ELECTRONICALLY REPRINTED FROM MARCH 2017
INTERNATIONAL BioPharm
The Science & Business of Biopharmaceuticals

Automating Bioprocesses

Automation of stainless-steel systems and single-use systems differs in complexity.

Both upstream and downstream biopharmaceutical processes have conventionally used stainless-steel equipment, but use of single-use systems (SUS) is becoming more established. An advantage of SUS is its flexibility—modular, disposable components have a lower up-front cost compared to conventional equipment, and the systems can be more easily replicated for installation in different locations to facilitate "in-country" production. One of the most significant differences is that SUS do not require the clean-in-place (CIP) and sterilize-in-place (SIP) systems employed in stainless-steel equipment systems, which saves initial capital costs and the ongoing production time associated with cleaning and sterilization. The process control and automation requirements of SUS also differ from those of stainless-steel equipment. *BioPharm International* spoke with Michalle Adkins, director of Life Sciences Consulting, and Bill Smizaski, vice-president of Global Life Sciences Operations, both at Emerson, about considerations for process control and automation of biopharmaceutical processes.

AUTOMATING SUS

BioPharm: What are the primary differences between automating a single-use system compared to a system that uses stainless-steel equipment?

Emerson: The complexity of automation is less for SUS because fixed, stainless-steel tanks require CIP/SIP, which increases the complexity of piping and instrumentation. In fact, 60–80% of instrumentation in a typical bioprocessing unit operation is associated with CIP/SIP, not the process itself.

Although automation of a SUS process is simpler, SUS do require more manual interaction. For example, tubing needs to be connected and operators must make sure that nothing leaks. All parts that come into contact with the product need to be tracked, including disposable parts and reusable parts (e.g., peristatic pumps). Tracking SUS parts is also more complex. These disposable parts may be irradiated by the vendor. For example, tubing sets typically are supplied gamma-irradiated by a third party, and sensors are typically precalibrated and gamma irradiated. All this additional information needs to be part of the batch record. Maintaining data integrity and traceability becomes more complex.

> "Not integrating individual skids ... presents challenges with alarm management, user security access management, and disparate operator interfaces."
> —*Emerson*

Another difference is in the sensors used to collect data and control the process. SUS employ either disposable or non-product contact instruments for measuring process control variables, such as conductivity, pH, and dissolved oxygen level. With traditional systems, sensors were designed to be highly accurate, long-lasting devices. In SUS, these sensors would be too expensive, because the sensor only needs to

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last for one batch. Disposable sensors are available today that are less expensive, but in some cases, are not accurate or reliable enough. Although advances have been made, there is room for improvement. To get the reliability and accuracy needed for certain processes, some manufacturers are choosing to use traditional sensors inserted into the process in a plastic, sterile sleeve; these sensors are sterilized for reuse. A new approach is completely non-contact—measurements are taken through the plastic container rather than inserting a probe into the product.

BioPharm: How can single-use material data be tracked?

Emerson: Material tracking and linking material information to a batch record is part of 'Level 3' of the ISA 95 model, which includes the definition of manufacturing operations management (MOM) applications. Manufacturing execution systems (MES) that implement MOM can be designed to track both process material consumption and generation as well as single-use (e.g., tubing, instruments) and reusable components consumption for material traceability purposes.

BioPharm: What are some considerations for automating the process as a whole rather than only at each unit operation?

Emerson: Companies can purchase an SUS skid with automation from the original equipment manufacturer and leave the individual skids as 'islands of automation.' Others are integrating all the skids throughout the plant using a distributed control system (DCS), while others are using a hybrid of these approaches. There are very few standards yet in bioprocessing, although over time, various options will likely consolidate and evolve into standards.

The integrated DCS approach has the advantages of providing overall recipe management and putting all the data collected in to production context at the factory level. Not integrating the individual skids leaves the production execution management and data collection isolated and not in the context of a recipe as well as presenting challenges with alarm management, user security access management, and disparate operator interfaces.

FUTURE TRENDS

BioPharm: What are some of the challenges with automating a continuous biopharmaceutical process compared to a batch process?

Emerson: We are starting to see the move to continuous manufacturing in bioprocessing, although it is in its infancy compared to continuous manufacturing of small-molecule drug products. There are several licensed products that use a continuous perfusion process upstream, but downstream continuous processing is still evolving. The control strategy and automation are important in continuous manufacturing. The keys to successful continuous manufacturing include synchronizing unit operations into one process, defining the process in such a way to quickly achieve steady state, and managing disruptions to the process automatically. In addition, good process analytical technology (PAT) and 'soft sensors' (i.e., predicting values based on modelling) are important to ensure product quality. It is important to understand how disturbances affect the process and the product including how residence time would be used to track materials during a change or upset in the process. The industry is still at an early stage, but companies are beginning to do multivariate modeling and gaining the processing knowledge needed for effective continuous manufacturing.

BioPharm: How will the Internet of Things (IoT) enhance automation?

Emerson: There are a couple components to IoT that are interesting for this industry. 'Smart' instrumentation has been around for some time, but it has not been pervasive in this industry. However, new data integrity requirements are starting a cultural change to use more of the data available from these devices. For example, a smart instrument measures not only the process variable it is designed to measure, but it tracks and records factors such as drift and vibration that can be used to look at the health of the device in real time. The IoT, as a concept, is a technology enabler to this change by making it easier to target the right information to the right user application. A device with a drift that would have a particular alarm meant for maintenance but not the operator, for example, will be sent to the appropriate person to take action.

We are also seeing a greater focus in the pharma industry on reliability initiatives. Smart devices connected to equipment and automation, for either stainless-steel systems or SUS, will give an early warning and facilitate an intervention before a deviation or out-of-specification condition occurs.

The IoT could also help enable continuous process verification (CPV) across the supply chain. Companies have been moving towards CPV rather than annual product reviews. Requirements are emerging, particularly for biopharmaceuticals, to provide CPV across all manufacturing locations for a product both internally and externally (e.g., at a CMO). ◆