Article

Cell culture

Scaling for success

Preparing your cell culture workflow

Protein therapeutics play a pivotal role across the modern healthcare landscape, offering treatment options for a wide range of indications. To meet the increased demand for these therapies, it is essential to be able to efficiently and effectively scale up a manufacturing workflow. However, without early planning this transition can be challenging, as a process that works well at small scale does not guarantee success at large scale. By factoring in scalability from the start, developers can surmount these obstacles and enable their therapeutic to reach its potential.

As workflows scale up towards clinical and commercial production volumes, failures or unexpected outcomes can result in costly delays for biologics developers, which would ultimately mean delays in manufacturing treatments for patients. Additionally, process performance and product quality may not translate exactly during scale-up, which could impact both the cost-effectiveness of the process and the safety and efficacy of the final product.

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Without early planning, life-changing therapeutics may struggle to reach the market. By proactively considering factors such as the medium and feed system, the manufacturing workflow, and the choice of supplier, developers can help reduce the risk of delays, mitigate unforeseen costs, and rapidly deliver the needed therapeutic to patients.

Finding the optimal medium and feed workflow solution

Identifying high-performance products

Continuing to meet the metabolic needs of a cell line throughout scale-up is a key challenge for developers transitioning to larger production volumes. As such, it is important that developers choose a cell culture medium and feed system that offers the nutrients required to deliver equivalent production performance and product quality across different scales.

Selecting an appropriate cell culture system is made more complex by the need for compatibility between the medium and feed. This can often require time-consuming screening of multiple feed options. A complete workflow solution consisting of an off-the-shelf medium and complementary feed can prove beneficial for efficiency. By reducing the need for additional screening, this approach can help streamline the identification of a scalable medium and feed solution that can meet a cell line's specific metabolic needs.

Media formats

A liquid medium format is a popular choice during early smaller-scale development due to its ease of use and off-the-shelf convenience. However, when scaling up to larger volumes, liquid media require larger amounts of storage space, resulting in greater shipping requirements and costs. Therefore, liquid may not be the most appropriate option as processes scale.

A traditional dry powder medium (DPM) format can offer solutions to the issues liquids pose, but some developers may consider the multi-component and multi-step reconstitution process more time-consuming and subject to variability risk. As a result, granular formats such as the Gibco™ Advanced Granulation Technology™ (AGT™) format have been developed to help alleviate these challenges by providing more complete, easily reconstituted "just add water" formulations that are preadjusted for pH and osmolality. These features can help to speed up the medium reconstitution process and can reduce risks from manual error and variability. Moreover, granulated formats offer the same benefits of reduced risks from storage requirements and shipping costs as dry powder media.

Consideration of media format early in the development process can allow for more effective forward planning and ease scale-up. A complete medium and feed workflow solution that is developed in both liquid and AGT formats can reduce the need for requalification with scale-up and provide more confidence in achieving equivalent performance, no matter the scale.

Media development

Some developers may also want to use a media development service to help test the scalability and manufacturability of novel or modified formulations with small-scale prototyping services, spent media analysis, and next-generation multi-omics analytics. Multi-omics can help identify key driving components that have strong positive or negative influences on a particular cell line's production and quality performance.

Although some developers may prefer custom formulations, the optimization of catalog products can be a good alternative, as these products can also be customized to suit the specific needs of a cell line. Media panels and analytics can be used to specifically modify a catalog formulation. This media development approach can result in final formulations that can help improve process productivity and enhance product quality, without the assumed challenges, risks, or costs of full media customization.

A custom or catalog media supplier that offers flexible packaging solutions can also help developers as they scale.

Early consideration of the key strategic aspects of the manufacturing process can help streamline the journey to commercialization.

For example, the availability of a wide range of bioprocessing container (BPC) sizes and configurations can help to efficiently scale up and future-proof a workflow by reducing processing time and manual handling.

Animal origin vs. chemically defined

Within bioprocessing, the use of chemically defined (CD) and animal origin–free (AOF) components in media and feeds has become more standard and highly preferred. Compared with products of animal origin (AO), these formulations can help improve lot-to-lot consistency and support streamlined regulatory approval. Additionally, reducing reliance on AO components, like serum, can help reduce the risk of a workflow being impacted by supply challenges and market uncertainties.

Optimizing large-scale manufacturing early

Capacity and availability

When developing a cell culture process, it is important to consider manufacturing capacity at a larger scale early on. This is especially key for developers relying on contract development manufacturing organizations (CDMOs). Gaining an in-depth understanding of the capabilities a potential manufacturing organization offers is critical to selecting the optimal partner.

Developers should know about the CDMO's mixing and bioreactor capabilities, such as whether stainless steel or single-use bioreactors are available. It is also important to understand the timelines and availability of a CDMO to help ensure they are aligned with internal project deadlines. Working retrospectively and obtaining this information after process development may cause delays and result in further development costs.

Process method

Developers will need to weigh the advantages and disadvantages of different available process options and production methods. Fed-batch, intensified fed-batch, and perfusion bioprocessing methods can be used by biologics manufacturers. Fed-batch processing is a popular choice and may provide a lower cost of materials and more manageable unit operations. Intensified fed-batch processing can provide similar benefits and shorter run times.

Perfusion processing also has its benefits, especially for proteins that are challenging to produce or pose stability issues. With the constant removal of spent medium from the bioreactor, the product can be protected from degradation and stress, helping to maintain protein quality. Additionally, perfusion has shown the potential to yield higher quantities of product than fed-batch processes.

Adherent vs. suspension platforms

The impact of cell culture platforms on scalability must also be considered when deciding between adherent or suspension culture. Adherent platforms offer versatility and simplicity at small scale; however, because adherent cells are attached to a substrate, scalability is limited by surface area. Adherent cultures also require additional process steps and labor associated with cell dissociation and more frequent subculturing.

Suspension cells are not attached to a substrate and grow suspended within the medium. A suspension platform allows for higher cell densities and can achieve significantly higher protein yields within a smaller vessel footprint, compared to an adherent culture system. This makes suspension cell culture more easily and efficiently scalable than adherent culture. Suspension culture platforms can also be operated as closed systems, with more in-process monitoring and controls that provide further enhanced operational efficiency.

Other considerations

Developers must thoroughly consider the many engineering process variables of their workflow to maintain optimal cell culture conditions and enable seamless scale-up. These variables can include maintaining control of pH and dissolved oxygen, as well as potential adjustments to agitation and gassing strategies. Selecting an experienced culture supplier that offers access to knowledgeable field application scientists can provide insights into challenging engineering process.

Choosing a trusted supplier

As developers progress their biologic to commercialization and scale-up, security of supply is essential. Working with a supplier that offers an extensive network of redundant harmonized manufacturing sites can help reduce supply interruption risks and provide additional confidence.

The right supplier should also support the regulatory approval process, which can be a daunting undertaking for some developers and delay their product commercialization. A supplier that can provide traceability documentation for products, including Drug Master Files (DMFs), Regulatory Support Files (RSFs), and Certificates of Origin (COOs), can help streamline the regulatory approval process.

Optimizing scalability with early strategic decision making

Scalability is a key challenge within the cell culture industry, and early consideration of the strategic aspects of the manufacturing process can help streamline the journey to commercialization. Strategic decision making is needed in areas including media and feed product selection, potential media development services, cell culture platform and process methods, and selection of an experienced, trusted supplier that can support a seamless transition to large-scale manufacturing. By considering all sthese factors, developers can minimize obstacles and ultimately accelerate the delivery of new treatments to patients.

Aim higher, reach new peaks
Scale your processes with confidence

With AOF formulations and high-performance options, Gibco™ media and feeds for cell culture have been designed to help you scale seamlessly.

An off-the-shelf, ready-to-use workflow solution, the Gibco™ Efficient-Pro™ Medium and Feeds System was designed with scalability in mind. The high-performance media and feeds are available in liquid or the AGT format, so you can be confident in equivalent performance, no matter the scale.

For custom formulations, the Gibco™ Rapid Prototyping Service offers small-batch custom media manufacturing solutions. This allows you to test and modify your formulations to improve cell culture performance and prepare for scale-up.

Through a global network of harmonized facilities and manufacturing redundancy, you can reduce the risk of supply disruption and focus on your journey to commercialization.

Learn more about how our portfolio of scalable products and extensive technical support services can help you unlock your cell culture edge at thermofisher.com/performance

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