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OVERCOMING OBSTACLES IN FINAL ULTRA-FILTRATION STEPS

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Preparing your product for for the vial

Cross flow filtration can be used in a range of applications within biopharmaceutical manufacturing processes. Microfiltration technology is incorporated into perfusion bioreactor operations for cell retention and can be used for harvesting bioreactors used to manufacture extracellularly-expressed products. In downstream operations ultrafiltration can play a significant role in concentrating intermediately purified product pools, thereby minimizing processing volumes. Ultrafiltration typically also plays a key role in enabling product to be diafiltered into solutions that permit subsequent chromatography operations to achieve maximum separation performance.

Often a critical application for ultrafiltration is at the end of the purification process prior to final bulk filtration. At this stage excipients are typically added and the final product concentration specification as it will occur in the vial must be met. Given the importance of the end purification step it attracts surprisingly little attention in literature and yet it can present great challenges to bioprocess engineers.

One difficulty is that the final product specification including the product concentration, excipient and aqueous delivery solutions are finalized late in the drug and manufacturing development processes. This immediately creates time pressures and demands flexibility from engineers. Single-use technologies that can readily accommodate design changes are beneficial in such circumstances.

Very often the concentration of the product entering this step is low and the volumes to process high which is determined by the elution conditions of preceding chromatography and virus filtration operations. Final drug dose concentrations can be extremely high indeed, sometimes exceeding 200 g/L. Some manufacturers will perform a large number of buffer exchanges (7-10 diavolumes) in order to enable complete removal of the previous product-containing solution components ensuring these impurities do not reach patients. These factors combine to create the need to remove significant volumes of filtrate and the most efficient way of achieving this is often to incorporate large filtration areas in order that the process completes in a reasonable time frame without concentrated product being cycled through high shear environments, which in turn, can lead to product aggregation and the failure to achieve key product quality specifications.

Incorporating large cross flow filter areas into these processes brings its own challenges. Firstly, this area represents a point at which significant yield loss can occur as the product can bind to these membranes and a suitable recovery step needs to be built into the process. Yield losses at this late stage of the process are particularly undesirable because they occur when the greatest value has been added to the product by the process. Secondly, having large filter areas in the process makes the fine control required to achieve accurate product concentrations at low volumes difficult. If the flux rate across the membrane is sufficiently high and the membrane area large, excessive over-concentration and increased product aggregation are real dangers. That being said, some level of over-concentration within limits is frequently required and systems should be designed to allow subsequent back dilution with the diafiltration buffer. Some manufacturers will choose to use two ultrafiltration systems for this step. The first set-up has adequate capacity to process the large volumes that are anticipated while the second allows the fine control needed to hit the final bulk product specification.

The final steps in this operation can be extremely critical. Membrane rinses designed to maximize product recovery must be added back to the concentrated and diafiltered product in the retentate container. This is challenging because the concentration of product in this rinse is unpredictable and thus the impact of adding it back into the retentate pool on the bulk product is difficult to determine. Excipients may be added at this point but are frequently added in low volumes requiring robust control of dosing into the retentate container and the avoidance of over diluting the product pool. Good mixing of the product pool is a pre-requisite for this step and it is likely multiple samples will need to be pulled from the product pool for protein concentration determination at 280nm.

The design of final ultrafiltration steps requires careful consideration given its critical role in ensuring bio-pharmaceutical products meet their specification when delivered to the vial. These considerations must encompass process and equipment design and operational requirements. Failure to do so results in significant deviations, difficult and expensive reprocessing operations and potentially even batch failure.

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