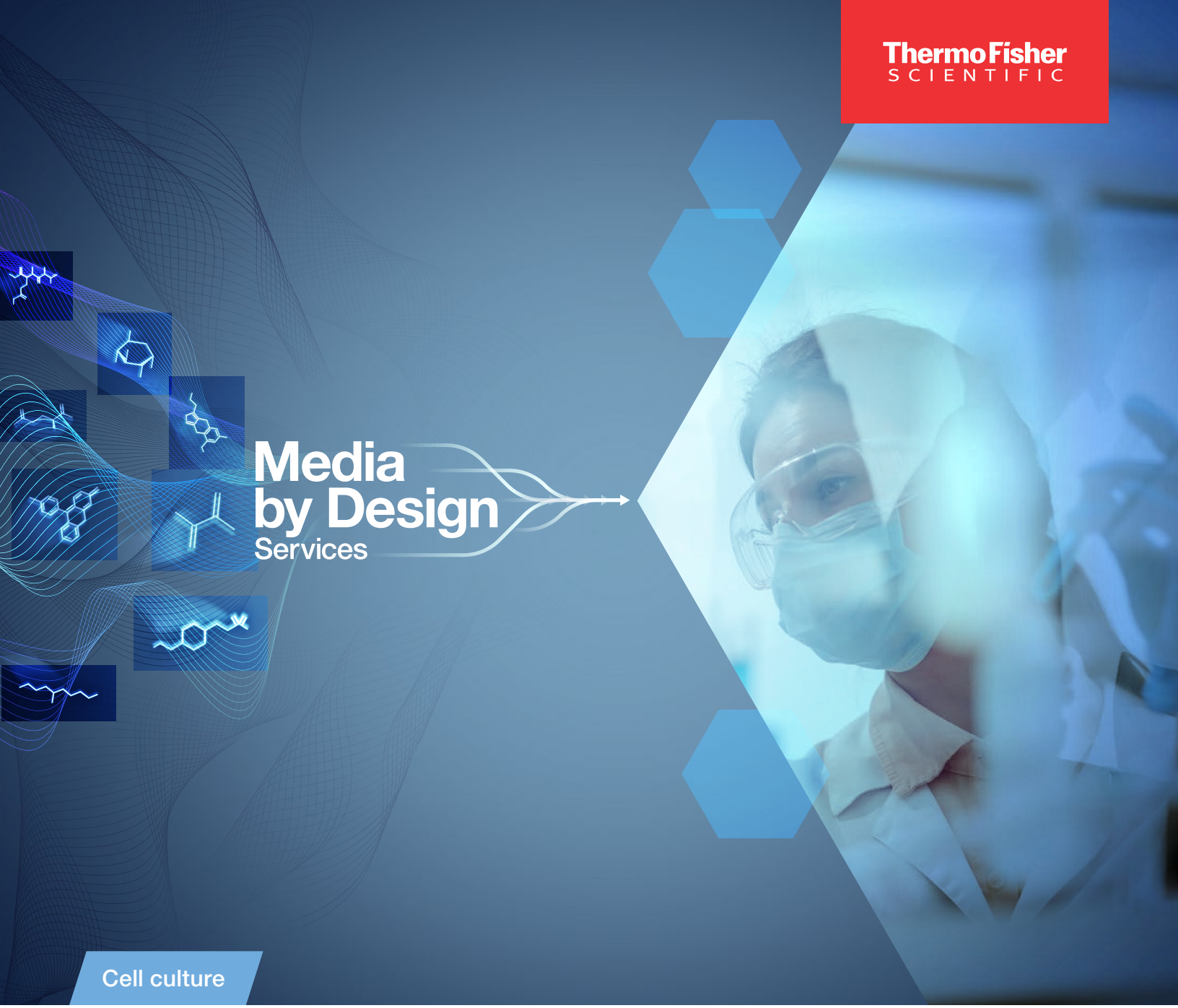


Media and feed development

A step-by-step guide to workflow optimization

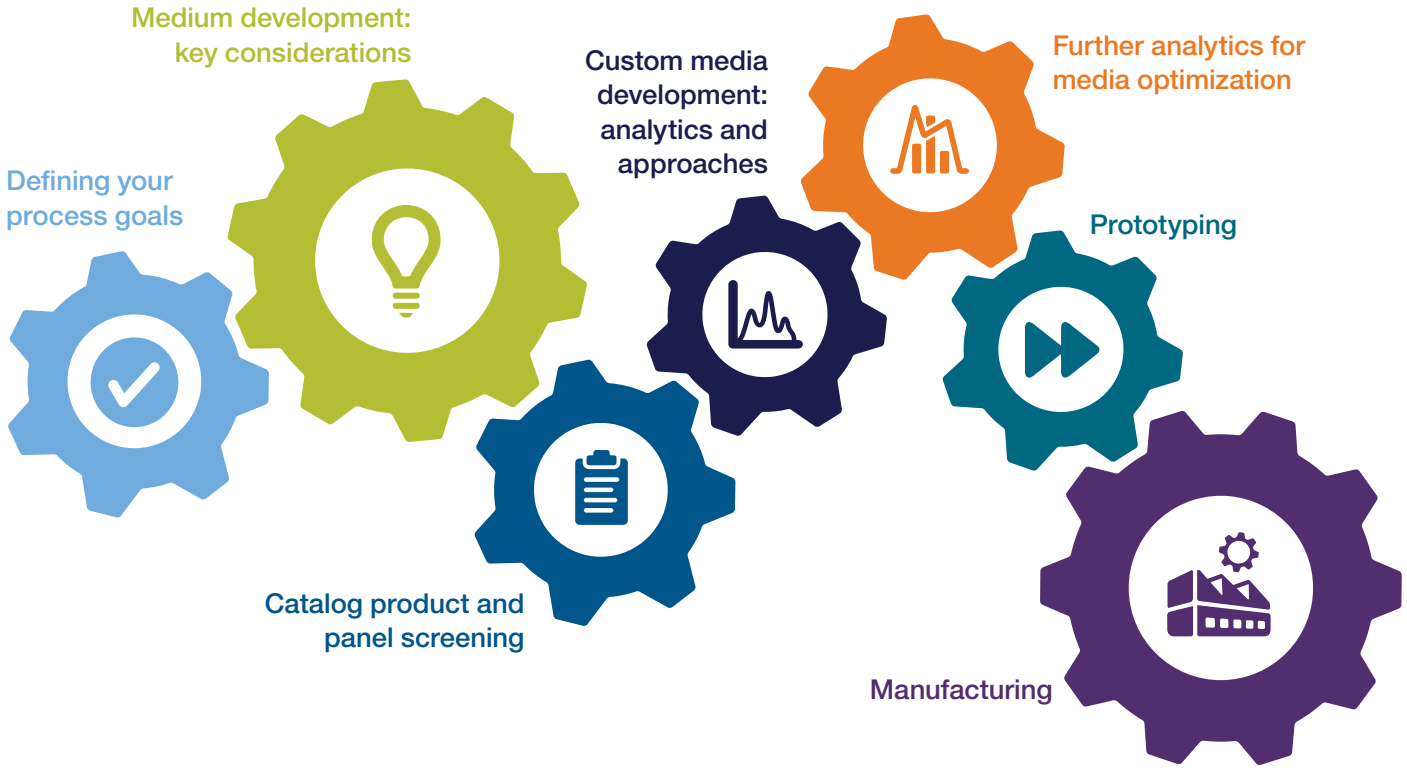
gibco

Optimize every step of your development workflow

Cell culture media is a foundational component of any biotherapeutic manufacturing workflow, crucial for maintaining cellular health and viability, maximizing titers, and supporting high product quality. As such, building a biotherapeutic manufacturing process with an optimized basal medium and feed system is vital to achieving optimal results and accelerating the speed-to-market of your product.

However, the process of finding the most suitable basal medium and supplementation strategy can be challenging, as it requires balancing many key cell culture process variables to achieve specific technical goals within budget and time constraints.

This guide will provide an insight into each development stage and offer best practices to help you achieve your project goals on time and within budget.



Defining your process goals

Before beginning development, it is important to examine your process and determine your goals. By comparing these goals with your internal capabilities and limitations, you will be able to pinpoint the solution that is right for you—be that choosing a catalog option, optimizing a pre-existing formulation further, or opting for a completely custom formulation.

The first step will be to clearly define your process goals. These could be specific productivity targets, such as therapeutic yields, product quality, or cell health and viability. There may also be wider project considerations regarding desired timelines and budgetary constraints. Pre-existing process pain points, such as process scalability, meeting downstream targets, or other workflow challenges, could also be addressed through media development and optimization.

The second step is understanding your capabilities and limitations. This will help you determine how much development you can conduct in-house and whether you could benefit from outsourcing to a third-party media developer. If you do want to outsource, it will also be important to understand which specific parts of the process you require support with (for example, whether you are looking for assistance with minor formulation adjustments or full formulation development).

Ultimately, your goals will be shaped by the biotherapeutic you are developing. Different biologics will have different workflows of varying complexity and resource requirements, all of which affect the approach you take. For example, innovator and biosimilar workflows will differ in their cost sensitivity, and recombinant protein workflows may be more straightforward than those for cell and gene therapies.

Gibco media insight: The experienced Gibco™ Media by Design™ Services team can work with you to understand your goals and help design a media development solution that will enable you to achieve bioprocessing success.

Medium development: key considerations

With your process goals clearly defined and your capabilities well understood, the next stage is to find the media solution that is right for you. Your project timelines, economic considerations, performance targets, and process type will all influence your decisions. In this section, the major factors that should be considered during this process have been outlined to help you determine the most appropriate pathway for your process.

Catalog vs. custom

A significant initial decision is whether you should utilize a catalog medium, conduct further optimization on a current formulation (if applicable), or develop a fully custom formulation. This will largely depend on your project timelines and the internal resources you can dedicate to media development.

Catalog media and feeds are typically ready-to-use formulations that can deliver strong yields and consistent product quality off the shelf within well-established workflows. They can also be an ideal starting point for further optimization, helping to drive improved titers and more consistent products without the need to develop a fully custom medium, which may be beyond the scope of some projects.

Custom formulations, on the other hand, can be a powerful way to drive even further improvements. For example, if working with more established modalities such as monoclonal antibodies (mAbs), a custom formulation can help improve process performance and drive an increase in productivity. Additionally, when working with less established modalities, custom media might be the only suitable option to help reach challenging product yield and critical quality attribute (CQA) targets.

Media components and format

The choice of media components can impact culture performance, so it is important to carefully consider which ones you want to include in your formulation. Animal origin (AO) components can come with variability concerns, particularly if not properly sourced, which may impact process consistency. These risks can be mitigated through the use of animal origin–free (AOF) components, effective raw material sourcing and medium optimization, or a well-understood key component analysis.

Medium development: key considerations

When it comes to the economic feasibility of your process, some components can add expense. However, their positive impact on productivity may justify their inclusion. This means their use often needs to be evaluated on a case-by-case basis and carefully considered alongside your goals and specific process requirements.

Choosing your desired media format will also be crucial, as both liquid and dry format media can be appropriate in different circumstances. Liquid media comes ready to use, without the need for reconstitution, but will take up more storage space compared to the equivalent volume of dry media. This factor would be particularly important in a perfusion process, which would likely require significantly larger volumes of media than a traditional fed-batch workflow. In these instances, it may be more suitable to opt for a dry format medium to mitigate storage and shelf-life concerns.

Feeds and feeding strategy

When developing a biotherapeutic manufacturing process, it is important to pair your basal medium with an appropriate feed to optimize titers and product quality. 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. Screening multiple feeds to see which perform best in your specific process is also worth considering.

Beyond the feeds themselves, feeding strategy should also be considered. Clones of the same parental cell line can vary in performance based on the chosen feed strategy, so in order to maximize process performance, you should consider the timing and volume of feed addition.

Gibco media insight: The Gibco™ Advanced Granulation Technology (AGT™) media format is a granular dry media format that supports the manufacture of serum-free, protein-free, and chemically defined media. Media in the AGT format are pre-adjusted for pH and osmolality, offering rapid reconstitution for increased workflow productivity.

Catalog product and panel screening

Off-the-shelf media and feeds can be ideal starting points for process optimization. This can be done by screening a variety of catalog media, feeds, and supplements to see which deliver the greatest cell culture performance. For some developers, this may be all that is required to reach their goals, and suppliers will often have dedicated teams available to walk them through the evaluation process. However, for those looking to optimize further, a media or feed panel screening can be an incredibly useful next step.

Typically, catalog products come with limited formulation information, making it challenging to set up evaluations that are truly diverse. In contrast, panels are made up of a selection of nutritionally diverse formulations designed to help identify key drivers of cell culture performance, facilitating the identification of the optimal formulation for a specific target clone.

After completing a panel evaluation, you can utilize more advanced tools and focus on the components that have the greatest impact on performance—this is where design of experiment protocols and analytics can prove useful.

Gibco media insight: Gibco™ media and feed panel evaluations can help you quickly narrow in on the components driving increases in productivity and product quality. Along with the panel, you have access to study plans and technical support to help interpret your results and decide on next steps.

Custom media development: analytics and approaches

Utilizing a custom formulation can be a powerful way to drive improvements in performance across a wide range of cell lines, therapeutic modalities, and process types. Some of the benefits include increased productivity, optimized product quality attributes, removal of undesired media components, and improvements in scalability and manufacturability.

Custom media development is typically conducted using a design of experiments (DOE) protocol. DOE is a statistical method of setting up experiments that can enable you to predict which components and interactions are going to have positive or negative impacts on process performance. This allows you to test a wide array of different components and concentrations without the experiment becoming prohibitively large.

The DOE methodology forms the basis of two custom media development approaches often used in the industry. The first is a spent media analysis workflow. This iterative approach looks at the media before, during, and after a bioreactor run to monitor the utilization of critical components over time. This allows for the calculation of consumption rates of components, the depletion of which may be limiting productivity. Once impactful components are identified, their concentrations can be altered in the formulation to enhance cell growth and product titers.

The second approach, multi-omics analysis, combines proteomics and metabolomics to look at additional components—including around 7,000 proteins and 1,000 metabolites—and provide a more comprehensive insight into metabolic pathways. Together with biological data, media analytics, and model statistics, it can help identify the key components driving productivity. If done correctly, multi-omics is a powerful tool that can be used to specifically tailor your formulation to increase the performance of your process and help you meet your goals.

Gibco media insight: Our media and feed development services, which include an advanced multi-omics workflow, provide a flexible range of options enabling us to work with you to deliver scalable formulations that can help you meet your product quality and titer goals.

Further analytics for media optimization

There are a wide range of analytical tests that can be used to investigate cell culture performance, both during process optimization and beyond toward commercial manufacturing. These analyses can help you make the most of your medium and, depending on your goals and capabilities, can be conducted in-house or with an external organization.

Protein analytics

When developing a biotherapeutic, the quality of the protein being manufactured is vitally important. CQAs, such as glycosylation profiles, are crucial for efficacy and patient safety. From understanding post-translational modifications to verifying base sequences, it is essential to have the analytical capabilities and expertise to ensure CQAs are not only being met and monitored, but also shifted when needed.

Stability testing

Certain media components can be sensitive to degradation. This can be due to a range of issues, such as interactions with other components or light sensitivity. The quality of these components can be monitored over time or through temperature excursions to verify the robustness of the formulation using stability studies. Not only can understanding a formulation's stability help during development of a manufacturing process, but it can also give you more confidence in the shelf life of your product. Stability testing is routine for catalog products; therefore, carrying this out for custom formulations is equally important.

Investigative analysis

Customized advanced analytical projects can help you troubleshoot any problems you may be facing in your process. If you are experiencing variability, a key driver identification (KDI) approach—using advanced analytical techniques and mathematical modeling—can be utilized to identify causes of inconsistent process performance. Additionally, investigative analytical services can also help address problems including extractables, leachables, precipitates, and more.

Gibco media insight: Gibco™ Media by Design™ Services include a full suite of bioproduction analyses. These services can provide powerful and insightful data that can help save time and money throughout your workflow. Our experienced team of analytical scientists can help you understand how to get the most from your cell culture and help shorten your time to market.

Prototyping

To reduce the risk of delays when moving to commercial manufacturing, it can be highly beneficial to verify that all formulations are both manufacturable and scalable.

This can be achieved by leveraging a pilot-scale media prototyping service. These services replicate the manufacturing process to rapidly produce small batches of media using cGMP-quality raw materials and methods. By evaluating the prototype media, you can accurately assess whether any changes need to be made to your media formulation before scaling up.

Prototyping can also give you access to further media manufacturing expertise, helping you add novel components or remove components not driving cell culture performance. In preparation for cGMP scale-up, you may also consider converting your formulation to a different media format to better suit your scale-up needs and streamline the transition to large-scale manufacturing.

Gibco media insight: Gibco™ Rapid Prototyping Services offer small-batch, custom media manufacturing solutions for research and process development to accelerate media development and scale-up.

Manufacturing

Once your basal medium and feed formulations have been finalized, you need to be able to manufacture them at the scale required for commercial production of your biopharmaceutical. This will require choosing an external vendor with cGMP-validated manufacturing services—either as your sole manufacturer or as a secondary supplier.

When choosing and qualifying a vendor, it is vital to fully evaluate its capabilities and confirm it can meet your specific requirements. You need to ensure suppliers follow best practices and have established standard operating procedures to confirm the quality and identity of raw materials. Confirming the reliability of its supply chain is also advisable. Evidence of a dependable supply chain should be provided up front, and establishing a transparent communication system to share data is critical. Ultimately, these systems can help identify any potential issues and streamline your scale-up to large-scale manufacturing.

Gibco media insight: Gibco™ cGMP Media Manufacturing Services can support your needs with a worldwide network of harmonized manufacturing sites. Our global redundancy helps provide assurance of supply and can enable us to meet the lead times required to help you maintain consistent production.

Working with a media development collaborator

Developing and optimizing a custom medium and feed system can be highly beneficial to enhance your workflow for manufacturing biotherapeutics. However, each step in the process requires a specific set of skills and capabilities.

External collaborations can enable you to benefit from next-generation technical capabilities without the need for investment in new equipment and employee training. You can also take advantage of knowledge from specialists who have experience at each development stage.

Leveraging the capabilities and expertise of an external collaborator can result in accelerated speed-to-market and help reduce long-term manufacturing risks, enabling you to successfully deliver your life-changing therapeutic.

Learn more at **thermofisher.com/mediabydesign**