Article

Media by Design Services

Cell culture

Scalable by design

Overcoming common media scalability challenges

Within the biopharmaceutical industry, maximizing speed to market is vital to rapidly deliver life-changing biologics and achieve commercial success. Efficient process scale-up is critical; however, struggling with process scalability is a common issue for developers. Challenges associated with cell culture media scale-up include format, supply, and consistency.

Media scalability is especially vital to consider during early-phase development, because if challenges are only discovered once regulatory filing has begun, developers may face expensive and time-consuming media redevelopment and qualification projects. Therefore, anticipating and avoiding these potential obstacles is essential. This article discusses four key media development considerations and outlines steps you can take to streamline the transition to commercial manufacturing.

Format

When working at bench scale during research and development, media in a liquid format is commonly used, reducing the need for additional reconstitution steps. However, when scaling up, you may decide to use a dry powder format instead to simplify shipping logistics and reduce storage requirements. As a result, it is crucial to confirm that your formulation can perform equally in both dry and liquid formats, as certain media formulations may not be suitable for format conversion. One way you can assess this is by leveraging a media prototyping service. Through this service, you can test small batches of media and verify that format conversion can be successfully completed.

The potential negative impact of a media formulation being incompatible with the desired format highlights the importance of establishing your process requirements during media development. By identifying the ideal media format for your scaled-up process early and developing a formulation with this in mind, you can help reduce the risk of scale-up delays.

In addition to dry powdered media (DPM), many suppliers are now offering more advanced dry formats, designed to streamline and de-risk reconstitution.

While DPM does streamline shipping and storage logistics, it requires additional preparation steps—including weighing, hydration, and mixing, as well as adjustment of pH and osmolality following reconstitution—when compared to liquid media. This can make DPM more labor-intensive and challenging to operators, who require additional protective equipment and procedures to minimize the risk of handling. Advanced granulated formats can help solve these challenges, providing all the economic benefits of a dry powder with the convenience of a liquid format. The Gibco™ Advanced Granulation Technology™ (AGT™) dry media format, for example, is pH and osmolality pre-adjusted, exceeding traditional dry format performance and accelerating time to market.

Manufacturability

During scale-up, media manufacturing vendors will attempt to match the original manufacturing process used during research and development. However, to achieve success at large scale, further optimization may be required. For an accurate transition, you should provide manufacturers with appropriate insights in the form of detailed media batch records.

The vendor's non-CGMP pilot manufacturing teams can also assess the feasibility of your custom formulation and suggest changes to improve manufacturability. This can include highlighting components that are difficult to source or raw materials that may not be appropriate for a cost-sensitive workflow. Choosing a prototyping service from a knowledgeable vendor can also give you access to further media manufacturing expertise, helping you add novel components or remove components not driving cell culture performance. You can therefore take advantage of in-depth expertise early in the process to develop a formulation that is both optimized and manufacturable at large scale.

Supply assurance

As commercial production volumes increase, maintaining a consistent supply of cell culture media is vital to prevent delays. To achieve this, it is crucial to consider a vendor's capabilities and assess whether it can meet your requirements, now and in the future. Working with a manufacturer with global redundant capacity, strong logistical networks, and demonstrable continuity of supply for raw materials can help reduce risks. Furthermore, seeking agreements with secondary and even tertiary media manufacturers can also help maximize the security of your media supply.

Minimizing the use of materials that are subject to volatile markets can further help maintain consistent supply and facilitate manufacturing efficiency. For example, a specialty raw material that is only supplied by one or two vendors on the market may not be feasible for commercial manufacturing. Whether animal origin (AO) components are appropriate should also be considered, as they can come with supply chain concerns that may impact availability, such as disease or drought. However, AO components, such as peptones and serum, can potentially improve performance.

Understanding these risks at the beginning of your media development project and taking steps to mitigate them is key to help reduce the likelihood of supply chain issues.

Batch-to-batch consistency

Another key consideration is maintaining batch-to-batch consistency of your formulation at large scale. Assessing manufacturing equivalency is pivotal when working with a media manufacturer that has multiple sites. Harmonization of these sites, in terms of raw materials, equipment, processes, and training, for example, is vital to achieve consistency.

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It is also critical to consider the potential variability of each raw material used in a process, as this can lead to cascading problems. You must consider that the same material from different suppliers can vary in performance and quality, which may affect process consistency. Therefore, it is important to confirm that the supplier has strict raw material characterization protocols.

Furthermore, AO and other non–chemically defined components can introduce variability, so it is vital to consider their role in your process. If these are used, choosing a supplier that employs strict manufacturing processes and robust quality control protocols to minimize lot-to-lot variability can help you optimize process consistency. It can also be advantageous to utilize advanced analytics to identify any raw material impurities that may have a particularly significant effect on process performance. These findings can then be prioritized during raw material screening to further reduce the risk of variability.

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Finally, in addition to the product itself, consideration should also be given to how factors within the process could impact variability. This includes any additional steps required, such as hydrating dry format materials or making adjustments to pH or osmolality, as highlighted when considering format selection and conversion for scale-up.

Making the right decisions early

An early understanding and consideration of scalability and the commercial manufacturing process is key to support rapid biopharmaceutical process development. By undertaking media development with these challenges and solutions in mind, you can help reduce the risk of costly delays during scale-up.

By working with an experienced collaborator that can offer prototyping services, analytical expertise, and vast industry knowledge, you can create a medium that is scalable by design. Crucially, this can help you streamline the transition to commercial manufacturing and accelerate your product's route to market.

Learn more about our comprehensive portfolio of customizable media development services at **thermofisher.com/mediabydesign**

For more information on streamlined media manufacturing, no matter the stage or scale, visit **thermofisher.com/media-manufacturing**