



Sep 15 2008 (Vol. 28, No. 16)

Feature Article

Disposable Use Proliferates in Production

Converts Insist that Single-Use Systems Are Surefire Way to Save Time and Money

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Disposable bioprocess equipment has achieved a level of acceptance that was largely unanticipated a decade ago. Single-use bags, tubing, connectors, and related products have profited from rising protein titers that have caused many processes to shrink in size. Disposables have become particularly attractive among contract manufacturers operating at up to the 500 L scale.

But disposables have their limitations. One senses reluctance to use process bags above 500 L in working volume. Bags much larger than that become difficult to work with, require mechanical support, and present disposal problems. Additionally, many biomanufacturers owe their accountants full amortization on their substantial investments in stainless steel fermentors, plumbing, and cleaning systems.

While new plants, particularly those of contract manufacturers, are specifying disposables as part of their facility plans, many more companies are incorporating single-use equipment as part of process and facility retrofits, says Denise DeTommaso, global technical support manager for [SAFC Biosciences](#).

"Companies are looking for spots where they can adapt a single-use product for part of a process," she says. "Everyone is looking for a way to reduce contamination, changeover time, and generally to make things faster." Other factors driving disposables are trends toward lean manufacturing, cost-cutting, and sustainability.

Familiar Technology

Vendors no longer need to trot out the benefits of disposables to bioprocessors, says Chris Mach, product manager for single-use products at [Pall](#). "At this point, customers are more interested in the specific advantages to them and what technologies vendors can offer."

Vendors increasingly design disposable equipment around specific applications, as users seek to duplicate the functionality of fixed-tank systems in flexible, single-use plastic. One emerging application, says Mach, is bioreactor sampling using disposable bags, which he describes as "an application within an application" for single-use products.

Tubing and fittings represent a critical component for integrated disposable processing, yet few vendors offer robust connection products. For example, Pall's KleenPak™ connectors allow sterile connections of two fluid pathways while maintaining the sterility of both.

Another recent introduction is the Allegro™ Biocontainer, a storage bag available in 2-D

and 3-D formats. The pillow-shaped 2-D containers are available in sizes from 50 mL to 50 L; the cubic 3-D bags range from 100 L to 500 L. Allegro biocontainers address problems of leakage, folding, and improper filling of process bags. Both versions unfold cleanly and predictably on filling without the need for operator manipulation, provide improved drainage, and utilize a highly transparent plastic material that allows operators to look inside for misfolding or precipitates, the company reports.

According to Mach, small molecule drug manufacturers are beginning to show interest in disposable containers. Problems of chemical compatibility with organic solvents remain, particularly at elevated temperatures, but the idea that chemical/pharmaceutical processors would even consider plastic process equipment is intriguing.

Vendors Making Improvements

Mani Krishnan, director for process systems at [Millipore](#), agrees that customers do not require a hard sell to adopt disposables, adding that end-users are beginning to think of single-use equipment for critical as well as non-critical applications. "It's not just for buffers any more. People have gone beyond that," he reports.

Millipore's acquisition of Newport Biosystems has given the company entry into markets that integrate process bags (Newport's specialty) with connectors and filters. Millipore's Lynx® ST (steam-to) and Lynx S2S (sterile-to-sterile) connectors are two enabling products that allow custom integration based on users' specific applications, Krishnan adds.

While chromatography remains a difficult adaptation for disposables, Krishnan believes that a good case could be made, in many instances, for single-campaign utilization (vs. truly single-use or single-batch) for even the most expensive resins. A manufacturing campaign might entail five or six batches, for example. Krishnan mentions pre-packed chromatography columns as products that might tip the balance in favor of single-campaign use. Another such product is Millipore's Prosep® Ultra Plus protein-A chromatography media, a resin with high binding capacity and high linear velocities—attributes that are desirable for high-productivity, small-footprint unit operations.

These products are just a start. Operating in disposable or single-campaign manner will require that vendors continue to innovate and that industry change its mindset regarding chromatography, Krishnan says.

For example, Millistak+® filters were first developed to be used in large stainless steel housings that required large CIP loops. Millipore launched the fully disposable Pod format containing the same filter media, which significantly minimizes the demands of the CIP loop.

Vendors also need to do a better job of making their single-use products more user-friendly, he says. "When customers take a disposable assembly out of the box it is a 'spaghetti' of piping and tubing. The more complex the process, the more complex the 'spaghetti'."

At a recent IBC conference, Millipore exhibited a Tangential Flow Filtration process skid that simplifies the task of unraveling and utilizing the bags, tubing, and connectors. The

skid features supports and connectors of its own that enable the various components to be installed in the correct location making the numerous components more accessible and enabling easier use of single-use processing systems.

More Competition and Choices

Despite the spate of mergers and acquisitions among vendors of single-use equipment, end-users feel there is a greater diversity of available products and more competition and choice today than ever before. Vendors are moving vertically and horizontally from their original positions as suppliers of storage bags, membranes, or reactors to supply integrated systems with broad processing ability in completely or nearly completely disposable format.

[GE Healthcare's](#) Wave Biotech division, a leader in bioreactor bags for years, now faces competition from [Xcellerex](#), [Thermo Scientific Hyclone](#), and [Applikon Biotechnology](#).

Working volumes in Wave bags, whose contents are agitated through rocking on a mechanical table, go up to 500 L, whereas the Xcellerex XDR™ Single-Use Bioreactors, which are supported by a stainless steel tank, feature volumes of up to 2,000 L.

Xcellerex has published an economic analysis on its website that claims its bioreactors can reduce capital investment by 75%, lower operating costs by 35%, and accelerate time to start-up by 10 months compared with conventional stainless steel equipment.

Xcellerex also offers a disposable mixing system at volumes of up to 1,000 L, the XDA disposable, single-use product contact assembly that includes gas filters, agitation system components, sparge components, probes, ports, pressure sensors, sampling ports, and gas and liquid transfer tubes.

Intermediate in size are Thermo Scientific Hyclone's BioProcess Container™ systems, with volumes ranging from 50 mL to 1,500 L. Applikon serves the low-volume side of the business with its Appliflex process bags, available in 10, 20, and 50 L sizes and fitted with sensors for measuring temperature, pH, and dissolved oxygen. Like Wave, Applikon agitates bioreactor bags by rocking them on a mechanical platform.

Disposable reactor bags provide many advantages over stainless steel tanks but scale-up with bags has its problems, notes Michiel E. Ultee, Ph.D., senior director for process sciences at [Laureate Pharma](#).

Scale-Up an Issue

"The amount of mass you have to rock back and forth, or otherwise mix in disposable fashion, becomes critical." Laureate Pharma currently uses bags of up to 500 liters in working volume, but is considering Thermo Scientific Hyclone's and Xcellerex' products with volumes of around 1,000 L.

While downstream operations have been adequately served for filtration and membrane adsorption, capture chromatography remains an area where disposables have not yet

made inroads. Bind-and-elute steps, which rely on expensive resins, are still the domain of reusable media, whereas flow-through steps like virus removal and polishing are nearly all carried out in disposable formats.

Laureate is considering an evaluation of a ready-to-use chromatography format from GE Healthcare's ReadyToProcess™ portfolio later this year. The columns come prepacked, sterile, and certified for packing efficiency but are not single-use in the traditional sense.

"Plus, they only come in predefined sizes," notes Dr. Ultee. "Processors who need an in-between size may be forced to pay for the next highest size, and with high resin costs, it's a drawback compared with pack-your-own."

The company, which mostly produces clinical trial material on a contract basis, frequently works in batches in the 200 L to 500 L range. While this is considered the sweet spot for disposable bioreactors, at this time, Laureate only employs single-use bags for scale-up of cell cultures to inoculate its stainless steel bioreactors. "Bioprocess bags of this size working volume were not available when we started our business," says Dr. Ultee.

Furthermore, process-monitoring and control systems were also less extensive on the disposable-bag bioreactors. The high cost of its installed stainless steel base, Laureate feels, is now behind them and encourages it to recoup its investment in that platform.

With an upper-limit operating scale of 2,000 L (in stainless), Laureate does not have any 100% disposable processes. While many of the tanks and storage vessels feeding this reactor are single-use, the company is wary of large-sized process bags due to the physics and logistics of operating at that scale in a disposable format.

"It can be done, but you have to build a steel tank to hold a plastic bag of that size," notes Dr. Ultee. "Plus, the bags are difficult to work with and quite expensive."

Analytics: The Final Frontier?

One hurdle to integrated, fully disposable bioprocessing has been analytics. This factor will grow in importance as PAT becomes more mainstream.

Several companies manufacture low-cost sensors suitable for disposable processing. These include [PendoTECH](#), [Fluorometrix](#), and [SciLog](#). SciLog's precalibrated pressure and temperature sensors hold serial number, lot number, and calibration offsets in memory.

Another company, [Finesse Solutions](#), recently entered the disposable sensor marketplace with its Tru line of sensors, cables, housings, and signal-transmission products. Sensors include TrupH (for pH), TruDO (dissolved oxygen), TruCell2 (cell density), and TruFluor (phase fluorimetry for simultaneously measuring temperature plus either dissolved oxygen or pH).

In April, Finesse entered a partnership with GE Healthcare to develop a control package for the Wave Bioreactor based on the Finesse TruLogic™ controller and TruBio™ SCADA (supervisory control and data acquisition) system. The project is expected to lead to a package for controlling Wave bioreactors for pH, dissolved oxygen, temperature, rocking speed, pressure, aeration, and weight, and support redundant sensor loops for pH or

dissolved oxygen as well.

Earlier in the year, Finesse teamed up with [Emerson Process Management](#) to integrate the Finesse TruBio bioreactor control system with Emerson's DeltaV digital automation system.

According to Barbara Paldus, Ph.D., CEO, the future looks bright for smart disposable systems with embedded sensing and control capability. The upper volume limit for disposable processing, about 2,000, should continue to serve biotech as customers become more comfortable with larger bag sizes and protein titers continue to rise.

"Eventually, there will be no reason to run a 15,000 liter bioreactor," Dr. Paldus points out. Rising titers and its connections with bag vendors Thermo Scientific Hyclone, Xcellerex, and GE Healthcare Wave were partly responsible for Finesse's revenues rising tenfold last year.

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