

# Increased Productivity and Seamless Scalability

## Advantages of an ATF System for Upstream Process Intensification

with Muhammad Shamim

**M**ost upstream processes use either batch or fed-batch methods because they are established techniques that have been validated over time. “People are hesitant to change because they feel the new intensified processes to be more complex and difficult,” said Muhammad Shamim (field application scientist from Repligen) in a December 2023 BPI webinar. However, batch and fed-batch methods have the disadvantage of fixed yields in finite culture durations. Shamim presented alternating tangential flow (ATF) and tangential-flow depth filtration (TFDF) systems for upstream process intensification. Such systems are designed to generate comparatively higher yields from longer processes.

### SHAMIM'S PRESENTATION

Although improved batch-mode technologies can bring some productivity gains, a fully intensified cell-culture process is needed for maximum output, and continuous capture is necessary to optimize product yield. Shamim introduced the XCell ATF and KrosFlo TFDF systems from Repligen. Both systems can be used to intensify upstream processes for diverse modalities. The KrosFlo TFDF system also harvests and clarifies challenging cultures.

**Case Study:** Shamim presented examples of successful intensification projects involving Repligen and several contract manufacturing organizations (CMOs) from around the globe. For instance, WuXi Biologics used the XCell ATF systems for long-duration dynamic perfusion runs. Dynamic perfusion simplifies process control because it does not require a cell bleed. It also helps in understanding cell-line and culture limitations, resulting in higher

viable cell densities (VCDs). Some facilities prefer this method because it can fit easily into their operations and existing infrastructure. In this example, WuXi increased VCD by >5%, cell-specific productivity by 10×, and total product yield by 10-20×.

**ATF Technology:** ATF devices from Repligen are linearly scalable and can accommodate processes from 0.5–1,000 L. The systems come in both stainless-steel and single-use formats, which are shipped as fully assembled and sterilized units. Repligen provides single-use tubing and accessories, which help in simplifying preparation, facilitate proper exchange of cell-culture material between the bioreactor and ATF device, and harvest target cells or molecules.

Shamim also introduced Repligen's newest large-scale controller. It can operate two XCell ATF devices simultaneously. It also has advanced process monitoring capabilities based on flow-sensor-based controls using intuitive software, which is compliant with 21 CFR Part 11. The new controller was tested in challenging process conditions, including high-viscosity cultures with high pressure settings in tall bioreactors. With the new controller, ATF processes performed consistently in both single- and dual-mode operations.

Intensification can provide significant productivity benefits over traditional methods across multiple applications. It can be applied at multiple upstream steps to achieve higher VCDs and productivity. The XCell ATF system is designed to simplify intensified upstream manufacturing processes.

### QUESTIONS AND ANSWERS

**Can you explain how to move from process-development to production scale?**

We have scalable ATF devices for

that purpose. You should keep a few key parameters in mind when thinking about scaling up or down. Some equipment and culture parameters remain constant when scaling up, such as consistency of filtration capacity, backflush efficiency, shear rate, residence time, and flux.

**What is the difference between concentrated fed-batch and perfusion?**

Perfusion is a continuous harvest technique where batches are determined by downstream processes. Concentrated fed-batch is a shorter perfusion run in which the product and cells are retained inside the bioreactor and harvest is completed as a single action at the run's end.

**How does the XCell ATF system maintain consistent performance in challenging culture conditions?**

It uses a flow sensor on the A2B (ATF to Bioreactor) line to maintain and optimize flow, depending on culture-fluid viscosity levels. The ATF controller increases or decreases the pressure as needed based on feedback provided by the flow sensor on the A2B line.

**How does the pressure sensor reduce fouling risk?**

We use a sensor on the ATF device to monitor pressures over time and understand how they occur. Within the permeate sensor port on the ATF device, we measure the pressure drop or the vacuum pull. When fouling is detected, a concentrated layer is built up within the device itself, and the pressure drops. We can minimize the pressure drop itself or the fouling of the filter.

*Learn more about the XCell ATF and KrosFlo TFDF systems online at <https://www.repligen.com/products/upstream-filtration/xcell-atf/xcell-atf-technology> and <https://www.repligen.com/products/upstream-filtration/krosflo-tfdf>.*

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