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Single Use Becoming an Established Tool

Vendors' Attention to Users' Requirements and Familiarity Are Driving Increased Implementation

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As single-use bioprocessing approaches its first decade, integration and standardization are on everyone's short list of desirable features. Suppliers are responding with significant initiatives to streamline the specification, acquisition, assembly, and deployment of disposable equipment.

Getting plastic components to work together with a minimum of validation has always been a priority. Now, it appears, acceptance may have reached a critical point and vendors are doing all they can to facilitate decision making by reducing or eliminating the interoperability question.

At IBC Life Sciences' upcoming "Single Use Applications for Biopharmaceutical Manufacturing," a number of presenters will make their case for specific systems, components, or approaches that reflect their vision of the disposables marketplace.

Two New Platforms

Integrating disposable bioprocess components requires more than simply hooking them together aseptically. The importance of configurability, flexibility, and speed will be the theme of a presentation by Thomas Paust, global director of marketing for integrated solutions at Sartorius Stedim Biotech. Paust will discuss the advantages of FlexAct, a centralized platform that enables the design and deployment of single-use equipment across biomanufacturing.

FlexAct consists of a central module on a portable skid that incorporates a touchpad-controlled user interface or central operating module borrowed from the company's BioStat® bioreactors and Sartoflow® crossflow filtration units, plus a pump, sensors, and controllers. FlexAct allows system design without having to design everything from scratch, Paust says.

"Think of FlexAct as a workstation that organizes the components and enables the first steps of automation."

Sartorius Stedim Biotech's first FlexAct unit operation will be buffer prep, followed by media preparation, cell harvest, ultrafiltration/diafiltration, virus removal, virus inactivation, virus adsorption, polishing, form/fill, and form/transfer.

Sartorius Stedim Biotech currently covers all these unit operations but not at this level of integration. “The other important component here is standardization,” Paust notes. “Today we see a lot of engineered systems customized for specific processes. This creates advantages for bioprocessors who are able to work this way. But there are some disadvantages as well, such as delivery times, the need for specific components of specific designs, and connectivity.”

Similarly, GE Healthcare’s ReadyCircuits single-use configuration platform will be the subject of a presentation by GE senior product manager Karen Green. As part of the company’s ReadyToProcess™ biomanufacturing platform, ReadyCircuits allows plug-and-play assembly of self-contained, fully disposable unit operations such as buffer filtration and tangential flow filtration.

GE is constructing an online configuration tool that will allow purchasers to specify bags, filters, tubing, and other components through a graphical interface. Components will arrive fully assembled and presanitized. “Validation is built in,” Green says.

ReadyCircuits will provide systems for upstream and downstream processing, for example normal flow and crossflow filtration, purification and polishing column chromatography, cell harvesting, and, of course, fermentation and cell culture based on the Wave bioreactor product line.

ReadyCircuits arose from customer feedback, Green explains. “Users were looking for a fast, flexible solution of disposable unit operations that could be assembled Lego-style.” GE already sells hundreds of sub-assemblies. “With the online tool, users will be able to design one from their own concept, or we can provide them with a head start consisting of a starter kit that they can then modify.”

Sensors

Erik Storm, single-use process engineer at Pall Life Sciences, will speak on single-use system design from the perspective of single-use sensors. Sensors for flow, pressure, pH, and temperature are core components of both single-use and stainless steel bioprocessing. Increasingly, processors are looking into probes for conductivity and ultraviolet absorbance. Fully disposable systems require single-use sensors, so in this respect disposable sensors can be viewed as an enabling technology that should greatly expand single-use through fully functional process containers compliant with the latest FDA quality and risk initiatives.

Rugged, inexpensive sensors have existed for years, and new probes are emerging almost weekly. “It all comes down to what people expect with regard to accuracy, ease of use, and calibration,” Storm notes. Other factors include ease of installation, connectivity, and susceptibility to process conditions for sensors in direct contact with process fluids. Designs for some sensors allow placement on the outside of the process container.

Another significant issue for disposable sensors is where the sensor/container combination is assembled—at the vendor’s site or on-site. Until fairly recently processors assembled their own systems from components purchased from multiple suppliers. This still occurs, but GE’s ReadyCircuits and Sartorius Stedim Biotech’s

FlexAct platforms suggest that major suppliers are betting heavily on standardization and/or preassembly, two trends that Pall has long recognized. “Users are looking more and more for integrators to do the assembly for them,” Storm says.

To extend preassembly and standardization to single-use sensors, users will either have to specify the sensor model before ordering the preassembled equipment or vendors like GE, Pall, and Sartorius Stedim Biotech will need to stock a range of standard sensor types.

It turns out that single-use sensors will be well-represented at IBC. One talk, by Lonza Biologics’ senior scientist David Valentine, will compare reusable dissolved oxygen and pH sensors to single-use varieties. Lonza is investigating disposable DO and pH devices for in-line measurements in cGMP fed-batch cell culture processes.

Another talk, by engineer Emmanuelle Cameau of Merck Serono, compares the performances of Finesse Solutions’ TruFluor single-use DO sensor with that of a Mettler-Toledo stainless steel probe. Finally, Philippe-Alexandre Gilbert, Ph.D., senior scientist at MedImmune vaccines, will present data on single-use sensors as they relate to process analytic technology and quality by design.

Vaccines

Parrish M. Galliher, founder and CTO at Xcellerex, will explain how universal, rapidly deployed single-use products represent a paradigm shift for vaccine manufacturing. Disposables, Galliher says, are enabling vaccine makers to “avoid traditional bottlenecks impacting quality, cost, time, and first dose.” Moreover, the benefits are accessible to vaccine manufacturers operating in subunit, live/attenuated virus, or virus-like particles in microbial, mammalian, or insect cell cultures.

Vaccines and disposables fit naturally together, Galliher argues, because “vaccine manufacturing does not occur on a mega-scale” as, for example, therapeutic antibody processes. “Many vaccine facilities run at 1,000 to 2,000 liters, up to about 6,000 liters. So you could say that vaccine manufacture represents a sweet spot for single-use equipment.” This trend is assisted by the slow but inevitable switch to cell-based manufacturing processes.

Biotech’s mostly positive experiences with single-use cell culture processing is the basis, Galliher argues, for disposables’ application to cell-based vaccine production. Xcellerex’ current volume leader for bioprocessing is a 2,000 L bag, with a 5,000 L reactor expected to debut by the end of 2010.

Disposables are not as useful for egg-based influenza vaccine manufacturing, which still dominates world markets. This begs the question: considering the known logistical shortcomings of egg-based manufacturing, why has cell culture-based production been so slow to catch on? Galliher cites lack of adequate clinical experience, difficulties in running large human vaccine studies, the low cost of egg-based manufacturing, and the huge legacy investment in the older technology.

“There has been very little incentive to innovate,” Galliher explains. “But now, with greater public and governmental awareness of the potentially devastating impact of

pandemic outbreaks, and with governments investing in cell-based vaccines, development will pick up."

Galliher's claim of a "sweet spot" for disposables in vaccine production is not mere boasting. His company has collaborated with Novavax on scaling its production process from several hundred liter disposable bags to 1,000 L disposable stirred-tank process.

In fact, at the meeting, Hua Jiang, Ph.D., senior manager for downstream purification at Novavax, will delve deeply into his company's use of single-use vaccine production. Novavax made headlines two years ago with its idea of regional, flexible, quickly deployed single-use production of H1N1 influenza vaccine.

Later on in the program, Jean-François Chaubard, director of viral production at GlaxoSmithKline Biologicals, will describe his company's efforts in upstream viral vaccine processing. Chaubard will focus on cost of goods and biosafety for a microcarrier-based process.

Selling the Idea

The maturation of single-use biomanufacturing has been accompanied by a more analytic, if not quantitative, approach to the question: "To dispose, or not to dispose?" Peter Latham, president of BioPharm Services will run a workshop at IBC that discusses drivers for and against implementation of single-use equipment.

It is often convenient to couch such discussions within the context of process-specific pros and cons—for example, the time spent on cleaning validation vs. the cost of single-use systems; the environmental impact of using and discarding all that plastic compared with the carbon footprint for creating thousands of gallons of ultrapure water; or for contract manufacturers, implementation costs vs. nimbleness, speed, and flexibility.

Latham suggests something perhaps as critical, namely "selling the concepts" of disposability internally, to colleagues and upper management.

"There's a broader issue around convincing people to take a chance on anything that might be different or new," Latham explains. "Even though this is less true for single-use technologies today, you still have to convince people. When you have a product with an 80 percent or 90 percent margin, you don't want to risk your supply chain.

"That's why it has taken years for single-use equipment to catch on, despite their obvious benefits. As margins go down and familiarity with single-use technologies increases, this internal sale is becoming easier every day."