Crossflow Filters Enter the Disposables Arena

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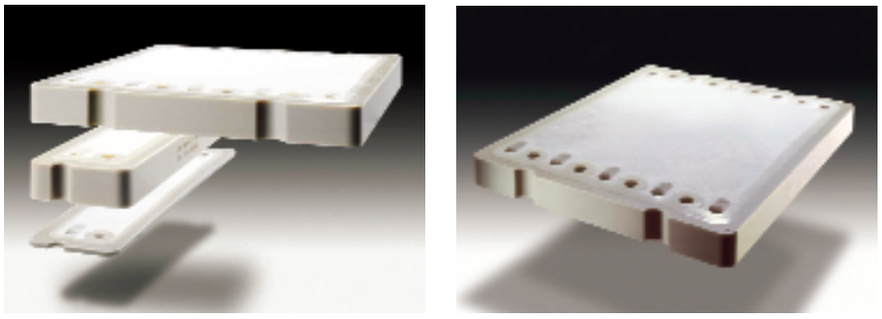


Crossflow ultrafiltration cassettes for protein purification, concentration, and diafiltration integrate different membrane polymer types well established in the biotechnological and pharmaceutical industries. Compact cassette design significantly reduces the hold-up volume. Availability of different filter areas supports scale up. Integrated self-sealing construction eliminates the need for additional gaskets and simplifies handling during filter exchange. SARTORIUS AG (WWW.SARTORIUS.COM)

Continuous cost approval and aggressive timelines at all levels in biopharmaceutical product development require flexible alternatives in fluid handling. Many disposable concepts are well established already. Plastic fluid handling bags and single-use capsules with sterilizing-grade filters are widely used. Because value is added to a product throughout the entire chain of bioprocessing steps, a major objective in using state-of-the-art purification technologies is reduction of cost. That can be achieved by eliminating "obsolete" production steps, such as clean-in-place (CIP) procedures. The decrease in the number of production steps is a major trend driving the biopharmaceutical industry.

Purification steps — such as chromatography, membrane chromatography (membrane adsorbers), virus removal, viral clearance, and ultrafiltration — are integral to biopharmaceutical fluid handling. Such process steps are primarily yield driven and cost sensitive. Many other cost-sensitive aspects — CIP and downtime, for example — are prompting biopharmaceutical companies to seek ways for continuous optimization of their processes. The industry is trying to reduce time-consuming and cost-intensive process steps to speed the time to market for its biopharmaceutical products. Additionally, regulatory bodies are beginning to focus on critical production steps such as CIP. Eliminating those critical points will lighten time-to-market pressure and should accelerate approval granted by regulatory authorities for commercial production and market launch. In addition to the advantages gained by reducing the number of process steps, disposables can minimize potential contamination of a product from within the process chain.

Cleaning validation should be performed to confirm the effectiveness of all cleaning procedures (**1**). Manufacturing processes must be designed and carried out in an achievable and verifiable manner that reduces contamination to predetermined limits. "Equipment and utensils shall be cleaned, maintained, and sanitized at appropriate intervals to prevent malfunctions or contamination that would alter the safety, identity, strength, quality, or purity of the drug product beyond the official or other established requirements." (**2**)

One trend promoting compliance with all the industry requirements described above is the single-use or "disposables" concept. This market-driven approach is already established in many applications as a standard operating procedure (SOP). Disposable concepts are strongly supported by existing products, such as sterilizing-grade filter capsules and plastic fluid handling bags that offer exceptional flexibility. Because of a growing demand from the biopharmaceutical industry, vendors are adopting the concept and extending it to other

process steps such as ultrafiltration and diafiltration. Single-use filters for crossflow ultrafiltration are the latest application of disposable technology.

What Does Single-Use Mean? It means using a filter only once without intensive cleaning. Reduction or elimination of time-consuming process steps such as CIP saves time and labor costs. Simultaneously, single-use filters also lower system downtimes. Products with consistent out-of-the-box performance deliver reliable results. They allow a significant increase in yield, which biopharmaceutical manufacturers can factor into their bottom-line numbers. In addition, disposable filters simplify documentation and are easier to handle than multiple-use filters. Moreover, when used in each production run, single-use filters for crossflow filtration preclude any discussion about cross-contamination issues right from the start.

Economical Aspects

Cost savings that accrue by reducing or even eliminating cleaning steps are mainly attributable to a significant reduction in consumption of water-for-injection (WFI). Are you aware of your current cost-per-liter for WFI? Also important are other costs: cleaning solvents, chemicals, labor, and analysis for CIP effectiveness and batch release. Although CIP of equipment is still required with disposable crossflow filters (**2**), it can be carried out in a shorter time by using more aggressive conditions (increasing the temperature and concentration of the CIP solution) than otherwise. Eliminating CIP steps and associated validation issues saves the most time and cost.

The following are key prerequisites of the biopharmaceutical industry when considering single-use filters designed for crossflow filtration:

- Consistently repeatable results
- High performance and yield increase
- Testable for integrity both before and after use
- Wide range of pore sizes (microfilters) and cut-offs (ultrafilters)
- Competitive unit costs for consumables
- Aseptic processing with steam-in-place (SIP) disposable filters.

The single-use concept is ideal for early stage research and development applications. New applications and process improvements are focusing on the single-use concept as well. Practical experience with the concept shows that aggressive clinical-phase timelines can be achieved only by integrating disposable or single-use designs and eliminating the CIP step. Single-use ultrafilter cassettes, sterilizing-grade filter capsules, membrane chromatography disposables, and disposable plastic bags are among the solutions presently offered. At each production step, more and more value can be added to the final product.

Contamination Issues: Total organic carbon (TOC) clearance and concerns about extractables can be addressed by disposable filters. Well-known sources of preservatives (**3**) combined with validated flushing procedures guarantee the lowest TOC levels.

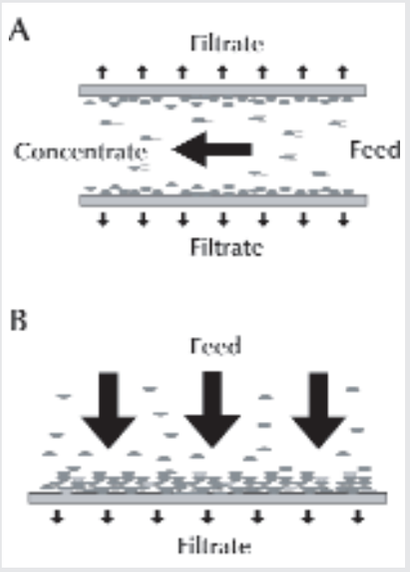
Most polymer membranes need to be stabilized as a result of reduced performance capabilities following the first CIP procedure. The phenomenon is mainly caused by highly caustic contact conditions. An alternate procedure must be established primarily for polyethersulfone membranes. With single-use system components, such procedures can be eliminated to save time and expense and enhance out-of-the-box performance. Large-volume processing under temporary conditions is best for this disposable concept. Contract manufacturers in particular are embracing the idea with their company policies stipulating that filters can be used only once. That significantly reduces the validation documentation necessary.

Case Study: A typical cost calculation example is given for a crossflow system with 5–7 m^2 of filter surface area that is currently in use. Annual batch cycles averaged 35 runs: preparation, integrity testing, and the necessary cleaning procedures. The cost of labor for one worker was factored in at US$35 per hour. The results presented in Table 1 clearly underscore that the CIP procedure is the most expensive step in the process. Even with a conservative price for WFI (here $4/L), a significant cost benefit can be realized by switching from multiple-use to single-use technology. The expected yield increase is not factored in here.

Table 1: Case study cost analysis for switching to single-use crossflow filtration

	Single Use	Multiple Use
A: Handling Cost (US$)		
Operating costs	1,470.00	5,414.50
Annual validation costs	+ 218.75	+ 501.67
Resulting annual handling costs	1,688.75	5,916.17
Value benefit for handling	*4,227.42*	
B: Cleaning Cost (US$)		
Annual cost of materials	157,290.00	374,863.61
Annual validation CIP runs (3/year)	+ 4,517.00	+ 7,100.39
Total CIP cost per year	161,807.00	381,964.00
Cost benefit for cleaning	*220,157.00*	
C: Cost of Materials (US$)		
Cost of materials	134,750.00	7,500.00
Difference in cost of materials	*127,250.00*	
Potential total annual cost benefit (A + B – C)	97,134.00	

Figure 1: Comparison of (A) crossflow and (B) dead-end filtration



Crossflow Filtration

Separation technology plays an important role in bioprocessing. One primary step is the use of crossflow ultrafiltration to purify biotechnology-derived products. As Figure 1 illustrates, crossflow filtration is distinguished from "dead-end" filtration, in that the fluid to be filtered flows parallel rather than perpendicular to the filtration surface (**4**). Such a flow generates shear that limits the thickness of the filter cake or gel layer. In dead-end filtration, the cake thickness increases with time, causing the eventual cessation of flow.

Crossflow filtration offers distinct advantages over other separation methods: improved throughput relative to dead-end filtration and elimination of aerosols (generated in centrifugation), filter aides (used in conventional filtration), and phase changes (freeze drying) (**5**). Because of those and other benefits of crossflow ultrafiltration, it is a widely used process in biopharmaceutical manufacturing.

Success in Purification

Single-use crossflow filters are well-established in biopharmaceutical manufacturing, both in the development of new products and of products in the final clinical phases. These filters offer several advantages: elimination of CIP steps and a consequent reduction of CIP validation work, lowered costs of consumables (mainly WFI), yield increases, and steam sterilization capability for crossflow ultrafilters. The single-use crossflow ultrafilter concept is a new purification process technology. Its acceptance will be based more on changing our way of thinking than on any technical barrier.

References

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