(Re)Defining Process Intensification

Sartorius shares its vision for better, faster, and cheaper bioprocessing

What is process intensification (PI)? There's currently no straight answer. But, in this roundtable, three of the company's finest lead us through Sartorius' bold mission to define, refine, and deliver PI to biopharma manufacturers across the globe.

Why has PI become such a hot topic for biopharma in recent years?

Martin Lobedann: Increasing cost pressures, diversification of product portfolios, and an expanding number of molecules in the pipeline have pushed PI to the fore. Every player needs fast and safe changeovers, high efficiency, and, of course, low product costs. PI can help by producing more molecules with a smaller facility footprint and lower demand in utilities.

Why do definitions of PI vary?

ML: There is little consensus on PI's definition. According to the very general definition, it's all about getting more by doing less. But diversities in methods and steps mean that every vendor handles PI differently, and thus we have no common understanding. At Sartorius, we're trying to define a new general and applicable standard for PI.

What does process intensification mean to Sartorius?

ML: Quite simply, PI provides companies with a framework to increase productivity and reduce costs. At Sartorius, we use a four-tier system to help define how well PI is integrated into a business. From no PI at all to completely continuous systems, we can accurately define PI integration at all levels.

JB: That's right. Our tiers help shed light on the use of PI within businesses. Level 0 is, per definition, our base case for reference without intensification. Level 1 then includes consumable intensification (RCC, high binding capacities), together with stand-alone system intensification (ILD; ILC; MCC), or combinations thereof. Level 2 would be a connected process of (Level 0 and/or Level 1 intensified) multi-step systems. Finally, level 3 would comprise continuous processes.

ML: To offer more details; level 1 PI features some intensification, but within a standalone unit operation – and with an increase in individual step productivity. An example of a Level 1 process intensification system would be a multi-column chromatography (MCC) solution, such as BioSMB. Even at Level 1, we already see a huge leap forward in volumetric productivity or space-time yield.

Level 2 PI describes connected processes. Here, process steps are connected in a physical manner, and subsequent steps start before the previous one has finished – in other words, they are all active simultaneously. The steps can be both level 0 or level 1 intensified. However, there is still no steady state in the flow through the unit operations. At this level, we recommend self-orchestration, but manual orchestration does remain on the table.

Level 3 PI is a true continuous process with a steady state flow between all active unit operations in an end-to-end process. Thanks to that steady state, only small intermediate elements are necessary. To keep the fill level constant, sophisticated software orchestration is needed to guarantee a steady state flow through all unit operations. At Level 3, residence times become predictable, and uniform characters and distributions are achieved. At this level, we also see long run times – at least three days for downstream purification and closed processing.

KR: Sartorius is also considering intensified control strategies when designing automation for intensified systems – in other words, we will set up our systems using a standard configuration with parameters that can be monitored and controlled from a supervisory control platform.

What factors and technologies can help drive PI?

ML: From a technical point of view, PI is driven by combining or connecting several unit operations. The correct orchestration software must then be put in place to monitor and control every unit. Here, data analytics is key to keeping the process robust and catching deviations.

An open mindset also helps. Though PI is a powerful tool, it can't work effectively without support from technical and management teams. Though these people often have many responsibilities to juggle, taking the time to understand how PI can lead to business improvements is important. Some may be hesitant to embrace the technology – PI can be costly after all – but the investment is sure to pay off.

JB: I'd add that, before embarking on any PI journey, the managers and technical teams need to ascertain and understand the parameters of the process. Here, a software platform is key to simulating, identifying, and facilitating process intensification. It will also be crucial for controlling and analyzing the product quality in real time.

The pharmaceutical industry is relatively conservative in its adoption of new technologies, thus these companies need support in any decision they make. For instance, to switch from batch to multi-column processing will require a shift in mindset, and so a simulation tool that can highlight the main impacts and changes on the current process will help inform that decision.

Why do monoclonal antibodies lead the game when it comes to biopharma PI?

JB: mAbs have been the leading therapeutic for decades, and thus mAb manufacturers are experts in developing and defining mAb processes – and that opens the door for PI to remove and improve any remaining suboptimal operations.

ML: As Jean-Luc says, it's because the platform processes are already available. But beyond this, the knowledge gained on mAb PI can easily be transferred to other modalities, such as viral vectors or cell therapy. We can also focus on fine tuning our existing processes, and identifying synergies across a whole field of molecule types.

Which other therapeutic modalities could benefit most?

JB: All therapeutic modalities could, in theory, benefit from PI. New as-yet unoptimized therapeutic modalities, such as mRNA and gene therapies, would be obvious candidates. The mAbs process is well defined by existing customer and process templates. But for new modalities, no such robust templates exist. This, combined with the sheer volume of demand means that process intensification could be the right approach for new modalities.

ML: As Jean-Luc says, many modalities stand to gain from PI – but it may take more time to see the benefits. As soon as a robust platform template exists, a PI effort can be enrolled. It could be envisioned to transition to higher PI levels very quickly due to the gained knowledge from mAbs. In all cases, data analysis and automation could improve process orchestration, chromatographic media, and membrane utilization

Karl Rogler: PI can help reduce companies' footprints, lower buffer consumption, and increase consumable utilization. These benefits can be seen across a spectrum of therapeutic modalities, but companies will have to invest time and resources into understanding the specific requirements of each drug type they produce before reaping these rewards. By measuring customers' adoption and transition rates, it's possible to evaluate which tools are suitable for the requirements of other modalities, such as vaccines or gene therapies.

Where does PI need further development?

ML: We need to put more effort into the orchestration of the multiple unit operations if we are to supply a fully automated downstream chain at PI Level 3. A new system must be developed to enable continuous unit operations that will then maintain a steady state flow throughout the whole process. Here, sophisticated software is under development – as is work to plug the gaps at the unit operation level. Sartorius is working actively – using customer feedback and internal knowledge – to ascertain which gaps are the most important right now, and how they should be closed.

JB: As Martin says, to maximize the potential of Sartorius' PI strategy, we need to ensure that the software platform can support our customers in predicting, running, and analyzing any unit operation in their process intensified suite. Our Biobrain control software platform should ultimately fill the gap. There is also some alignment needed around the equipment platform to improve integration.

What is the one thing about PI that everyone should know?

KR: For me, process intensification is the bioprocessing term for "lean manufacturing." It is about reducing waste in a production process. There are many types of waste in bioprocessing from inventory to excess capacity – and depending on one's process, different strategies can be used to make the process more efficient.

ML: Everyone should know that process intensification makes life easier and can be implemented stepwise; for example, starting with automated buffer preparation and multi-column chromatography. It can then be extended to a level two or level three integrated process. An open mind may be the most important aspect – from both a technical perspective and in management.

JB: Lots of process industries – including the automotive, electronic, and food and beverage industries – have switched from batch to continuous processing to manufacture more at a lower cost without jeopardizing quality, while increasing their agility in adapting to changes in demand. Biotechnology and biopharma should be next.

Interviewees

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