Bioprocess for Beginners: From Shaker to Bioreactor

An interview with David Solbach, M.Sc., Scientific Communications Manager at Eppendorf AG Bio Process Center.

A Q&A

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A new eight-blade impeller is designed to ensure gentle mixing and reduced cell settling compared to pitched-blade impellers at the same agitation speed.

Stem cell-based technologies are one of the most promising approaches in the advancement of cell therapy and regenerative medicine. To make progress towards commercialization, researchers are evaluating standardization of their cultivation and efficient scale-up.

David Solbach, M.Sc., Scientific Communications Manager at Eppendorf AG BioProcess Center, recently spoke with *BioPharm International* about the advantages of changing from shake flasks to stirred-tank bioreactors, the problems that can occur, and aspects to consider to ensure proper cell growth.

BioPharm: Why switch from a shaker to a bioreactor?

Solbach: This is a commonly asked question, especially from scientists who work with flasks and plates and are afraid of switching to a stirred-tank bioreactor. Shake flasks are an easy-to-use and inexpensive choice for basic applications and do not need advanced equipment or sensing and control technologies. However, this very simplicity is also the biggest disadvantage. For example, there is already a significant difference between shaking and stirring in terms of fluid dynamics, which are directly influenced by the agitation mode, stirring direction and speed. This has a direct impact on parameters like heat transfer and cell homogeneity. A bioreactor provides diverse insights into culture performance and the opportunity to monitor and control the process parameters at any given time point. Thus, critical parameters can be adjusted, including temperature, dissolved oxygen, or pH on demand, or an automated process can be programmed.

BioPharm: Where do you see the biggest potential in using bioreactors?

Solbach: The biggest advantage can be found in the possibility of automation, constant monitoring of a process, and automated adaptions controlled by intelligent software to decrease the risk of failures that naturally appear when multiple manual steps are involved. Consider the risk of a contamination, especially when working in larger volumes such as hundreds of liters. Stem cell media is quite expensive and can be lost to contamination.

For stem cell customers, another advantage is the availability of single-use vessels. For example, our BioBLU Single-Use Vessels are pre-sterilized and strongly reduce the risk of cross-contamination, which might appear with traditional glass vessels as a result of failures during the sterilization process. An additional advantage of single-use vessels is they are lighter weight than glass vessels, which makes them easier to handle.

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BioPharm: What aspects need to be considered when scaling up with a bioreactor?

Solbach: There are several things to consider. One of the most important parameters is oxygen. The availability of oxygen in a bioreactor is the key to success for bioprocessing. For a microbial fermentation, it is fairly easy to ensure proper oxygen supply because bacteria cells are more robust than stem cells. A Rushton-type impeller with high agitation speed can ensure good oxygen transfer to the medium. In contrast, stem cells are very sensitive to shear stress and have to be treated carefully. Therefore, an impeller with pitched blades and slow agitation speeds is typically used to ensure gentle culture mixing.

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In bioprocessing, the oxygen transfer rate (OTR) describes the oxygen transfer from a gauge space to the culture medium. The OTR is considered a key engineering process parameter to culture scale-up and is influenced by many different factors: bioreactor dimension, agitation speed, gas flow rate and concentration, and impeller design. Most scale-up strategies aim for keeping one or more parameters constant across scales. For example, it is important to adjust the steering speed to maintain assimilative speed. For proper cell culture scale-up, it is important to select equipment of different sizes with similar kLa capabilities that offer sufficient overlapping so that the small-scale success can be replicated in larger volumes.

Stirred-tank bioreactors provide the design that is comparably easy to describe with classical engineering approaches such as the vessel geometry, impeller diameter, vessel diameter, liquid height and ratios. This is the design that most research concerning scale-up phenomena has been conducted on and was transferred to our single-use vessels.

BioPharm: Are there innovative impeller adaptions in the field of stem cell cultures?

Solbach: There is an increasing tendency in the field to move from shake flasks to stirred-tank bioreactors, especially with the focus on scaling up standardization and reproducibility. In classical microbiology, the Rushton-type impeller with high agitation speed is used, while for stem cell applications, a pitched-blade impeller with slow agitation is preferred to ensure equal mixing and low shear stress for the cells. This is one aspect that frightens stem cell scientists who start working with a bioreactor. Particularly with stem cell culture, it is important to find the right agitation speed that does not harm the cell while ensuring a good oxygen supply and prevents the cell from settling.

A pitched-blade impeller does a great job of mixing efficiency and low shear stress simultaneously. However, a common problem is that cells settle when the stirring speed is too slow. To overcome this challenge, Eppendorf has developed a new impeller with eight blades—together with Professor Zweigerdt from the Hannover Medical School—designed to keep cells in solution even at low stirring speeds. The eight-pitched blades ensure gentle mixing and reduce cell settling compared to pitched-blade impellers at the same agitation speed.

BioPharm: Can you provide an example of how automation in bioprocessing can be advantageous?

Solbach: Automation is especially useful for processes running in perfusion mode. In the Zweigerdt group, the effect of manual-fed-batch feeding and perfusion on the performance on cell growth have been tested. In the perfusion set-up, feeding and harvesting were automatically controlled, while in the fed-batch run, the medium was manually exchanged. The automated process not only decreased the workload, it also reduced the risk of contamination, which is highly undesirable when working with stem cell cultures. Cells grown in the perfusion set-up had an overall better performance resulting in a higher yield compared to the manual fed-batch run.