From Data to Control: Process Analytics in Upstream Bioprocess Development

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To say that developing biologics is a complex undertaking is the height of understatement. That's why it's so important that labs establish a 360-degree view on the development process from its earliest stages through manufacturing. Yet doing so requires making sense of massive amounts of data—and that, in turn, requires deploying sophisticated analytical tools that transform raw information into knowledge that permits sharper control of upstream bioprocesses.

Jörg Schwinde, key segment manager for vaccines and monoclonal antibodies at the Eppendorf Bioprocess Center, is no stranger to these challenges, and he shared with *BioPharm International* his view of which strategies will help labs best optimize upstream bioprocess analytics both now and in the future. His key takeaway: Only with a thorough understanding of processes can labs improve finished-product quality, while also streamlining process efficiency.

BIOPHARM INTERNATIONAL: Upstream bioprocess development is an integral part of the development of new biologics. What are today's main process-development challenges? How have they changed in recent years?
SCHWINDE: The main challenges are time, cost and safety. Biologics process development aims to create a product that will be used in medical treatments. Therefore, it's very important to get as much information as possible about the process—and in the early stages of development. Among the key tools in this area is process analytical technology (PAT), which provides critical support in subsequent stages, including manufacturing.

What has changed in the past few years is the success of "platform technologies," which contribute to improving the time and cost aspects. For example, cultivation media components that have already been prepared can be put together without the need to search for a newly composed one for a given strain or cell line. This dramatically shortens process development timelines.

BIOPHARM INTERNATIONAL: Besides pH, temperature, and dissolved oxygen, what relevant parameters are important to consider in antibody upstream bioprocess development, and why?
SCHWINDE: First, there's the behavior of a strain or cell line—for example, the determination of the growth kinetics, the ratio between total cell density and viable cell density and the productivity of the cells. Additional parameters include the characterization of substrate consumption and the metabolic state.

Furthermore, the product needs to be characterized: Is it the target one? Are there undesirable byproducts that can significantly affect

product quality? Monitoring all of this is quite a complex task.

BIOPHARM INTERNATIONAL: When it comes to the most relevant process parameters, do we see major differences between processes for monoclonal antibody production and processes for other biologics, like vaccines, enzymes and hormones?
SCHWINDE: When the focus is a protein or protein subunit, the processes appear quite similar. There may be some different safety requirements for the process—as in vaccine development, where pathogens or inactive pathogen components can be used.

But where we see more notable differences is in the techniques for developing messenger RNA, DNA and vector vaccines. Here, parts of the processes are even cell-free, so traditional parameters—for example, oxygen control—don't have to be considered.

BIOPHARM INTERNATIONAL: What strategies is industry applying to monitor and control relevant process parameters?
SCHWINDE: The monitoring of parameters can be offline, as with external analyzers in combination with sampling devices. This sampling can be automated, but the challenges here include the additional manual workload and the absence of automated feedback loops.

Automated feedback loops are possible through online analyzers, which provide almost real-time data and spare sampling steps. They're installed at the bioreactors, which are dedicated to cell culture, or at the fermenters, which are dedicated to microbes, and they're an integral part of the reactor setup.

Then at least two more components are necessary—namely, bioreactor- or fermenter-control software, which receives the sensor signals and controls the acting units inside the process-control system. This may be a pump or an aeration unit, to mention just two examples. And the challenge here is to have sufficient ports available at the bioreactor or fermenter. This is most often the case with smaller-sized units in the range of 50 milliliters and 1,500 milliliters in terms of working volumes.

In any case, to reduce the workload, speed up the process and more, the online solution with the option for automated feedback control is very attractive.

BIOPHARM INTERNATIONAL: When integrating external analyzers and implementing feedback control loops, what are the considerations for working at different scales from R&D to production?
SCHWINDE: It's desirable to have a process already characterized such that production doesn't need those analyses to that extent—pH, temperature or oxygen control aside. Apart from this, the different working volumes can affect the response time for control. But in principle, the feedback control loops work similarly.

BIOPHARM INTERNATIONAL: Eventually, bioengineers need to monitor and control various process parameters using external analyzers. What challenges does this pose to bioprocess control systems, and which bioprocess hardware and software capabilities are especially important?
SCHWINDE: We already touched on some aspects around external analyzers, but in addition to that, it's important to ensure communication between the control software and the analyzer hardware.

Analog and digital options are available, and the latter can be understood as a signal transfer through bits and bytes. One communication standard in this frame is what's known as open-platform communication, abbreviated OPC, and which typically works via Ethernet.

Between the software and hardware there's a kind of "sending-and-receiving" relationship defined as the server-client relationship.

BIOPHARM INTERNATIONAL: In your opinion, which developments in data acquisition, analytics and process automation will become more important in upstream bioprocessing in the coming years?
SCHWINDE: While we've mentioned quite a few in our conversation so far, acquisition, analytics, and automation will get faster, even more precise, and more powerful. This will be supported by predictive analyses (i.e., design-of-experiment approaches) and by artificial intelligence.

And those options provide tremendous opportunities to simulate processes ahead of time and predict where challenges lie and how to bypass them successfully—all of which contributes to time, cost savings and safety.