

# Introducing a Multitiered Classification System for Downstream Process Intensification

with Martin Lobedann

**P**rocess intensification (PI) provides a holistic framework to maximize the overall productivity of unit operations, manufacturing processes, or complete facilities. In a recent BPI Ask the Expert webinar, Martin Lobedann, PhD (process technology manager at Sartorius) described how PI reduces cost of goods (CoG), whether applied stepwise or in an end-to-end process. It can be driven by targets relating to the use or chemistry of consumables, cycling strategies, durations of unit operations, batch definitions, and levels of process integration (e.g., upstream processing batch or perfusion mode). Orchestration can interlink standalone systems to construct connected or continuous processes by optimizing tank levels and liquid flows towards periodic and steady state behavior, respectively.

## LOBEDANN'S PRESENTATION

Lobedann defined five levels of downstream PI. **Level Zero** describes standard standalone unit (batch) operations such as single-column chromatography with a pool tank before and after the unit. **Level One** involves increased productivity and improved automation at the unit level. **Level Two** refers to a connected process of two or more unit operations, either standard or intensified, running simultaneously. The output of the first unit is immediately processed by the second in a cyclic manner. **Level Three** denotes a continuous process of multiple unit operations, totally integrated and with steady flow between them. Only small intermediate tanks are needed. Software is required to orchestrate process steps. Such an operation entails long run times and

closed processing. A further increase in PI is **Level 3.1**, a complete, steady-state flow between unit operations, enabled by replacing bind-and-elute steps with flowthrough steps.

**Chromatography:** Most discussions about PI begin with chromatography operations, which are the most expensive and time-consuming steps in drug manufacturing. CoG can be reduced by integrating multiple unit operations, reducing a company's footprint by enabling simultaneous unit operations and requiring fewer systems overall.

In a case study of an intensified chromatography operation, the Sartorius Resolute rapid-cycling chromatography (RCC) membrane chromatography supported Level One batch purification, and the Resolute BioSMB assembly was used for Level One multicolumn chromatography. Level Two was supported by the Resolute BioSC assembly for connected downstream processing including multicolumn chromatography. Lobedann explained the differences between mass transport for chromatography media (diffusion-limited) and membranes (convective-driven). Resins can be used across multiple batches, whereas membranes can be used as single-use or single batch-use consumables.

Sartorius now offers a resin-free chromatography solution based on membrane adsorbers bearing immobilized protein A. For the bind-and-elute step, the company offers RCC to reduce membrane volume and support the lifetime capacity use, reducing CoG and increasing productivity. It requires less preparation with no packing or column

requalification after storage. It supports quality control and improves stability, which lessens risks during column storage. Lobedann described how the convective membrane's small diffusion layer on the surface creates a high binding capacity. He outlined two options for RCC processing: increase membrane volume and flow rates to reduce processing time at nearly constant costs, or reduce membrane volume and flow rate to minimize costs at the same time frame.

In addition to membrane chromatography systems, Sartorius offers multicolumn chromatography systems. BioSMB systems are multicolumn units that are available in three scales. They feature high resin utilization, reducing the CoG and providing a three- to five-fold increase in productivity. Lobedann's slides detailed examples of resin loading and benefits from efficiency gains.

He concluded by describing the BioSC unit for supporting Level Two PI, which the unit connects multiple unit operations into a senior system. It can be configured for either batch or multicolumn modes, or a combination of both modes. The system supports three chromatographic steps and up to six columns.

## QUESTIONS AND ANSWERS

**Has PI been implemented successfully in downstream operations?** PI has been successfully implemented in downstream operations due to its compatibility with perfusion.

**What would be the capture column solution for Level 3.1?** Because of the difficulty in capturing at this level, Lobedann recommends filtration steps to remove impurities from the product.

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