BioProcess Insight

Reducing risk in continuous downstream bioprocessing:

3 innovations process engineers can use today

Introduction

As the biopharmaceutical industry moves toward more efficient and flexible manufacturing models, continuous bioprocessing is gaining traction. While continuous upstream processes, such as perfusion, are becoming more common, downstream operations often remain batch-based due to technical, regulatory, and quality challenges. For process engineers, process development scientists, and MSAT professionals, how can risk be reduced while reaping the benefits of continuous downstream bioprocessing?

Understanding the risk landscape

Transitioning from batch to continuous downstream operations introduces new complexities. Unlike traditional processes with clearly defined start and stop points, continuous systems operate for extended, uninterrupted durations, often 30 to 90 days. This shift changes the concept of a "batch," challenging existing regulatory frameworks that rely on discrete lot definitions for testing and release.

In addition, the downstream portion of the process must handle continuous feed streams from upstream without compromising product quality or process stability. Key risk areas include:

System complexity: Continuous downstream setups integrate multiple purification steps and often require parallel systems for reliability, increasing both capital and operational costs.

Buffer logistics: Extended operations demand large volumes of buffer produced in discrete lots—raising concerns around consistency and storage capacity.

Contamination control: Maintaining a closed, sterile system over long production periods is critical yet difficult, requiring advanced containment and monitoring.

Real-time quality monitoring and control strategies: Without robust analytics, process deviations can persist undetected, risking off-specification product and regulatory noncompliance.

Technological and operations solutions

To reduce these risks, leading manufacturers are implementing targeted innovations and strategic process designs that enhance control and robustness.

1 Advanced analytical and control systems

Integrating real-time analytical tools such as Raman spectroscopy allows inline visibility into process parameters, including concentration and, in some applications, pH. These tools may also support real-time release testing (RTRT) strategies. When used alongside automated control systems, live process data can inform adjustments to operating conditions, supporting tighter process control and reducing possible downtime due to manual intervention.

2 Smarter buffer management

To address storage and operational variability concerns, some facilities are adopting an alternative approach utilizing concentrated buffer stock solutions. These can be diluted in-line or on-demand, minimizing storage volume and ensuring uniformity across long campaigns. Producing and storing buffers from a single lot also simplifies documentation and helps maintain consistency needed for regulatory expectations.

3 Flexible, single-use systems

Single-use technologies are becoming central to de-risking continuous downstream processing. They reduce cleaning and sterilization requirements, accelerate changeover between campaigns, and lower contamination risk. For multi-product facilities or early-stage process development, single-use systems also decrease capital investment and enable modular scalability, allowing teams to adapt quickly as production demands evolve.

Proactive collaboration

Cross-functional collaboration among MSAT, QA, and regulatory teams is essential. Risk mitigation should go beyond equipment and process controls to include data integrity, deviation management, and knowledge transfer between development and manufacturing teams. By applying Quality by Design (QbD) principles, manufacturers can proactively identify critical process parameters and define control limits that support consistent, high-quality output.

A path forward

Continuous downstream bioprocessing is emerging as a more practical and evolving approach, supported by its potential benefits in efficiency, flexibility, and cost. Yet, its success hinges on risk reduction strategies grounded in real-time process intelligence, modular design, and regulatory alignment.

By integrating advanced analytics, adopting flexible single-use systems, and redefining control strategies for long-duration operation, bioprocessing professionals can transform potential risks into opportunities for innovation. Those who master this balance could be better positioned to deliver consistent, high-quality biotherapeutics faster and more efficiently than ever before.

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