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Continuity Promotes Bioprocessing Intensity

Moving From Batch Mode to Continuous Mode Concentrates Bioprocessing Wonderfully

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Just five or six years ago, bioprocessors viewed continuous bioprocessing skeptically. Now, seemingly, almost everyone is interested.

For example, fully continuous bioprocessing has become a top priority at Pall, which maintains a continuous processing laboratory in Westborough, MA. The company has also demonstrated its commitment to continuous bioprocessing through significant acquisitions of critical technology.

To enhance its downstream processing capabilities, the company has acquired Tarpon Biosystems' BioSMB (simulated moving bed) multi-column chromatography system. For upstream processing, the company has purchased the LifeSciences business of ATMI, which includes the iCELLis[®] Bioreactor for adherent cell culture.

To bridge the gap between the bioreactor and downstream processing, Pall has purchased an exclusive license to acoustic wave separation (AWS) technology from FloDesign Sonics. AWS, which uses acoustics to trap and collect cells as they pass through a flow channel, complements Pall's own line of depth filters.

Continuous bioprocessing capabilities may be introduced along segments of processing lines, resulting in hybrid systems that accommodate continuous and batch processing. In hybrid systems, however, it is still necessary to harmonize upstream and downstream operations. For example, in a process architecture that combines batch upstream and continuous downstream operations, it is important to match mass capacities between harvest and subsequent steps. Within continuous processing segments and in fully continuous processes, aligning volumes is more critical.

Consider the integration of perfusion cell culture, which generally involves dilute feed streams, which means high buffer volumes—lots of media. High buffer volumes tax purification trains and counter the philosophy of continuous processing. "Buffers are the biggest thing moving into and out of continuous processes," says Michael Egholm, Ph.D., Pall's president of biopharmaceuticals.

To solve the problem of dilute feed streams, Pall uses an inline concentrator—a simplified version of tangential flow filtration—which provides two- to fourfold concentration. Buffer usage also drops, but by how much depends on eventual optimization. Bottom line: By the time a batch reaches the capture column, the volume of a 25 L bioreactor is reduced to 5 to 10 L.

Small process volumes are tailor-made for continuous chromatography. Whereas conventional columns are sized according to the anticipated mass or yield, resin volumes in multi-column formats (as in BioSMB-simulated moving bed chromatography) are based on process volumes. Providing volumes remain constant, no surprises will derive from any titer increases that should occur.

Resins are underutilized in standard chromatography, limited to occasional (on the time scale of a

purification) binding and elution. “In continuous mode, every grain of resin is occupied for the entire run, which makes possible scaling down and easier linking of unit operations,” Dr. Egholm explains. “In continuous mode, balancing the production line becomes critical.”

Specifically, volumes for column elution, virus inactivation, polishing, diafiltration, virus filtration, sterile filtration, etc. must be comparable. Balancing is invaluable for connecting unit operations, which is a cornerstone of continuous processing.

Regulatory Issues



Regulatory concerns will be different, but not necessarily more onerous, for each unit operation in continuous mode. Yet companies must think more deeply about bioburden, which causes filters to fail. They must also assure that product on day 27 is the same as on day 17, which is not an issue in batch mode. Industry-standard thinking regarding the very definition of “batch” must change as well. In many instances, bioreactors and separations are no longer discrete events.

“We believe these issues are solvable,” Dr. Egholm declares. “Regulations are a barrier, but they will be overcome as well. We have engaged the FDA and our industry in a very transparent manner.”

The history of disposable bioprocessing suggests this will take time, which is okay since adoption of continuous bioprocessing will also take time, and is more likely to be evolutionary than revolutionary. “But we’re already quite far on our journey,” asserts Dr. Egholm.

How continuous processing will alter the industry’s view of process analytical technology (PAT), quality by design (QbD), and quality in general is what Dr. Egholm calls “the 64 million dollar question.”

Pall’s development strategy involves addressing less-risky downstream processing first. “We obviously must work with the FDA to determine everything that can possibly go wrong, and verify that they’re not going wrong,” states Dr. Egholm. “So most of the emphasis should probably be placed on QbD since fully characterizing antibodies as they’re produced is impractical and not very meaningful. A greater need for PAT may be needed as well, particularly for bioburden monitoring and control.”

Flexibility and Facilities

Continuous processing, process intensification, and process miniaturization go hand in hand in hand, and their interplay will affect how tomorrow’s biomanufacturing facilities are built. As processes become smaller and more efficient, facility planners must rethink the traditional, says Maik Jornitz, president of G-CON Manufacturing. G-CON specializes in PODs, which are self-contained, autonomous, and mobile cleanroom units, each with a separate HVAC system.

“Single-use process technology is excellently flexible, but its benefits are thwarted by existing cleanroom infrastructure,” Jornitz says. Using disposable manufacturing involves moving a lot of equipment around. PODs are designed to facilitate moving from one operation to the next, and bringing equipment in and out or transferring product via aseptic connection from one POD to the next.

“Autonomous” relates to the cleanroom’s HVAC system itself and says nothing about the potential connectivity among unit operations. The value of self-containment becomes obvious when one

considers recent contamination issues at large bioprocessing facilities.

“If the PODs’ air-handling capabilities were connected and contamination occurred in one cleanroom, other cleanroom areas are immediately affected. ‘Autonomous’ means you can continue working if one POD needs to be shut down,” Jornitz explains. “This POD may be cleaned and sanitized with vaporized hydrogen peroxide while the other POD units continue to function. PODs are essentially walk-in isolators.”

Jornitz predicts that with the adoption of PODs, autonomous cleanroom clusters will spring up in shell buildings that will be capable of producing multiple products. “That’s possible,” Jornitz asserts, “because the cleanroom infrastructures are not connected.” Were they connected, he argues, serious contamination would potentially force the entire facility to shut down. Cleaning large, complex ductwork is almost always impossible without a general facility shutdown.

The future evolution of bioprocessing and multi-product facilities will cause their paths to cross at what Jornitz calls “the crossroads of processing and facilities,” whereby process equipment become less multiple-use and facilities more so. “Multiple product facilities are the wave of the future,” Jornitz predicts, “even for large biomanufacturers.”

Building a single-product facility in a relatively small country makes no sense based on capital expenditures and ongoing operational costs. “But constructing a flexible, multi-product plant in such a location makes perfect sense,” Jornitz insists.

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