White paper

Bioproduction analytics: supporting optimized media development today and tomorrow

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Cell culture, process development, biopharmaceutical manufacturing, media, analytics, spent media analysis, multi-omics, investigative analytics, stability studies

To establish an economically feasible biopharmaceutical manufacturing process, it is vital for developers to meet their targets during process development. Whether they are looking to increase yields or achieve a specific product quality profile, optimizing cell culture media can play a crucial role. Ideal media formulations can help increase product titers, enhance product quality, reduce the cost and time required for cell culture, and increase the efficiency of downstream processes.

However, designing and optimizing a cell culture medium can be a complex and time-consuming process due to the many variables that must be carefully considered and balanced. The presence and relative concentrations of specific nutrients, growth factors, and other components within the formulation can all affect the growth and health of the cells, and therefore, process productivity.

Accurate analytics are vital in streamlining the media development process and achieving long-term success. They provide manufacturers with the necessary information to make data-driven decisions about their formulation. This can help them optimize their formulation, troubleshoot issues, and minimize the batch-to-batch variability of their medium—all of which are critical for consistently manufacturing a safe and effective biologic.

Media development and analytics

Every cell line and medium are different. Different cell types have unique requirements, and even clones from the same parental cell line can vary in their nutritional needs. Making a single change to a formulation can have many effects, so the media development and optimization process is about finding a balance and re-evaluating against the end goals at every stage. Furthermore, the optimal formulation can change over time as the cells adapt to the culture conditions.

The design of experiments (DOE) approach is widely used in media development workflows to enable developers to reach a final formulation that meets their process targets. DOE alters the relative concentrations of different media components and assesses the impact on process performance attributes, such as titer and product quality. This statistical method allows developers to test a wide array of different components and concentrations without the experiment becoming prohibitively large.

A set of test cases will vary the factors being evaluated and measure the effects on the cells. DOE might include test cases that adjust the concentrations of different nutrients, the presence or absence of certain growth factors, and the pH of the medium. The data collected from these test cases are then analyzed using statistical methods. This iterative process allows researchers to systematically identify the most favorable conditions for cell growth, such as the optimal concentrations of nutrients and growth factors.

Analytics are the foundation of a successful DOE process, in particular, media and product quality analyses. There are also additional approaches—including investigative analytics and stability studies—that can help developers further optimize their process.

Media analytics

Media development typically involves using spent media analysis to assess how the concentrations of key components are changing throughout the process.

Commonly analyzed components include amino acids, water-soluble vitamin components (such as riboflavin or folic acid), advanced water-soluble vitamin components (such as pyridoxine or biotin), and trace elements. A series of different assays can reveal which components are being utilized by the cells, and which component concentrations need to be increased to obtain higher titers, greater productivity, or optimal cell growth.

Upstream process development scientists with expertise in optimizing media can often adjust the formulation in response to spent media analysis by using their knowledge and experience.

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The adjusted media then forms the basis of the subsequent experiment to evaluate the impact on viability, yield, and quality.

While spent media analysis has been the industry standard for media optimization for the last few decades and continues to be a critical and powerful tool for development and optimization, it is limited. Developers can only see components that have been either accumulated or depleted within the spent media, not how the cells are using the components. For example, spent media analysis will reveal that alanine is accumulating, allowing developers to reduce its level in the formulation, but cannot explain why the accumulation is happening. In another example, if cells are utilizing large volumes of cysteine, developers can add more to the media, but their ability to do this can reach a limit based on the component's physical properties. More in-depth analysis of metabolic pathways could reveal how the cells use the cysteine and whether there is another, more effective, way of satisfying this need within the culture.

Multi-omics offers a far more comprehensive analytical approach. By combining the outputs of proteomic and metabolomic analysis, developers can take a "deep dive" inside cells to identify key pathways of influence upstream and create a model of what is happening inside the cell.

While this approach requires more time and resource investment, alongside a broader skill set, it can provide much more information on the nutritional requirements of cell lines. A traditional media development workflow involves spent media analyses of fewer than 50 molecules. However, taken in iterative steps, a multi-omics workflow combines spent media and cellular component analyses of thousands of proteins and metabolites. The result is an advanced, more efficient media design and optimization process that can potentially lead to a final formulation that increases cell productivity and enhances product quality.

The data generated during multi-omics analysis can also be used to create models to further advance formulation development. The more data collected, the more these metabolic pathway models become a vital part of the process. Over time, this could support developers to overcome the challenges of relying on traditional, collective knowledge, and, instead, give them direct access to detailed information from across companies and industry.

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Biopharmaceutical quality analytics

With a growing focus on optimizing biopharmaceutical manufacturing to maximize productivity, it is increasingly important to predict and control the critical quality attributes (CQAs) of therapeutics.

Consistently meeting the required CQAs for monoclonal antibodies (mAbs), for example, is essential for manufacturing a safe and effective therapeutic. Such CQAs include protein aggregation and post-translational modifications, such as glycosylation. Charge variance is another important attribute. Charge can vary throughout the production process as well as during purification and storage, which can impact the molecule's yield, structure, stability, and biological function.

Optimizing product quality during media development—accurately measuring and interpreting CQAs through robust quality control—is vital in fine-tuning the final product to meet therapeutic requirements. By optimizing the medium itself using these analyses, it is possible to monitor and even shift CQAs to consistently deliver a safe, effective therapeutic.

Investigative analytics

Investigative analytics requires a completely different approach to media development and optimization. It seeks answers to problems, such as: Why is the process no longer producing the required titer or quality of product? What can explain the sudden drop in performance? Why is there a color change, or why has a precipitate formed?

Standard quality tests can identify any changes in the formulation. For instance, excess manganese can affect the glycosylation profile and components such as vitamins may degrade in response to light. However, these tests cannot identify every issue. As a result, achieving the insight required often necessitates using a tailored approach through more in-depth analytics, including utilizing data on laboratory conditions. A wide range of different analyses can be utilized in combination to investigate the causes of variable process performance and improve consistency.

Some tests identify causes of raw material variability, including contamination from trace elements such as the aforementioned manganese, as well as chromium, nickel, cobalt, selenium, copper, tin, iron, vanadium, zinc, and molybdenum. Further analytics and statistical methods can also be implemented to conduct key driver identification. This can help developers understand to which elemental impurities their process is most sensitive. This enables them to implement more robust raw material screening processes and reduce the risk of variability arising.

Stability studies

Cell culture media stability testing enables manufacturers to assess the shelf life of their formulation and set accurate expiration dates. This can help developers ensure that packaged media remains consistent over time—crucial for maintaining the health and viability of cells, and for achieving reliable and reproducible performance.

Stability testing also helps identify any changes in the cell culture media that may occur over time and allows for corrections to be made before these changes have a negative impact on cells. Some components may be naturally more labile or especially sensitive to degradation in response to light or chemical interactions within the formulation itself.

The exact analyses required are dependent on the stability-indicating factors in the specific formulation.

Optimization from development to manufacturing

From evaluating key drivers during media development to troubleshooting during commercial production, there are a range of analytical techniques that can support developers at all stages. Consequently, high-quality analytics and accurate interpretation of results are essential to provide the insights required to enable manufacturers to achieve commercial success.

Moreover, in addition to supporting developers to establish efficient workflows and maximize productivity in their process, next-generation techniques, such as multi-omics, can have further benefits. By enabling collaborative sharing of knowledge throughout the industry, these techniques can have a wider positive impact—supporting developers around the world to further streamline the delivery of new, life-changing biologics.

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