SARTORIUS

Article

January 31, 2023

Keywords or phrases:
Media Preparation, Mixing Performance, Scaling, Single-Use Mixer, Cell Culture Media , Powder Properties, Critical Process Parameters (CCPs)

Considerations For Media And Mixing: Developmental, Clinical, And Commercial Phases

Ahmed Abouzeid and David Menahem, Sartorius

There are a number of key considerations drug developers must evaluate in the early phases of preclinical and clinical work. While each is important to delivering an optimal final product, some organizations may neglect to adequately prioritize certain elements in favor of agility or short-term cost savings. Media and mixing are two such considerations – while many developers are keen to optimize media and mixing for a given application, they may lack the incumbent expertise and experience necessary to evaluate all of the key variables that influence media preparation and scaling.

Regardless of phase, media and mixing optimization can afford operators an advantage in speed and efficiency for drug processing; likewise, failing to prioritize media preparation can serve to compromise it. Ultimately, there are three core factors that influence media preparation that organizations must consider in order to optimize media at each stage:

- Media and mixing performance
- Analytics and data
- Process optimization

By prioritizing these factors at the developmental, clinical, and commercial phases, organizations can establish a robust, reproducible media preparation process that incorporates advanced analytics and supplier expertise to ensure consistency and quality. In doing so, they can establish process control and monitoring that minimizes or eliminates suboptimal or compromised media batches.

Process Optimization for Peak Media Performance

Cell culture media preparation is one of the key factors impacting cell growth and drug product yield. Media provides an energy source to enable cell growth; media selection hinges on a range of variables, including cell type, raw material selection, and mixing rates and volumes, among other variables. While some applications can be adequately served by off-the-shelf media, the intricacies that attend certain emerging cell therapy modalities can often necessitate customized media development.

The importance of consistently meeting the critical quality attributes (CQAs) of media requires operators to focus on a broad range of considerations, including pH, osmolality, dissolution times, raw material solubilization and sourcing, and equipment and single-use technology (SUT) selection. Different media have different compositions and thermodynamics, necessitating different mixing times. Additionally, the size and shape of bags selected for media mixing, coupled with mixing rates and approaches, can serve to greatly impact the final media quality.

When considering process optimization for media, the efficiency of the chosen mixing or dissolution times when transitioning from powder media to liquid media is an important facet of scale-up. Mixing times should be optimized to match the realistic needs of the media to ensure ideal dissolution, as longer dissolution times can enable the growth of microorganisms. In conjunction with this, developers must establish a thorough understanding of all raw materials utilized in the formulation, including whether they solubilize completely at room temperature, as well as whether any materials necessary for the formulation may be poorly soluble. Good knowledge of the raw material properties and sources must be established during the optimization phase – without detailed knowledge of the product, a process cannot be efficiently optimized.

Media and Mixing Performance: Scaling with Purpose

Optimizing the media preparation process early is critical to later success; equally critical is ensuring that media and mixing optimization is retained as a process scales. One of the core measures of consistency in scaling media preparation relates to pH behavior – changes or spikes when scaling up mixing can indicate issues with mixing rates that need to be addressed. Careful monitoring during the mixing process must be established, with measures such as conductivity, to ensure complete media and raw material dissolution. Early indicators of incomplete media dissolution in water are often visible to the naked eye, such as the presence of colored filters after filtration. Determining how filterable a media is going to be is critical, particularly at larger scales, as neglecting to address dissolution can result in bottlenecks and manufacturing delays.

Media dissolution times must be correctly scaled up to match the target, particularly as an application reaches larger scales. Any major unexpected dissolution time deviations can be a result of incomplete dissolution and can result in contaminated or unusable media. For best performance, the media and mixing must be optimized to occur at a specific range of temperatures; selecting media and raw materials that require different temperatures at mixing is untenable, as it can cause serious media stability issues and enable microbial growth. The question of temperature must also, of course, be applied to storage: operators should carefully monitor liquid media upon storage (typically between 2 and 8 degrees Celsius) for any possible precipitation or any other undesirable chemical reactions that may result in obvious color change. Darkening of the media upon storage may be a natural occurrence, but more drastic changes in color can indicate problems with the media.

Another factor influencing mixing time is whether the equipment used is capable of providing enough speed and torque to mix efficiently. This, coupled with the size and shape of the mixing bag or container, represents the two key variables to establishing an optimal turbulent flow and eliminating "dead zones," or areas of the container where no mixing is occurring. Ideally, a mixing strategy will be well-balanced enough to result in a vortex inside the bag, pulling powder into the water and resulting in optimal mixing. Again, issues related to inefficiencies in mixing can sometimes be readily seen in the form of powdered lumps at the corners of a bag, alerting operators to inefficiencies in one of these two arenas. Finally, material loss during preparation can harm a final media product. Media preparation steps can be simplified thanks to the ergonomics of the mixing system. The robustness of the tank and the powder transfer system, combined with the robustness of the bags, serves to help operators circumvent any issues that might come from mishandling.

Incorporating Analytics to Complete the Picture

There are a number of important analytical approaches to consider when working to establish a media preparation protocol. Two of the most important assays in this regard involve measuring final pH and osmolality, which can each be measured and checked using appropriate probes and assays. The use of internal sensors allows for real-time monitoring of pH and a reduction in handling steps. For this level of monitoring, even the placement of the probe is essential – especially at large scales, placing a probe in one spot over another will result in different pH readings and the potential for pH spikes. Additionally, the integration of analytics to check amino acid composition of the media can help operators spot any possible degradation, as amino acids are the building blocks of proteins.

Ultimately, media selection and preparation are crucial in virus-based, cell, and cell product therapeutic development. From the moment an operator opens a container of powder media, a level of confidence should exist in not only the media's biological or cellular performance but also the physicochemical properties that determine its overall performance as part of a manufacturing strategy. To achieve this, a thorough understanding of the variables that impact media optimization, as well as the potential challenges that can result from neglecting certain key variables that influence media preparation, is required.

Sartorius, a leader in media preparation and formulation solutions, specializes in a number of key products across the sector related to cell cultivation, fermentation, filtration, purification, and fluid management. Sartorius' expertise in customized media, coupled with its flexibility in helping customers explore solutions to increase titers, improve cell culture performance, and reduce risk, makes it a premier partner for media and mixing. With its own manufacturing and R&D sites in Europe, North America and Asia, and an international network of sales companies, Sartorius possesses a global reach and extensive expertise. Furthermore, its incumbent understanding of the challenges associated with each manufacturer's unique intensification pathway, from development to manufacturing, positions Sartorius as a reliable partner able to support troubleshooting, scale-up, and optimization for biotherapeutic developers.

Sales and Service Contacts

For further contacts, visit
www.sartorius.com

Germany
Sartorius Stedim Biotech GmbH
August-Spindler-Strasse 11
37079 Goettingen
Phone +49 551 308 0

USA
Sartorius Stedim North America Inc.
565 Johnson Avenue
Bohemia, NY 11716
Toll-Free +1 800 368 7178