

Filtration requirements for small-scale bioreactor harvests

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Introduction

Due to high cell concentrations inherent to cell culture media processes, the harvesting and product clarification (cell removal) of batch and fed-batch bioreactor systems typically poses a significant practical challenge to a biopharmaceutical manufacturer, even at the small-scale.

The requirement to maintain a high level of product quality coupled with the ever-increasing pressure to maximize productivity while reducing operational costs creates further considerations during the specification of any new process.

Traditionally, techniques such as centrifugation or coarse filtration have been employed to provide clarification of bioreactor outputs prior to more refined downstream purification steps. However, operations of this type may require significant financial outlay in terms of initial equipment investment and ongoing maintenance while cellulose-based depth filters need to be pre-flushed, requiring time and additional manual operations.

When correctly sized, specified and controlled, single-use normal-flow filtration (NFF) systems can provide the biopharmaceutical manufacturer with high-quality, rapid and cost-effective clarification of bioreactor outputs.

Methodology

NFF trials were performed in conjunction with a large biopharmaceutical manufacturer on the output stream from single-use, 25 litre bioreactors used to grow Chinese Hamster Ovary (CHO) cells for research purposes. The typical viable cell concentration of the bioreactor output used for testing was 7×10^7 cells per millilitre.

The key system performance criteria were speed of processing and ensuring that filter blockage did not occur mid-batch.

Testing was conducted with Parker domnick hunter's range of biopharmaceutical filtration products, primarily the PROCLEAR GF prefiltration product and PROPOR HC, high-capacity sterilizing-grade membrane filter.

These filtration devices were used in conjunction with Parker domnick hunter's SciLog FilterTec laboratory-scale monitoring and control system. The system provides analysis of throughput volumes and system pressure parameters in order to provide comparative performance data for optimum system selection.

Results and Discussion

Initial disc testing indicated that a 5 micron or 10 micron PROCLEAR GF prefilter followed by a PROPOR HC sterilizing-grade filter offered optimum throughput performance levels. These products are described in more detail in Table 1.

Subsequent scale-up testing conducted using large-scale MURUS capsule PROCLEAR GF and PROPOR HC filter products provided confirmation of the initial results and were used to establish approximate sizing guidelines for systems of this type which are shown in Table 2.

Conclusion

The proposed system for harvesting small-scale bioreactors provides plug-and-play functionality, allowing for immediate use without the requirement for any initial flushing. This allows extremely rapid bioreactor harvest times to be achieved for small-scale processes.

Incorporating automation into single-use NFF

Parker domnick hunter's SciLog bioprocessing platform is designed for use in disposable NFF applications from discovery to production-scale. Patented technology within the platform enables constant pressure or constant rate NFF via a pump PID loop including disposable inline pressure sensors. Automated systems prevent manual errors while allowing walk away operations and higher levels of safety.

SciLog NFF systems incorporate the patented RP-stat mode, an innovation which has resulted in significant improvements in filter life expectancy. This is done by selecting three simple process variables including initial flow rate, maximum inlet pressure, and minimum flow rate. By using the RP-stat method, as the membrane begins to foul, the SciLog NFF system dynamically adjusts the flow rate which allows additional product to pass through the filter. This is shown graphically in Figure 2.

Figure 1 : Small-scale bioreactor harvest process

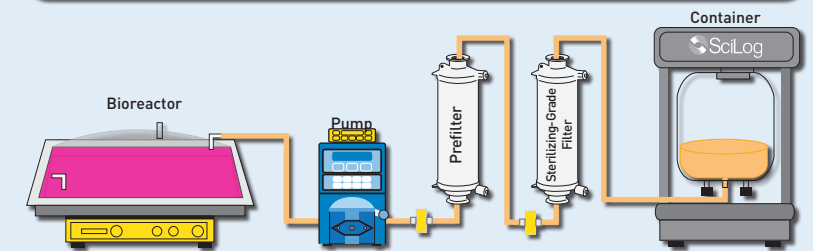


Table 1 : Filter product descriptions

PROCLEAR GF

- Pharmaceutical grade, glass-fibre depth media prefiltration product.
- Designed to provide exceptionally high dirt-holding capacity and low extractable levels making it well-suited to biopharmaceutical applications.

PROPOR HC

- Pharmaceutical sterilizing-grade, high-capacity polyethersulphone membrane filter.
- Designed to provide assurance of sterile filtrate but without compromising on filtration system capacity.

Table 2 : Filter sizing guidelines

Bioreactor Volume (litres)	PROCLEAR GF (5 micron)	PROPOR HC (0.2 micron)
5	10"	'A' Size
10	20"	5" ('K' Size)
20	30"	10"
25	2 x 20"	10"

Figure 2 : Dead-end filtration by R/P stat method

