Photo courtesy of Millipore Corp.

Single-Use Technologies & Trends

In the wake of H1N1, single-use technologies are picking up steam

By **Gil Roth**
CONTRACT PHARMA

SINGLE-USE TECHNOLOGIES — THE DISPOSABLE components and systems that replace portions of the biopharma production chain — are surging. Within the past decade, single-use as a concept has moved from the exotic and untested nearly to the mundane, with pharma and biopharma companies large and small implementing one-off bags, connectors, and entire (small scale) bioreactors into their processes.

Flexibility is the key word for single-use systems, with no fewer than three companies using "Flex" as part of their product branding: FlexReady (Millipore), FlexAct (Sartorius), and FlexFactory (Xcellerex). Vendors are expanding the range of process steps that can be served with single-use technologies, while fulfilling user demands for enclosed single-use systems.

Adam Goldstein, senior manager, clinical research at Genentech, leads that company's disposable technology team. When asked about the adoption of single-use technology in recent years, he remarked, "It's not even worth discussing, when it comes to disposable biobags for buffers and media prep. Those are in place; we're past assessing the benefits and risks. We know they save us a lot of time and money in terms of CIP and steup time for tanks."

Mr. Goldstein added, "They're not used as much bulk freezing applications, although we do use them in clinical. About 50% of our drugs go into disposable biobags for freezing. That has saved us a great deal of money, in shipping and validation. We don't have to track the cleaning and validation of the different freeze-tanks."

Maik Jornitz, group vice president of global marketing & product management for Filtration | Fermentation Technologies of Sartorius Stedim Biotech, commented, "Cleaning can actually be the bottleneck of a commercial facility. You have to use a lot of WFI to clean equipment. It has a high energy input and high carbon footprint. If it takes you eight to 10 energy-intensive, labor-intensive hours to clean a tank, you're losing an entire shift."

In his other role as chairman of the board of the Parenteral Drug Association, Mr. Jornitz recently gave a presentation on advances in disposable biopharma processes at the PDA's annual meeting. Discussing the time To implementation of a single-use fermentation system compared to a multi-use one: four to seven months vs. two to three years. The reasons for the time savings, he contended, were threefold: qualification of equipment, cleaning validation, and qualification of set-up.

Maturity

Mani Krishnan, program director for Millipore's Mobius Single-use Processing Systems, said, "I consider single-use to be a maturing market, insofar as the customers are gaining a greater understanding of the technology and its applications." He noted that users began employing single-use components

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and systems in non-critical areas, but have lately been moving toward use in critical steps of processes themselves. He remarked, "We're seeing a shift toward putting product — both intermediate and finished bulk substance — in single-use bags, and using these technologies for critical applications like filtration."

The key, Mr. Krishnan contended, was end-users not just understanding the risks of single-use technologies, but also understanding the risks in their current systems. He remarked, "At a conference a few months ago, a gentleman from GSK spoke about implementing single-use technology for final fill/finish. This is the tail end of the process, with commercial scale product, where the only thing standing between you and the vial is single-use technology. What he was trying to show was that there are risks in the existing process, and it's only when you assess those that you really understand the value single-use can bring."

Brian Lee, president of PBS Biotech, contended that the biomanufacturing field can be a little slow to change. He remarked, "Theres's a hesitance to adapt to changes; I think it starts in validation but tends to permeate the culture at larger biopharmas." It's understandable, he noted, that these companies don't want to create regulatory waves, but he contends, "Changeover from stainless to disposable is accepted by the FDA."

Rate of Increase

Several of the vendors, end-users and CMOs we spoke to echoed the same sentiment about recent growth in the single-use market. "The H1N1 event definitely boosted interest in single-use systems," said Mr. Jornitz. "Vaccine makers realized that they have to be able to move their production facilities around more quickly."

Chris Mach, global product and marketing manager at Pall Corp., commented, "Let's face it; the technology exists such that we shouldn't have a shortage of vaccines like we saw in 2009." He noted that, even before H1N1, vaccine makers were helping drive the single-use market. "Many companies have been moving into the vaccines area in the last few years. They understand that the capital layout for stainless steel is immense, so they've been exploring single-use applications. After the H1N1 episode, we're starting to see single-use applications filter out from flu vaccines and into other prophylactic ones."

PBS Biotech's Mr. Lee likens the adoption of single-use systems to the uptake of cell-phones in the U.S.: "The stainless steel infrastructure is like the land line telephone system. Once upon a time, people only had cell phones for emergencies; they were clunky and not reliable. A decade later, more than half of households don't have a land line anymore."

New Technologies

Greater flexibility and reduced capital costs drive the market, but vendors aren't resting on their laurels. Companies like Millipore and Sartorius Stedim have developed system-based solutions and are increasing the level of sophistication in single-use steps. Said Mr. Krishnan, "We're showing the market that it's not just about putting a bag and a piece of tubing together. There's a lot more to it. If you think about how people design stainless steel systems, there's a lot of design work there to optimize it. When you slap together a tube, a bag and a filter, you're designing an inefficient system. What we tried to do is break that cycle and put a lot of effort into designing a single-use system."

In a similar vein, Sartorius Stedim launched FlexAct BP, a buffer prep system that uses a central operating module to accommodate pre-configured single-use assemblies. The company plans to roll out FlexAct systems in several more steps — including media prep, cell harvesting, virus removal, and ultrafiltration/diafiltration crossflow — in the next year or two.

Mr. Mach agreed that it's "not just bags." He pointed out that Pall Corp.'s new Allegro 3D Biocontainers are a big step in terms of reducing contamination risk with bags, but also stressed the company's focus on technical services and on-site support. "There are lots of validation concerns — E&L, filters, tubing compatibility — so we've made a major focus on services in those areas," he told us.

Scale Up?

PBS Biotech is focused on disposable bioreactors, using a novel method of mixing and a user-friendly control system. The mixing mechanism doesn't input power to the shaft, and so shouldn't face some of the physical limits of other single-use reactor setups. "It's been tested at smaller sizes, but we haven't built a 5,000L model yet," said Mr. Lee of the company's Pneumatic Bioreactor System. He contended that the system will mix more quickly than current systems and that the company is exploring whether shorter mixing timeframes may open doors for new, previously unscalable processes.

While PBS is pursuing large scales with its single-use bioreactor system, other suppliers and providers feel that there's no need to rush after the massive scale of the largest stainless steel tanks. Mr. Jornitz remarked, "Will we see 5,000L or 10,000L bioreactors? I don't think so. Maybe it'll go up to 2,000L, but I think we'll end up coming up against mechanical restrictions. And with increasing expression rates, we likely won't need such large volumes as we once saw in stainless setups."

Mr. Mach at Pall Corp., noted, "Using several smaller — think 1,000L — single-use bioreactors can also be a better move from a risk standpoint. Viral contaminants are still a real threat for cell culture media, so if you introduce that media into a 20,000L reactor, then realize after five or 10 days that you have a microplasma contamination in your reactor, that's a lot of time, resources, energy and costs wasted. If there's a contamination in a one of the disposable bioreactors, the volume that's discarded is much smaller."

Gene Yoshioka, director, manufacturing at Avid Bioservices, concurred, noting, "There's definitely less risk with smaller runs." Avid, a CMO based in Tustin-CA, installed a 1,000L single-use bioreactor (SUB) last year and is quite pleased with the results. Peregrine Pharmaceuticals, Avid's parent company, gave the go-ahead to work with 100 and 1,000L reactors. The company gave a presentation demonstrating that results from the SUB were comparable with a stainless steel setup in terms of consistency, scalability and efficiency.

In the presentation, Richard Richieri, Avid's senior vice president, technical operations, remarked, "Data from both our 1,000L and 100L SUB show our process is consistent and scalable, allowing us considerable flexibility to manufacture products using either the SUB or traditional stainless steel bioreactor systems to meet our clients' clinical trial materials requirements."

Chris Eso, vice president of business operations at Avid, remarked, "We have increased demand for 1,000L reactor, and the facility wasn't set up to support more steel." If studies on further production runs continue to bear out the comparability of the SUB, then the company will design a process and facility with multiple 1,000L SUBs for commercial requirements.

That said, even the most die-hard proponent of disposable components and systems wouldn't argue that stainless steel is going away. It'll definitely stick around for larger volumes or highly specific applications, although we may see more hybridization, where disposable components are integrated into established multi-use systems.

Mr. Jornitz remarked that, beyond bioprocessing applications, traditional pharma companies are also seeing the benefits of single-use systems and components. He said, "We see it not only in biotech, but also in small-molecule pharma, particularly as hold vessels. There's a lot of stainless steel equipment out there, and that costs money. Every pharma and biopharma is looking for opportunities to add value and cut costs. Large pharma companies are facing big patent expirations in the next few years, and implementing single-use where they can is a way to reduce WFI input, energy consumption, downtime, even staff. They may even optimize product flows by moving additional products into existing facilities."

The Next Step

So what's next for single-use? We'll see new technologies and applications, but Mr. Goldstein at Genentech thinks that there's one more advance that could really open things up. "The biggest hurdle still out there is that the vendors need to come up with a common setup of multi-solvent strategies," he commented. "They need to have consistent compatibility data and extractable data reports. That way, when you go to an end-user, they don't have to do extractable studies. That'll speed the entry of disposable components into companies, by lessening the times that quality folks will have to spend searching for that information. Creating a set of standards that industry will find acceptable will be the big breakthrough."

We need to remember, he pointed out, that stainless steel and teflon went through the same problems: "Plastic is at that point in its development, where people are arguing about appropriate testing standards. Getting that fixed will be the key." ■