Make the most of your medium: optimization strategies for biopharmaceutical developers

As the global biologics market continues to grow, it is vital that developers stay ahead of the curve. Advancements in manufacturing technologies, workflows, and cell culture media over the last 30 years have driven substantial increases in product yields and process consistency.

This has had a positive impact on the biopharmaceutical industry, with a broad range of life-changing therapeutics progressing through the drug development pipeline and reaching the market. However, this progress has also increased competition. Developers are under increasing pressure to establish scalable and sustainable processes that can reliably deliver safe and effective therapies, while simultaneously bringing down costs.

These trends are particularly challenging for biosimilars developers, who need to match the critical quality attributes (CQAs) of the innovator biologic while minimizing their cost of goods [1]. For newer modalities, such as cell and gene therapies, growing demand has led to expedited clinical and regulatory pathways which, in combination with recent supply chain challenges, have further compressed process development timelines [2].

Time and internal capabilities are already limiting factors for biologics developers, particularly for those in the early stages of process development. These limitations can make it difficult for them to fully optimize their process. However, there are a range of strategies developers can implement to help them efficiently and successfully meet their goals for product titer and quality.

Getting the most from the medium

One powerful option in the process development toolkit is media optimization. Cell culture media are significant drivers of process performance, as they provide the necessary nutrients for cell growth and biologic production [3]. Furthermore, since changes to the cell line or workflow can often require larger resource investments, optimizing the cell culture medium can be an effective solution for achieving higher yields of biologics with the desired quality attributes.

There are a range of optimization strategies available to developers, which include the use of media panels, spent media analysis, and multi-omics analysis. These solutions can all enable them to home in on the media components that are affecting performance—either positively or negatively—and optimize their levels within the formulation.

Media panels can be an excellent starting point for developers looking to optimize their formulations, giving them access to a range of nutritionally diverse formulations and a predesigned study plan to simplify evaluation. By testing a wide range of media and seeing how they impact titers and product quality, developers can quickly identify key productivity-influencing components. This can help them streamline their optimization process and support the development of an ideal formulation.

For developers looking to build on the results of their media panel evaluation, or for those with an already established formulation looking to optimize further, the next step is conducting spent media analysis. This iterative approach compares the levels of specific media components, such as vitamins and amino acids, over time to help developers understand how the cells are using those components during the process. This can be taken a step further with multi-omics analysis—specifically, proteomics and metabolomics, the characterization of proteins and metabolites respectively [4]. Taken together, these approaches can help developers gain a better understanding of their processes and identify opportunities for formulation optimizations.

Managing variability

The inherent variation between cell lines—and even within cell lines—means that each workflow is unique, with differing nutritional requirements for every chosen clone and process. Additionally, any variability present in media, such as trace elemental impurities introduced during manufacturing, can also affect process performance. As a result, utilizing key driver identification (KDI) as a method to optimize the raw material sourcing process can be highly advantageous. This is particularly useful when using non–chemically defined components.

The process involves leveraging powerful statistical analyses for in-depth insights into key performance drivers [5]. For process optimization, this means looking at media, feed, and supplement components—such as the levels of certain trace elements—to see how they impact yields and product quality. Once key drivers are identified, it is then possible to screen certain raw material lots to assess whether the levels of key components fall within their optimal ranges. Some media suppliers will conduct these analyses on non–chemically defined raw materials as part of a dedicated program, which can help developers reduce variability and mitigate risk.

Evaluating the supplementation strategy

Alongside media optimization and minimizing variability, there are other approaches that can be implemented to boost process performance. Firstly, it is important to use a feed (and associated feeding strategy) that works with the final, optimized medium. Multiple clones from the same parental cell line, producing the same protein in the same basal medium, can vary in performance purely based on the chosen feeding strategy. Consequently, it is critical for developers to determine which formulation and feeding strategy (starting time of feed, volume of addition) is best for their specific process. Some suppliers may have feeds specifically tailored to certain media and/or cell lines, which could help maximize titers and product quality while reducing initial optimization requirements.

In addition to a feeding strategy, developers may choose to include supplements such as peptones, insulin, or immunoglobulins to improve yields. As part of an appropriate feeding and supplementation strategy, these additions can be a useful way to boost performance, but their inclusion should always be considered based on the individual process. Some developers may also have concerns surrounding variability from supplements of animal origin; however, a good supplier will conduct rigorous raw material sourcing and auditing to maximize the consistency and reliability of their products. As mentioned, some vendors may also have a dedicated raw materials program where they can work with developers to implement risk mitigation strategies.

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Other considerations for maximizing process performance

Beyond media and feed optimization, it is worth considering other factors that may be affecting performance. Critical process parameters (CPPs) are the other components of a protocol that can affect the CQAs. For biopharmaceuticals, this pertains to the cell culture environment, which includes parameters like temperature, pH, and dissolved oxygen and carbon dioxide levels. By controlling these parameters, it is possible to maximize cell health, thereby optimizing product yields and quality.

Streamlining the optimization process

Media optimization can be a valuable and cost-effective strategy for developers looking to improve their titers and meet their CQAs. Moreover, utilizing additional process optimization strategies can help developers to further maximize performance and sustainability, while also reducing variability and risk.

When working with limited process development resources, developers also have the option to work with a vendor providing media development services. This can help them reallocate internal resources to maximize efficiency, potentially accelerating their overall journey to market.

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