Process Intensification: Getting More From Less

Intensifying or simplifying your bioprocess can mean more product, shorter manufacturing times, or lower costs – understanding what matters most is key to making the right decisions.

By Serena Fries Smith

It's no secret that the biopharmaceutical industry is under intense pressure to reduce costs – especially in manufacturing – and getting more output from a given process is a clear win. Process intensification does just that. It can take an existing process and optimize it to increase output: more product in a shorter time, with fewer steps, and from a smaller working footprint. Process simplification, on the other hand, focuses on streamlining activities to increase efficiencies.

Which option is best: intensification or simplification? It ultimately depends on the type of molecule you're making, the current manufacturing challenges and bottlenecks you're facing, and the stage of development your product is in. Process changes can occur at any stage during development, even post-launch, and the better characterized your existing process and product are, the easier it will be to evaluate the impact to the critical quality attributes of your product and implement changes (1).

Evaluating impact

During early-stage development, there's usually pressure to quickly identify a first-generation process and get the molecule into the clinic as quickly as possible. After this point, there is typically time to consider where opportunities for process intensification and simplification exist. These pre-launch changes are driven by commercial requirements – can I effectively and efficiently manufacture enough material to meet patient demand? And manufacturing needs – is this process robust enough to run consistently for the lifetime of the product?

During late-stage development, there may be pressure to minimize changes and focus on finalizing the commercial process to prepare for launch. But while late-stage and post-launch process changes can be more difficult to implement, they should still be considered when there are opportunities to reduce risk of manufacturing failures, increase throughput, and improve the consistency of the product and process. Regardless of where you are in the lifecycle of your molecule, there will be no shortage of potential opportunities for improvement. The key is determining which ones to pursue:

- Should I streamline?
  To streamline a process is to reduce unnecessary steps or operations. Focusing on these areas of improvement could reduce processing time and the risk of manufacturing and contamination failures. One common area that can usually be streamlined is cell expansion. It may be possible to reduce the number of expansion steps in the process, or reduce the amount of aseptic manipulations required during cell expansion. Another area to consider would be release testing. With current advancements in analytics, it is possible to replace cell-based assays, which take weeks, with significantly shorter assays.

- How do I intensify?
  Process intensification enables you to get more out of your process. For an upstream process, you could consider transitioning from fed-batch to perfusion, or implementing a hybrid, high cell density process enabling you to increase the amount of protein produced without increasing batch size or processing time. For a downstream process, you could optimize chromatography resins to improve cycle times and increase yields. All of these changes would result in an increase in material throughput.

- Could this be simplified?
  Identifying tasks that are labor or time intensive, and simplifying those operations enables you to focus resources on more critical activities. Some areas to consider are media and buffer preparation, as well as material handling and transfer. There are likely opportunities to outsource or automate these tasks.

Before making any change in a manufacturing process for a biologic however, it's important to understand the impact of the change on the molecule as well as the business. First, the change must not affect the safety or efficacy of the molecule being produced. And second, the change should have a positive effect on the manufacturability of the molecule. Depending on the process and how well it is understood, demonstrating that there is no impact to the molecule is sometimes the most challenging part of implementing a change. For this reason, you may feel that it is better to continue with your existing process, especially post-launch. I believe it is important to look at each situation independently prior to determining if the reward is worth the effort.

Improving manufacturability

Overall manufacturability is a key consideration to whether or not a product will be commercialized. Process simplification or intensification could greatly improve the manufacturability of the molecule through improved robustness, increased throughout, reduced supply concerns, or reduced cost of goods. These activities have the potential to make a bad process good or a good process great. (2).

Process intensification is used to get more out of the process, whether it's by producing more product upstream, or retaining more product downstream. Intensifying the process requires changes in manufacturing – different media or resins, new operating ranges, or even replacing specific unit ops, and therefore has the potential to have the greatest impact on the molecule. For this reason, these activities are typically done during early phase development. They can still be pursued during late-stage development or even post-launch, but you would first need to demonstrate no adverse effect on the identity, quality, purity, and potency of the biological product.

One area where process intensification may be critical is in the rare disease space. The majority of biological products in development for the treatment of rare diseases are not the more common monoclonal antibodies, but rather are enzymes, fusion proteins, and cell therapies. These products are typically more challenging, and therefore more costly, to manufacture, which makes process intensification crucial to successfully bringing these products to market.

"We are exploring opportunities to use more efficient purification technologies to reduce the number of purification operations required to generate purified drug substance. Our ability to simplify processes improves likelihood for successfully validation, reduced scope of process development and characterization, reduced number of manufacturing deviations and failed manufacturing campaigns, and improved yield."– Andrew Keefe, Principal Development Engineer at Shire.

Process simplification can also have significant positive impacts on manufacturability, and most simplifying operations are likely to have no impact on the molecule, and are, therefore, routinely implemented even post-launch.

Analytical testing is an area where simplification can improve the release of biological products. For all sterile products, sterility testing is required for release and may be the longest test to complete. This is a challenge for all of those molecules, but for cell therapy products it is even more of a concern. Monoclonal antibodies, for example, are targeted to specific diseases and, once purified, are typically stable for multiple years. Cell therapies, on the other hand, are live cells and may be patient specific. Therefore it is imperative that the material gets to the patient without delay, and identifying viable solutions to streamline analytical testing is crucial to getting those products to the patients that need them.

"Microbial testing is required at different points throughout a manufacturing process, but standard methods take too long to be useful for cell therapy products. USP mycoplasma testing takes 28 days; Vericel's method has reduced that to about six hours [with the] MycoSEQ™ mycoplasma detection assay."– John Duguid, Ph.D, Senior Director of R&D at Vericel Corporation (3).

Conclusion

Simplifying or intensifying a process may make the difference in whether or not a company can manufacture or even launch a successful biologic. Choosing what and when to intensify can be difficult. With any change, the benefits must always be carefully weighed against the potential risks. But understanding your rationale for change, conducting thorough reviews of the impact to the product and process, and leveraging the expertise of a trusted partner, can lead to tremendous success and result in more product at better costs by transitioning your bioprocess from good to great. A former colleague of mine who worked in the CMC group would say, "Keep the patient first when evaluating product and/or quality risks." For all situations, the patients' best interests should be top of mind when you are making these assessments.

Serena Smith is Director of Strategic Customer Engagements at Thermo Fisher Scientific, and a bioprocessing leader with over 17 years of industry experience.

References

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