Keys to Consistent Bioprocessing

The development of a robust and consistent bioprocess requires a systematic and risk-based approach to identify the right process parameters and raw materials.

By Serena Fries Smith

This is a very exciting time in the biopharmaceutical industry. While we continue to see companies investing in new therapeutic proteins and biosimilars, we are also seeing an emergence of gene and cell therapy treatments. Each of these therapeutics present unique complexities in process development, but for all, the development of a robust and scalable bioprocess is critical to process consistency and long-term manufacturing success. Ultimately, it's all about developing a quality process that delivers the desired performance and product every time.

So what are the main things to consider when developing a robust and consistent bioprocess? The first step is to define what the critical quality attributes (CQA) are for the biologic you are producing. These are typically tied directly to the safety and efficacy of that biologic. But in the case of biosimilars, they may also include other measurements necessary to demonstrate comparability to the novel molecule. Second to the CQAs are the key process attributes (KPAs). These are the measurements that will demonstrate that the process is in control, and may include cell growth and product production profiles. Once the CQAs and KPAs are defined, take a risk-based approach – based on internal experience and publically available information – to determine which process inputs are likely to impact them. In upstream process development, it's easy to first think about bioreactor parameters such as pH and temperature, but additional inputs to consider should include raw materials, cell inoculum, and processing time.

Developing and characterizing the process

Once CQAs and KPAs have been identified, and an assessment has been completed to determine which process inputs may impact them – now what? It is not just important to recognize that temperature may impact cell growth (a KPA) and your raw materials may impact glycosylation (a CQA). To ensure you are developing a consistent process, it is critically important to define the operating ranges or material specifications that will achieve the defined KPA and CQA ranges for your molecule.

"For autologous cell therapies, variability in the donor material and its performance in the process is the greatest source of variation. So process characterization and the control of raw materials is even more crucial [than with mAbs]." – Michael Laska, PhD, VP Bioprocess Development and Manufacturing at Cobalt Biomedicine.

For your specific process, consider the following questions when preparing for development and characterization work:

- How will I measure my CQAs? mAbs have been around long enough that it is generally accepted that glycosylation profiles and charge variants are two critical quality attributes. And there are reliable and high throughput methods to measure them (including some online tools). But what about gene and cell therapies? Many scientists rely on ELISAs, which are labor intensive and potentially variable, when there may be more manufacturing-friendly assays.
- Which raw materials are critical? This will vary based on the type of biologic, as well as any process or cell line sensitivities. It's easy to focus on "complex" or undefined components, including animal-derived materials or plant-based hydrolysates, but chemically-defined raw materials can also pose challenges. All components could possibly bring in trace impurities that can have a big impact on the process. Understanding where the risks are early in development is key to success.
- What is the right scale-down model? Whether your manufacturing approach is to scale-up or scale-out, having a reliable and representative scale-down model is necessary for process development, as well as for future troubleshooting or process improvement activities.

"Validating your scale-down model is very important. In my mind this should be done not by just direct comparison of product and/or process attributes between scales, but also by understanding (and modeling) the differences in variability of process parameters between the scales. This needs to be understood and correctly modeled so that the small-scale is representative of the large-scale." – Peter Slade, PhD, Sr Principal Scientist Late Stage Development at Pfizer

Of course, a high performing cell culture process is important, but this means more than just maximizing titer. Characterizing the critical attributes of your system leads to a process that delivers the expected product every time. Raw material control and bioreactor process conditions are clearly important here, but scientists are also beginning to utilize an –omics approach to better understand intra-cellular pathways. This information can be leveraged to optimize the system, maximize productivity, and to identify and mitigate process risks.

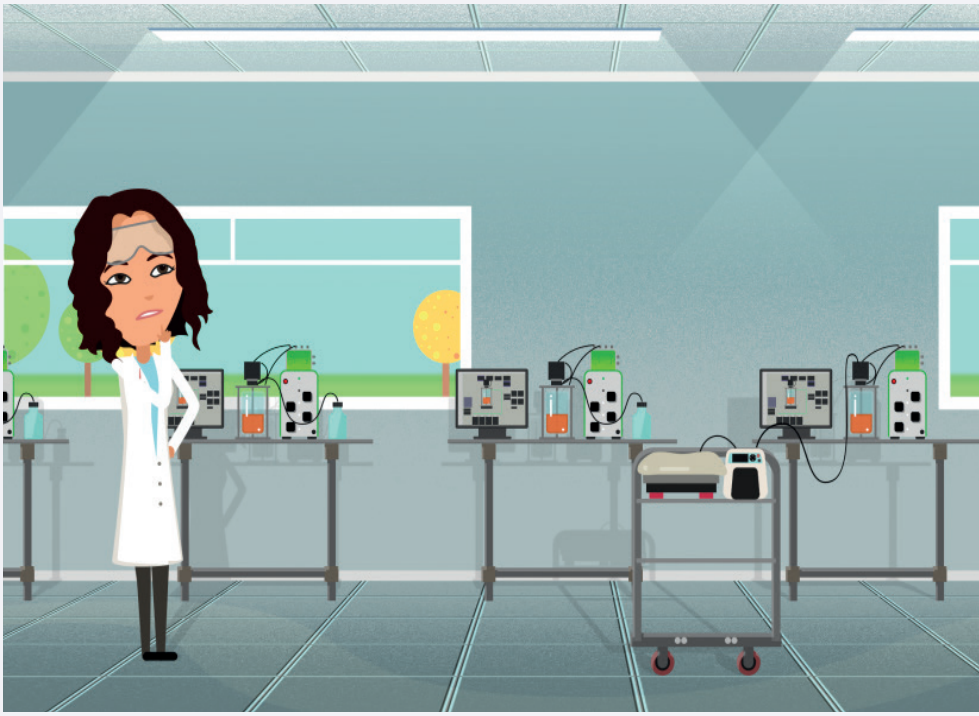
Preparing for cGMP manufacturing

The complexity of transferring from a process development lab to a clinical or commercial manufacturing suite is sometimes underestimated. Frequently, processes that ran smoothly in the lab fail when operated in a cGMP environment. Many times, this failure is due to the difference in equipment.

A mAb process that I developed is one example of this. It was a CHO fed-batch process that worked perfectly in 3 L glass benchtop bioreactors – consistently achieving 3 g/L – but when we scaled up to a 1000 L stainless steel bioreactor to produce toxicology material, the titer fell to 1 g/L. We were operating this bioreactor with a backpressure of 7.5 psi, but didn't take into account that the higher pressure would result in an increase in the dissolved carbon dioxide (pCO_2) in a culture. The increase in pCO_2 resulted in an increased demand for base, which resulted in a corresponding increase in lactate production – ultimately resulting in the lower than expected titer. Bioreactor pressure, one process parameter unique to large-scale production ultimately resulted in poor performance. Once this was understood, we implemented a specification, setting a maximum pCO_2 level prior to starting base addition, and were able to achieve 3 g/L at pilot-scale. This experience highlighted how important it is in process development to collaborate with manufacturing to understand, and then account for, the differences in production equipment.

Leveraging analytics

The last few years have seen significant advances in analytical technologies used to develop and characterize a consistent bioprocess. The use of omics – specifically proteomics and metabolomics – in early phase development can optimize cell lines and media through improved understanding of intra-cellar pathways.



Throughout process development, identifying and using reliable assays and online tools for the measurement of CQAs is critically important to define operating ranges. And extending the use of analytical tools to measuring and controlling variability in raw materials helps to ensure a consistent supply.

"In my experience, raw material sourcing is the most often overlooked aspect of clinical manufacturing preparation. Scientists in the development space must ensure GMP sourcing channels are available when choosing materials in their laboratories. This enables identical material usage and performance in manufacturing." – Ray Ducoat, Associate Principal Scientist, Biologics Pilot Plant at Merck & Co.

A great example of this is cell culture media, which can comprise over 100 different components, each with the ability to introduce impurities into the process that may impact productivity or product quality. When you have determined (through process characterization) which raw material impurities pose a threat to your process, it is critical to partner with your raw material supplier to analyze, monitor, and control for that impurity.

Conclusion

The complexities of manufacturing biologics reinforces the importance of a systematic and risk-based approach to developing a consistent process. This approach means using past experience to estimate how each variable may impact performance or product quality, and then defining operating ranges and raw materials based on how your specific process behaves. Designing the right scale-down model, leveraging analytics, and working with trusted suppliers is key to establishing a plan for long-term, consistent bioprocessing.

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