sterilization technique most often used with single-use systems is gamma irradiation, so systems need to be gamma-stable,” he says. “Drug manufacturers need protocols for this method of sterilization if they are accustomed to autoclaving or steaming their process lines. And, there are tracking issues with single-use systems involving the clear identification of all components and readily available quality certifications. Tracking systems, including the use of radio frequency identification (RFID) with comprehensive tracking software, are being developed to address this.”

“Size and scaling appear to be the biggest hurdle,” explains Bibbo of HyNetics. “Moving up from a lab-bench shaker flask to a production mixer or reactor is difficult, and not all of the current technologies can be applied efficiently or economically. What is developed in a laboratory and reviewed by the FDA cannot always be duplicated at clinical or production levels. And therein lies another problem — regulations, compliance and filings. We live in a world of FDA regulations, and all of the process steps, contact surfaces and manufacturing techniques must be
well-documented and validated,” he notes.

Size is limited by the width of the cast films used to make the disposable bags, the capacity and size of the machines currently used to make the products, and the availability of clean-room manufacturing space.

There is also a limitation on how much energy can be transmitted through plastic components and their ability to withstand process temperatures and pressures beyond ambient. Single-use/disposable processes are further limited to the size/capacity and availability of pumps, fittings, and tubing.

On the upstream side, disposable bioreactors for large-scale (>2,000 L) microbial fermentation are not yet available, notes Natrix Separations’ Crossley. Microbial fermentations are inherently challenging to perform in disposable plastic reactors, because it is difficult to achieve the high agitation rates required using plastic components. In addition, microbial fermentations are typically highly exothermic, and it is difficult to achieve tight temperature control in a plastic bioreactor.

“While the disposable bioreactor suppliers are currently working on developing the requisite technology to support the commercial launch of disposable microbial bioreactors beyond the 2,000-L scale, one would have to question the true need for these products,” she says. “Microbial cultures are typically used to produce recombinant proteins of lower value than those produced in mammalian cell expression systems, and microbial fermentations are much less vulnerable to contamination than their more-sensitive mammalian cell counterparts. Thus, while disposable bioreactors provide advantages in mammalian cell processes at all scales due to the reduced risk of batch-to-batch contamination, their true value in microbial processes is largely at the small scale, where they allow companies to manufacture pre-clinical through Phase III supply without having to invest in significant infrastructure. Beyond the 5,000-L scale, it may always make more sense, from both engineering and economic standpoints, to conduct microbial fermentations in standard stainless steel reactors.”

On the downstream side, options for disposable capture chromatography for use in primary purification have been very limited, Crossley explains. Although several resin companies have launched disposable products, these consist of the standard resin beads in single-use plastic housings. The result has historically been products that are almost prohibitively expensive.

Natrix Separations has recently launched a line of membrane chromatography products with binding capacities that are 3–5 times those of conventional resins, in a disposable format. This design is said to reduce capital and operating costs and to be cost-effective to implement in place of reusable chromatography technologies.

Furthermore, Natrix claims to be the only company to offer a fully disposable solution for simultaneous clarification and capture. Natrix Crossflow Chromatography systems allow users to separate cells and other solids from soluble product while simultaneously achieving highly specific, selective capture of the target molecule. As a result of combining the harvest and primary purification steps into one unit operation, users have observed significant increases in yield and purity, along with reductions in processing time and operating costs, Crossley reports.

“The continuous improvements we’ve seen in upstream productivity (in terms of product titers, or concentrations) have put a lot of pressure on the downstream side of production. Any disposable technologies that can help reduce processing time and eliminate the downstream bottleneck will definitely feel a pull from the marketplace,” she says.

“Currently, we see practical limitations for single-use process steps at about the 2,000–5,000-L volumes. We expect volume capabilities to increase slightly from there, with more focus on higher yields at lower volumes,” notes Kranjac.

“Efforts in the industry are geared toward increasing titers, to upwards of 15–20 g/L. Increasing the productivity of cells from a molecular biology perspective effectively reduces the operating volume required. This trend will make single-use equipment more appropriate for a larger part of the overall process,” she predicts. “That said, as a result of increased titers, we expect to see the need for innovation and improvement in filtration steps and downstream purification to manage the higher titers. Process analytical technologies and automation will play an increasingly important role in biopharma.”

Gottschalk states that the limitations are the result of the widening gap between upstream titers and downstream capabilities. He believes that downstream productivity increases...
are overdue, and can only be achieved with new paradigms and disruptive technologies, such as precipitation instead of chromatographic capturing and disposable membrane chromatography for polishing (i.e., the removal of trace contaminants such as DNA, host cell proteins and viruses).

Furthermore, “the use of disposable technologies may ease some of the current issues, but only if the overall productivity is increased. Whether a disposable strategy makes sense depends on a variety of parameters, such as scale, development phase, product type, and the user’s business model, notes Gottschalk.

Mach, of Pall Life Sciences, believes that, from the user’s perspective, the biggest limitation is overcoming the hurdles associated with actually starting to use single-use systems (e.g., validation/regulatory requirements). “Most users know they want to implement single-use systems, but not understanding how to get started delays the introduction. Suppliers should be designing products that users are looking for, as well as providing the appropriate validation and product specifications,” he explains.

**Future drivers**

Mach further states that the drivers will always be based on the voice of the end user. As biopharmaceutical manufacturers become more comfortable with single-use systems, their needs and ideas will begin to grow, and this will push suppliers to meet those needs. This will also help the regulators feel more comfortable regarding the benefits of using disposable formats in production.

There is widespread agreement that the main driver will be cost. “Cost will always be a primary factor driving the adoption of single-use systems,” says AdvantaPure’s Stover. “Production engineers are under constant pressure to reduce manufacturing costs associated with making pharmaceuticals, vaccines, and other important high-purity fluids. Suppliers of disposable systems will come under the same pressures to reduce the cost of manufacturing these systems.”

HyNetics’ Bibbo concurs and elaborates on some of the hesitation to move to disposables. “The main driver will be the cost of the disposables, and whether that justifies moving from traditional stainless steel process equipment and all of the capital-intensive burden it carries,” he says.

He also points out that some in the bioprocessing industry are reluctant to use disposables because of concerns about leachables and leaks. “Leachables and extractables can be addressed by advancements in chemistry and the use of new and more-resistant polymers and resins,” as well as the fact that there are few materials in contact with the process fluids. As for leaks or the perception thereof, “it is a matter of material selection, proper handling, care and use, as well as the design of the products themselves,” he notes — adding that the same is true for stainless steel process equipment as well. It all comes “back to proper care and use, and choosing the right technology for a particular set of conditions.”

Bibbo continues: “We do need more clean-room-based manufacturing, larger molding and casting machines in controlled spaces, and more vendors willing to move into those challenges, much like the semiconductor business demanded.”

GEHC’s Kranjac remarks, “We anticipate an increased awareness with regard to environmental benefits of disposables versus conventional stainless steel systems. Because this can be rather dependent on the specific process steps, we see the need for comprehensive studies and mass balances to determine the benefits. Several biopharma companies have already found that the significant reduction in water usage when employing
single-use technologies outweighs the disposal of single-use components. We do anticipate additional studies around individual process steps to show the environmental benefits. Some of these activities may lead the industry to increased usage of disposables and the development of more eco-friendly films and components.”

Colder’s Boehm sums up the key driver as the joint effort of biopharmaceutical manufacturers working directly with the suppliers to ensure that disposable technologies are meeting the market needs for cost reduction, efficiency gains, and product safety. “This is one of the main reasons that the BPSA has opened membership up to biopharmaceutical manufacturers — to allow open communication between the industry’s leading suppliers and top drug companies,” he says.

Outlook

The consensus is that the future of disposables is a promising one. “There will be significant expansion as more disposable systems are used for different applications in research and development and bioprocessing. There will also be a significant consolidation around standards as the benefits of certain designs and technologies emerge,” says Warren.

As stem cell and cell therapy applications evolve, the need for specialized tools and ease of use in hospital environments will yield continued innovation around disposables, notes Kranjac.

“We will see a further streamlining of manufacturing processes with the use of platform development strategies and generic processes. Antibodies will continue to be the most successful class of molecules and need to be produced in tonnage amounts, at least for the current generation of molecules,” explains Gottschalk, of Sartorius Stedim Biotech.

“The typical amount for an antibody will remain in the 100 kg/yr range and may even go down as a result of individualized therapies and more-effective molecules and treatment options. This, together with high-titer processes, will lead to typical fermenter sizes of no more than 200–1,000 L.”

Crossley adds that as upstream titers reach levels that were unheard of five years ago (with some manufacturers reporting antibody titers of >20 g/L in CHO cell cultures), the demand for large stainless steel bioreactors is waning, and smaller-scale disposable bioreactors are filling the gap. There has been significant innovation in single-use technology for upstream processing over the past five years, and the next five years will likely produce similar advances in disposable technology on the downstream side.

Opportunities exist for single-use suppliers to become leading providers of components, systems and design capabilities as more users recognize the utility of disposable bioprocessing, BPSA’s Ott believes. For end users, he says, there is a substantial economic upside with disposables, beginning with the avoidance of large capital expenditures for steel plants, as well as the flexibility and cost savings inherent in processing with plastics, including the avoidance of steam-in-place and clean-in-place costs and expenses associated with re-validation.

“The outlook for single-use systems and disposable components is very bright,” AdvantaPure’s Stover says. “There is already a large demand for these systems, and many component manufacturers are scrambling to keep up with the demand. Capital investments in manufacturing equipment needed to make disposable components and systems are being driven by current demand along with projected demands for the next five years.”

The global demand for biopharmaceutical therapies, according to Boehm, will increase due to several factors, including: advancements in personalized medicine; new vaccine development to address pandemic concerns; introduction of biosimilars as biologic therapy patents expire; and market expansion into developing countries. “The immediate opportunities presented by many of these factors are driving companies to implement new, smaller facilities based on single-use systems,” he says. “These facilities can reduce production costs, but they also allow the manufacturer to build, validate and start production years earlier than would be possible with a traditional stainless facility.”

Bibbo points out that there is also a social side of single-use technology that is of great concern — how to dispose of these products after use. “Certainly, landfilling is not the answer, since most of the polymers and resins will not biodegrade and will remain UV-stable for many years (we have purposefully engineered them to be robust). Incineration, cogeneration and recycling have limitations as well. Exposure to and releasing of pharmaceutical/medical waste and byproducts is a reality that we need to address if we are to properly dispose of these products.”