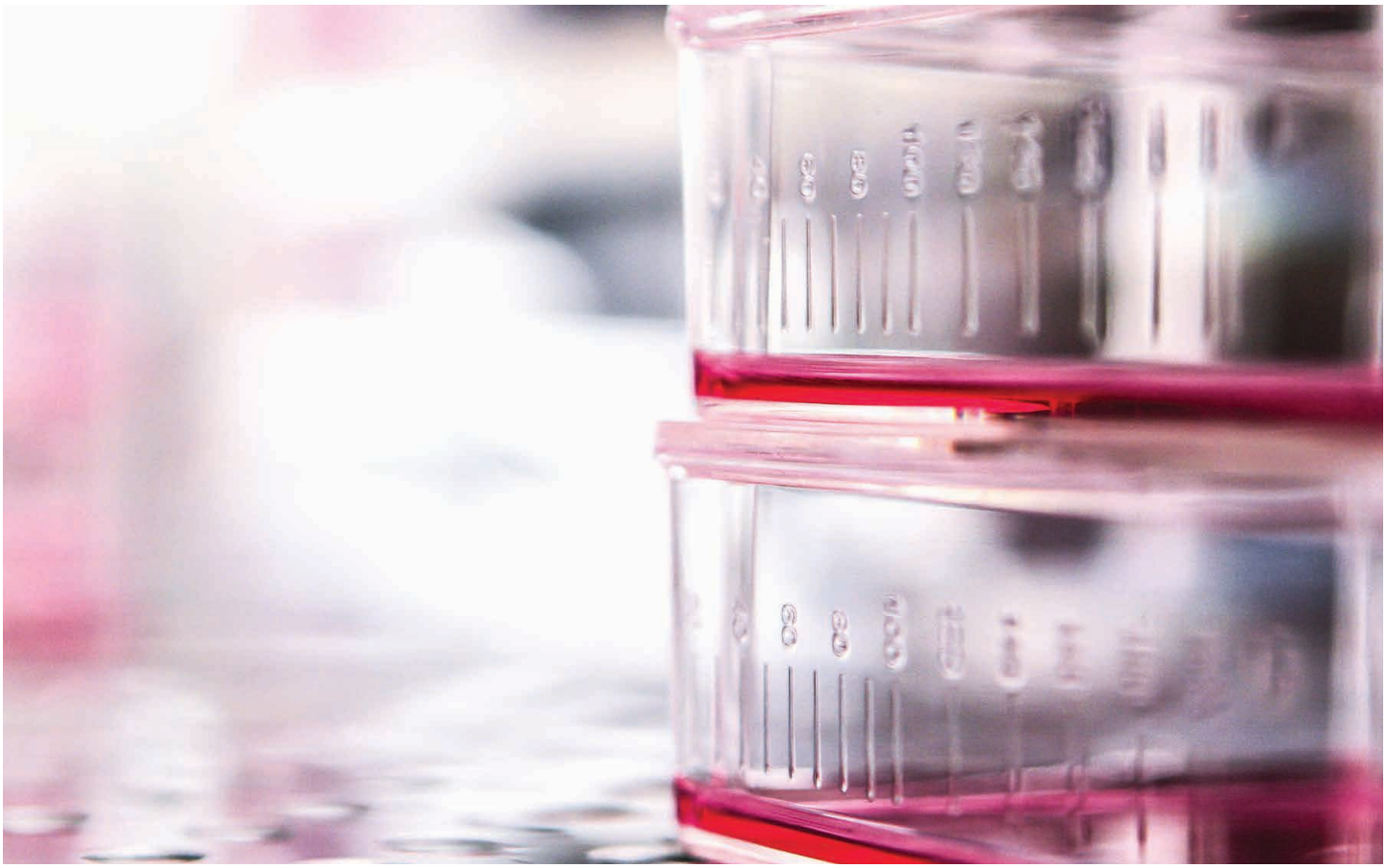
Raw materials in upstream bioproduction: challenges and solutions

Developing, optimizing, and manufacturing cell culture media formulations can be a challenge and a barrier to the bioproduction process. Media formulations supporting the production of biologics, such as cell-, gene-, and protein-based therapies, consist of a large number of raw materials sourced globally from different suppliers. Media are key upstream materials that can directly affect the safety, quality, and activity of the desired product. Slight variations in the sourcing and quality of raw materials, the manufacturing process, and specifications may result in batch discrepancies, production delays, and unnecessary added costs from resource utilization and materials. Supply chains and business continuity are also key factors in ensuring a reliable raw material supply and mitigating risk from variability.

Read about the challenges related to raw materials and find your optimal solution.



Challenges

With digitalization on the rise, a focus on optimizing, sourcing, monitoring, and characterizing at all points in the bioproduction process is necessary for transitioning biopharma and biotech companies to desired industry 4.0 standards. This has also raised awareness and concern over the impact of raw material impurities in bioproduction.

So exactly how can raw materials in media affect your product?

Chemistry

Raw materials that make up a media formulation can come from a variety of sources, including bacteria, yeast, or a synthetic process in the laboratory. The chemistry of your media formulation must be carefully considered during the development process. Different components can interact within a formulation and causes changes in solubility and/or pH, ultimately leading to variable yields and batch failures. In addition, different raw material salt forms can influence final solubility and composition, and should be considered.

Impurities

A variety of impurities may be present during raw material production or introduced during bioproduction, leading to raw material variability. Trace amounts of impurities within raw materials, such as iron sulfate and copper salts, can negatively alter formulations, affecting the viability and productivity of cells, along with protein quality, product yield, and other downstream processes.

Common process contaminants:

- Manganese (in iron salts): affects glycosylation, protein activity, and structure
- Excess aluminum and cobalt: produce reactive oxygen species (ROS) and drive cells to apoptosis [1]
- Viruses: cells can become infected by viruses, most often introduced from animal-origin materials
- Mycoplasmas: contamination commonly occurs from laboratory transfers and can significantly impact cellular metabolism

Scalability and consistency

Raw materials from different sources and vendors can contain different levels of impurities that can significantly affect cell viability, product quality, and yield. As a process transitions from a bench-scale lab to a commercial-scale bioreactor, media manufacturing also requires bigger batches; in many cases, companies will start outsourcing media manufacturing when scaling up. This could result in differences in the presence of impurities between in-house manufactured media and outsourced manufactured media. Batch-to-batch variability in raw materials, resulting from changes in raw material sourcing and also the volume-to-stir-tank ratio, is a large contributor to scalability issues. Additional optimization may be required at the preclinical and early clinical stages to compensate for impurities and synergistic effects. Unfortunately, in some incidences, a new formulation may be required if the product does not meet regulatory requirements, driving up costs.

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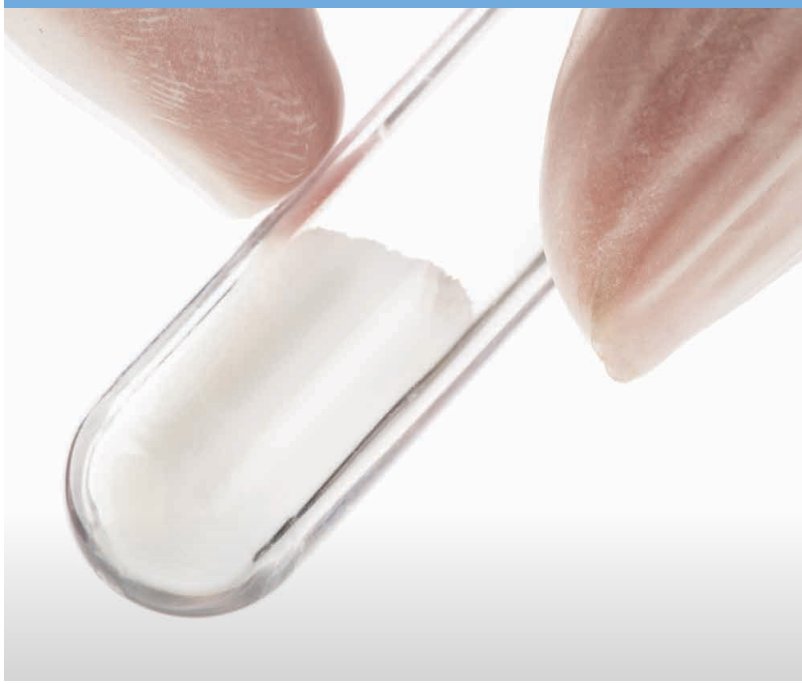

Solutions

Early process optimization and scaling

Investing in and optimizing formulation composition during the early bioproduction stages are critical for predicting and reducing variation in large-scale manufacturing from variability in impurities. Early optimization should include testing multiple batches of media, preferably manufactured with the same raw materials that future large batches of media in GMP facilities will use. Early-stage optimization should also include assessment of key drivers of performance and protein quality. Interestingly, some of those key drivers could be the same chemical component impurities in certain raw materials. Available design of experiments (DOE) programs, using statistical analysis and data from early optimization tests, can help predict the effect of your raw materials during bioproduction scaling.

Testing and characterization

A wide range of analytical techniques can be utilized for characterization of raw materials, including inductively coupled plasma mass spectrometry (ICP-MS), liquid chromatography–mass spectrometry (LC-MS), gas chromatography–mass spectrometry (GC-MS), nuclear magnetic resonance (NMR), and Raman and infrared spectroscopy (IR). ICP-MS is commonly used to quantify trace metals alongside techniques such as LC-MS and GC-MS, which evaluate the purity of and quantify various cell culture media components.

Analytical testing is critical at every stage of the supply chain to improve process control and take necessary mitigation steps.

Every stage of your raw material supply chain should be monitored for inconsistencies, impurities, and lack of conformance to specifications that affect cell viability and product quality. An integrated inventory management system can help identify which part of the supply chain has caused process issues. It can also provide immediate notifications to designated quality control teams, which can then execute actionable recovery plans [2].

Shifting toward serum-free media

In recent years, bioproduction is trending toward the use of serum-free and chemically defined media to improve batch reproducibility and purity, and to facilitate DOE-based media design. Chemically defined media do not introduce biological contamination such as immunoglobulins or viruses to the process. Despite this benefit, serum is still an important component in many bioprocessing applications due to its versatility and support for certain cell lines [3].

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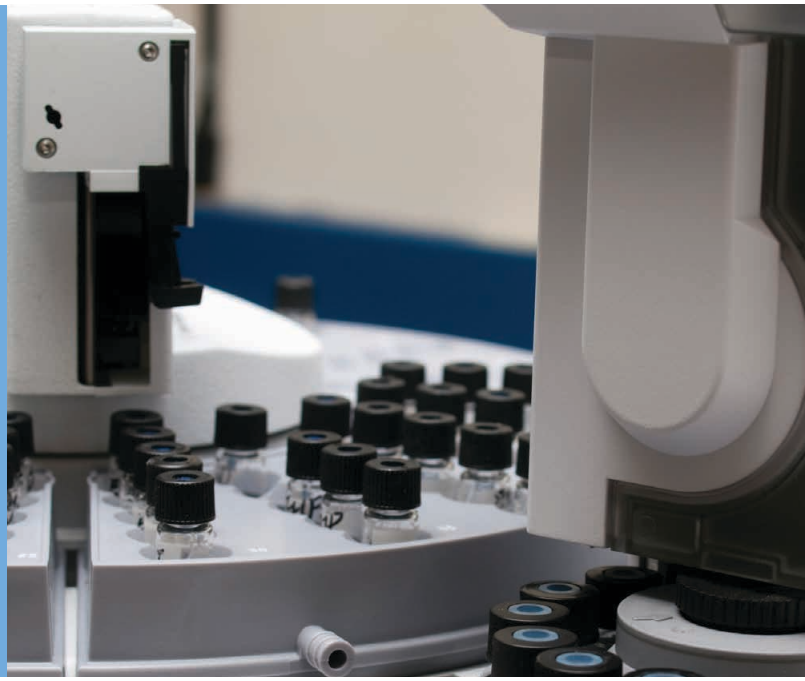

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Selecting reputable and transparent suppliers

Media manufacturers can help you maintain raw material consistency and mitigate bioproduction risks by sourcing only from reputable and strictly qualified vendors, and monitoring with rigorous internal raw material testing programs. Ongoing monitoring with a risk scoring matrix is critical to identifying areas of the supply chain that might need to be closely supervised [2].

Transparency in the supply chains for cell culture media is vital, because they are multifaceted and issues can arise at any stage. The employment of deep analytics by manufacturers can provide quantitative data between batches, permitting any variability to be flagged and assessed quickly. Batch records are particularly useful for keeping track of consistency and for collecting data that can be used for regulatory filings. Making sure that only trusted vendors and experienced media manufacturers are involved in the process will reduce the chances of variability in your end product.

Experienced scientists and manufacturing professionals are beneficial for not only manufacturing and testing products, but also producing materials for and advising on formulation optimization, including consultations on how to move away from the use of animal-origin components.

This experience can be outsourced to speed up process development, allowing you to focus on the next stage of the development pathway. Communication during this process needs to be clear, and this includes not only supplying accurate knowledge but also sharing information, providing immediate change notifications, and acting in collaboration towards a common goal [2].

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Transparency in the supply chains for cell culture media is vital.

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