Enabling Broader Adoption of Process Intensification in Biopharma

July 9, 2021 | by Ganesh Kumar

The benefits of process intensification (PI) in biopharmaceutical manufacturing are well established: PI enables manufacturers to increase volumetric productivity, reduce timelines, decrease facility footprint, lower costs, or improve flexibility. However, knowledge about PI implementation — from the costs to the technological and regulatory aspects, and risk mitigation — is less ubiquitous.

PI means different things to different organizations, depending on the manufacturer's goals and the drug modality. One of the most common misconceptions about PI is that implementation always applies to the entire manufacturing platform, which would involve a semi-continuous flow from upstream to drug substance. But no set pathway exists.

As is commonly observed, a stepwise approach helps build confidence and familiarize the manufacturer with PI, allowing them to equip for a more platform-level intensification in the future. Numerous manufacturers around the globe are implementing PI strategies based on data-supported business- and process-improvement decisions.

Successful intensification implementation has become routine, quashing another common PI misconception: the fear of being a "test bed" versus being an early adopter. Manufacturers and many solution providers are gaining substantial experience in navigating implementation challenges, whether the manufacturer wants to adopt a stepwise approach or an end-to-end implementation of PI. Guidance in selecting and developing the right intensification strategy, as well as implementation and regulatory process assistance, are no longer difficult to secure.

Decision-Making Tools Guide Effective Process Intensification Strategy Evaluation

Implementation cost versus return on investment (RoI) represents another less-understood aspect of PI. In determining both up-front costs and total cost of ownership, value chain services that comprise process mapping, economic modeling, and conceptual design tools can empower manufacturers to make a more informed decision in selecting the right PI strategy for their process(es).

"The key challenge is that there is no single massive step-change that brings cost reduction if you are just looking at the prices. You need to consider where you can get the best benefit in terms of investment," explains Andrew Sinclair, President and Founder at Biopharm Services, a pioneer in developing process and economic modeling tools for the biopharma sector.

Manufacturers looking to evaluate process intensification that achieves productivity gains and cost savings in an existing facility or process commonly adopt a high-inoculum fed-batch process which involves operating the N-1 step in a perfusion mode and inoculating the production bioreactor at a higher viable cell density. Using this strategy, manufacturers can increase productivity up to 1.6 times and decrease the associated cost of goods (CoGs) by up to 50%.

Another current trend is manufacturers seeking long-term perfusion approaches in upstream production bioreactors. Over the next decade, a significant number of non-mAb modalities — high potency, low-dosage products — are primed to enter the market. These products generally require low throughput (e.g., up to 300kg/year) to manufacture, making perfusion approaches more attractive as manufacturers can drastically reduce facility footprint, capital expenditure (CAPEX), and operating expenses (OPEX) — allowing them to scale-out/up and enter new markets more swiftly.

For manufacturers seeking strategies applicable to high-throughput production of blockbuster therapies (typically >1000kg/year), adopting a concentrated fed-batch-based intensified process enables them to switch from legacy stainless steel (SS) manufacturing facilities to single-use (SU) facilities. With this approach, manufacturers can significantly lower their facility CAPEX and footprint in USP compared to SS facilities, and achieve almost 3-4 times the productivity compared to standard SU fed-batch approaches.

In any scenario, interaction with solution providers at an early stage is paramount; it provides both the customer and the solution provider data to determine if and where PI implementation makes the most sense.

Proper Timing Eases Implementation

When intensification alters a process, it must be validated again. Consequently, manufacturers should aim to implement PI changes at a stage that minimizes regulatory hurdles.

"Experts agree that manufacturers considering process intensification for new products should implement it as early as possible in the molecule life cycle — ideally during or before phase 1 clinical trials,"

Kurt Brorson, Ph.D.
VP, Technical at Parexel

A manufacturer in the discovery, toxicology, or even a preclinical phase, is in the "sweet spot," the ideal time to evaluate intensification, to compare results — in terms of product attributes and quality — to a baseline reference, whether it is batch data or the information comes from another process.

Early-stage intensification evaluation helps the manufacturer build a framework: an idea of the work packages, deliverables, and the interactions they may need to have with regulators to implement such a change during the preclinical or clinical phase (or even the commercial phase). As noted above, the earlier a manufacturer is in product and process development, the less impactful hurdles like the required effort, costs, process validation, and timeline impact are likely to be.

High-Throughput Scaled-Down Tools Drive Efficient Development and Scale-Up

Process development inherently offers an opportunity to characterize and optimize a process. The following elements enable manufacturers to efficiently develop and scale up an intensified process that would include a (high-titer) cell line, clone selection/optimization, media, and process characterization:

1. The manufacturer should leverage high-throughput representative scaled-down tools that mimic the process on a production scale as closely as possible.

2. The scaled-down tools should be intensification-ready. If this is not the case, one must spend significant time and cost in retrofitting or building custom equipment to accommodate intensification approaches. For example, performing scaled-down experiments with intensified-ready, multi-parallel bioreactor systems such as ambr® perfusion can help to accelerate the manufacturer's decision-making process in choosing the right PI strategy.

3. Integration of the high-throughput scaled-down tools with in-line/at-line process analytical technologies (PAT) and multivariate data analysis (MVDA) tools for an efficient Design of experiments (DoE).

With the elements outlined above, manufacturers can not only select and develop the right PI strategy but also significantly reduce costs, de-risk projects, improve success rates, meet requirements for Quality by Design (QbD), and accelerate time to Investigational New Drug (IND) approval by ~2 months during the process.

Process Automation Enhances Control Over Critical Process Parameters

Automation, meanwhile, can depend on the type of manufacturer. A large pharma company might have a different set of automation requirements for its manufacturing network in general — more advanced concepts like virtual twins, electronic batch records, or having a "facility of the future" — leading to different intensification integration requirements. A small or medium-sized company may still be getting used to single-use processes, which involve a lot of manual interaction and are not conducive to a high level of automation.

Again, a stepwise approach that initially addresses specific pain points is the most logical, and intensification-ready tools are vital. An intensified process requires adequate process analytical technologies to measure the critical process parameters (CPPs) — including, but not limited to, cell density, dissolved oxygen (dO_2), titer, etc. — in real time, combined with process automation with integrated data analytics-based approaches that can then enable real-time prediction and control down to the individual unit operations.

Early Collaboration Drives Efficient Implementation

PI is becoming increasingly well-understood, and its utility is continuously evolving to meet specific manufacturer needs, driving its popularity and opening new applications. Not all processes require end-to-end intensification that would result in a semi-continuous process/continuous process. Proper decision-making tools can aid manufacturers in determining a viable intensification strategy — applied to either existing or new processes/facilities — based on factors including facility type, molecule, cost, flexibility, productivity, timeline, and drug demand/output.

Total solution providers understand the challenges associated with each manufacturer's unique intensification pathway, from PD to manufacturing, whether approached stepwise or end-to-end. Through its experience and know-how in implementation of PI gained by working with pioneering manufacturers, Sartorius offers solutions and services that guide its partners in selecting and implementing an optimal intensification strategy.

To learn more about how Sartorius can help in your intensification journey, please visit:
www.sartorius.com/en/applications/biopharmaceutical-manufacturing/process-intensification.

About the Author

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As part of the Protein-Based Therapies team at Sartorius, Ganesh collaborates with clients and business areas on process positioning, building the technical platform, and solution packages for process intensification. He has over eight years' experience in the biopharmaceutical industry, both as an end-user and a solution provider. He is based in Göttingen, Germany.

Ganesh started his career at Lonza, Singapore, where he was actively involved in the tech transfer, validation, and large-scale commercial manufacturing of blockbuster mAbs. Ganesh joined Sartorius in 2016 as a Process Engineer | Consultant and was one of the key contributors to the development of the P4S® conceptual design platform.

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The Sartorius Group is a leading international partner of the biopharmaceutical industry and the research sector. We help biotech scientists and engineers across the entire globe to develop and manufacture medications from the initial idea to production.

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- Benefits of Process Intensification: Key Considerations and Expert Insights
- Process Intensification: Understanding the Optimal Way to Maximize Productivity
- Adapting Bioprocessing to Meet the World's Changing Demands

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