



Moving Toward Unified Process Control for Biopharma

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Traditional barriers between upstream and downstream bioprocessing are slowly starting to break down, as biopharma embraces more advanced analytics and process control.

Since the early days of biopharmaceutical manufacturing, upstream and downstream primary processing have been considered separate worlds. There was no profound reason for this separation, explains Charles Cooney, professor emeritus of chemical engineering at the Massachusetts Institute of Technology (MIT). “It goes back to the pre-biotech days of industrial bioprocessing, when the people involved upstream were mainly biologists, microbiologists, biochemists, and chemists, and the downstream people were usually chemical engineers, because they were engineering unit processes for product recovery,” he says.

Still, these historic disciplinary roots have continued to organize and define the industry for decades, and the re-

sult has often been isolation, rather than integration, Cooney says. More recently, however, as financial pressures intensify and interest in continuous biopharmaceutical processing increases, distinctions between up- and downstream are starting to disappear. “The conversation is no longer split by differences in vocabulary and has become much more integrated,” he says.

Greater integration is also seen, he says, in the move to fed batch processes (now standard for monoclonal antibodies [MAbs]), perfusion processes (standard for therapeutic enzymes and more unstable products), and continuous chromatography, enabling, for instance, a continuous capture step using a perfusion culture. The industry may still be years away from adopting inte-

grated, end-to-end biopharmaceutical process control, but it is getting closer. Enabling this move has been greater acceptance of approaches that had already been in use for years in other industries, such as food and chemicals.

FDA’s support of process analytical technologies (PAT) helped drive this change, says Bob Lenich, life-science business director at Emerson Automation Solutions, but economic pressures also play a role. “In the past, pharmaceutical manufacturers didn’t have to optimize manufacturing, but now they do, and they are applying more advanced analytics and control to help reduce costs,” Lenich says.

Now that automation standards such as the International Society of Automation (ISA’s) S-88 and S-95 (1) have been adopted by the pharmaceutical industry, the current focus is on “plug-and-play” solutions that will reduce the cost of automation, says Christie Deitz, engineering manager at Emerson Automation Solutions. “Equipment vendors are looking at unit operations that can run continuously, and skids on wheels, whether for chromatography, filtration, or bioreactors, that they can reconfigure to get to the next run,” says Deitz. Emerson, meanwhile, is extending use of its flagship DeltaV product, through the Discovery platform, into the R&D lab, secondary manufacturing, and packaging, and automation standards are moving from the plant floor to the lab and to secondary manufacturing.

PAT foundations

Enabling this change has been greater adoption of PAT, the use of which is now widespread in biopharmaceutical manufacturing, both upstream and downstream. “Even though downstream processing is still practiced as individual batch processes, the use of PAT with those batches is quite standard,” Cooney says.

Initially, use of PAT was limited to monitoring specific culture attributes upstream with near-infrared (NIR)

spectroscopy, or performing transition analysis and performance studies with ultraviolet (UV) and NIR spectroscopies downstream, but there were challenges with sensitivity and specificity (2), explains José C. Menezes, CEO of 4Tune Engineering, Ltd.

An important evolutionary step for PAT in biopharma came when companies moved from simply monitoring parameters to using PAT for process state estimation and to explore control opportunities. As Menezes explains, multivariate analysis was used to provide a complete estimation of the bioprocess state over time (e.g., a process trajectory during upstream cultivation, creating the opportunity to define guided sampling and endpoint determination strategies). NIR, mid-infrared (MIR), and Raman spectroscopy are all being used in this type of approach (2,3).

Recently, Menezes says, some manufacturers have begun to use in-situ mass spectrometry in multiple attribute methods (MAM), a term coined by FDA's Emerging Technologies Team to describe a method that aims to connect process condition-monitoring to accurate product quality-control during processing. "The ability to use mass spectrometry (MS) as a PAT [tool], and to aggregate the multiple attributes that it can very specifically measure, is a real breakthrough," he says.

Using new approaches such as MAM to monitor product quality attributes, end-to-end, both upstream and downstream, will open up new uses for PAT in biopharma, Menezes predicts. "Not only will it be used earlier in biopharmaceutical development to build very fast process and product understanding, but to support process performance qualification (PPQ, Stage 2) and the entire commercial lifecycle (Stage 3)," he says.

Most biopharmaceutical manufacturers are now at a stage where they are integrating quality measurements (typically spectral measurements) inline, so that they know they're producing what they expected to produce, and connecting those measurements to

closed-loop control, says Lenich. "That approach is everywhere," he says, "but the question has now become: Where can you take a new measurement that you didn't have inline before, and how can you apply that measurement in a model to show that the process is working better?"

Biopharma is also relying more on model predictive control (MPC), says Deitz, and a number of presentations at the International Forum on Process Analytical Chemistry (IFPAC) 2018 focused on this area, which is still relatively new for biopharma.

"Today, many of our biotech customers are using MPC to look at an individual unit operation (e.g., a chromatography column or a bioreactor process)," says Deitz, "and some are also using it to synch connected operations downstream, for example, when a chromatography column and a tangential flow filtration (TFF) skid are connected, and a specific liquid level must be maintained in the feed tank to the filter skid. MPC can help prevent disturbances (e.g., a tank overflow or insufficient liquid level) from impacting unit ops down the line," she says.

At this point, MPC is being used more widely in secondary than in primary biopharmaceutical manufacturing to control more straightforward processes such as filling and powder management, says Lenich. Modeling is also being applied to optimize facility operations. Rather than focusing on yield, companies are using MPC to examine throughput more closely and improve manufacturing, he says.

Modeling downstream biopharmaceutical processes remains challenging, however. "It's not an easy thing to do. You need to know what's going on in the process and you need a good understanding of the technology. You have to have the right people involved, and they need to be taking the right kinds of measurements," says Lenich. At this point, he says, some crucial measurements exist offline in the lab, and it may take hours or days to get this information. "These data need to be moved inline or at line so that

things can be done in real time," he says, noting that Emerson is collaborating in a BioPhorum Operations Group study that is determining what kinds of measurements are needed to optimize manufacturing and improve quality in biologics.

Having a digital strategy is the key to fast, successful biopharmaceutical process development, says Cooney, who notes that analytics and good data are fundamental. "Analytics is the vocabulary with which process development people communicate with each other and regulators, and the chemistry, manufacturing, and control (CMC) filing is all about this," he says. "What is new is the ability to use those analytics more effectively to learn what is important and to improve the quality of control. We are beginning to see the use of machine control techniques that will be the hallmark of process development strategies in the future."

The final obstacle to increased use of MPC is regulatory. "Everyone appreciates that these approaches work. But FDA and industry are not sure how to validate what is essentially a black box approach," says Lenich. "Guidance is starting to come but no definitive ruling, so, for many companies, the question is: when you are using MPC, how can you be sure you're using the best approach and that it can be validated?"

Increased uptake of PAT has also led to more use of soft sensors in bioprocessing, not only within unit operations, to provide real-time estimates of hard-to-measure parameters or end-point predictions, but across operations, says Menezes. "As data-management becomes sophisticated at most companies, the possibility to retrieve and aggregate data from critical process parameters (CPPs) and critical quality attributes (CQAs) in real-time will allow CQA estimates during processing for subsequent operations. That opens many possibilities for end-to-end optimization and feedforward control that will make pharmaceutical quality by design a reality in bioprocessing," he says. Examples already

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exist in areas such as media, relating quality attributes to upstream yields or stability (4).

Continuous manufacturing

Although the use of continuous manufacturing is much more evident in small-molecule oral solid dosage form manufacturing, all major biopharmaceutical companies are evaluating continuous, at least at the unit operations level. Some companies, such as Merck, Bayer, and Sanofi, have begun to explore the potential for continuous end-to-end primary biopharmaceutical manufacturing.

End-to-end continuous biopharmaceutical manufacturing will require global integrated control. At this point in biopharmaceutical manufacturing, control is typically handled locally, says Cooney. However, growing interest in end-to-end continuous manufacturing is stimulating development of global control strategies. One prototype employing this approach has been developed by Chris Love, associate professor of chemical engineering at MIT. It involves a fully-integrated biologics process done at a very small scale, in an installation that is roughly the size of a refrigerator (5), says Cooney.

Love's project, part of MIT's Biomanufacturing Research Program (BioMan), was originally sponsored by the US Defense Advanced Research Projects Agency (DARPA), with the goal of developing a process to make biologics on demand to manufacture small lots of material in response to emergencies. It uses a continuous, highly integrated process that can deliver doses of biologics, says Cooney, and would enable highly distributed biopharmaceutical manufacturing strategies. All of the major biopharmaceutical manufacturers with continuous manufacturing research in progress are paying very close attention to the control strategy, says Cooney. "If you're going to run an

integrated process, you have to have an integrated control strategy in place. The systems control industry is prepared to deliver the technologies (e.g., DeltaV) that are needed for this approach."

"Bottlenecks often come when a biopharmaceutical manufacturer tries to put a business case together for moving to continuous or integrated processes," says Cooney. "The right business case must be in place, and that case is typically based on one or more of four metrics: cost, quality, speed, and flexibility," he says. "If you own a big stainless-steel manufacturing plant and are making a good product, you'd be hard pressed to throw that all away and start over again with continuous, but if you're expanding capacity and you want to be able to respond with greater agility to market trends and forecasts, then continuous becomes very attractive," he explains.

Batch processes do pretty well, Cooney says, but if one or more of the four business-case criteria are of concern, then continuous processing can offer an effective solution. Improved quality can be one incentive, he notes. Reduced capital expenditure and operating costs can be another.

Obstacles to integration

Other issues make the move to continuous manufacturing and integrated process control more challenging. For example, Cooney says, continuous process requires adaption and use of different unit operations, and different integration and interfaces are required between them. The biopharmaceutical industry is just starting to learn how to handle these interfaces," he says.

The third challenge is operating existing, successful batch processes if the batch unit operation is different from what would be done continuously. The emergence of single-pass TFF has been somewhat enabling to the adoption of membrane filtration to continuous

manufacturing, says Cooney, as has the use of multicolumn or continuous chromatography, or replacing batch acidification for viral inactivation with a continuous reactor. Menezes sees the following as the top challenges to integrated control:

- Operations stability over long periods of time
- The integration of upstream and downstream processes with very different unit operations, in terms of dynamics and duration
- Insufficient data aggregation capabilities and a dearth of IT platforms that can extract information automatically to support effective decisions and control actions
- Insufficient end-to-end lifecycle risk and knowledge management
- Limited ability to provide regulatory reviewers and inspectors with evidence and rationale for risk-based change management.

Menezes predicts that plant modularization and new designs will be a major driver in reshaping the industry, and process control, for the next decade.

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