

PRODUCT SIEVING CHALLENGES IN TFF PERFUSION CELL CULTURE

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Integrated continuous biomanufacturing has gained significant interest because of its potential to streamline production by integrating upstream and downstream processes. Combined with an intensified perfusion bioreactor, continuous processing can greatly reduce cost, space requirements, and handling steps, while improving production efficiency.^{1,2} During perfusion operation, product and spent media are removed while cells are retained within the bioreactor with a cell separation device. In particular hollow fiber membranes, attached externally to the bioreactor, permit tangential or alternating flow filtration (TFF, ATF), as cells are recirculated through the unit and permeate is harvested for downstream processing.^{3,4} However, membrane fouling and issues with product sieving, especially associated with a TFF setup, have a direct impact on total product yield from the process, and can cause hollow fiber reliability issues which in some cases can result in premature termination of a bioreactor run. It is hypothesized that membrane fouling from host cell proteins, cell debris, or additives such as antifoam can result in decreased product sieving as product transmission through the membrane decreases over time.^{5,6} Toward addressing issues with product sieving, we aim to identify the underlying causes of membrane fouling, associated with host cell proteins and antifoam, and to develop new methods to lengthen their lifetime during perfusion operation. This presentation will focus on some tools and experiments that we have conducted to address this issue with the goal to identify factors within the bioreactor that lead to reduced product sieving and implementation of new strategies to mitigate the effects of these factors during operation.

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