Production-Scale Disposable Filtration in Biomanufacturing

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The trend toward disposable manufacturing is gathering momentum among biomanufacturing companies. Much of it involves filters, tubing, and biocontainers for smaller batches, typically from 5 to 500 L (1–3). A parallel trend can be seen in the manufacture of large-volume biofluids, such as serum or tissue-culture media. For manufacturers of serum, tissue, and cell-culture media, large batches (2500–25,000 L) have become more common, depending on the fluid. Production-scale use of disposable filtration systems does not necessitate smaller batches. In fact, disposable filtration systems can be designed with enough capacity to produce large volumes of biofluids. Some early experience suggests that this can be accomplished with no loss of productivity and with significant cost-savings. This article surveys the economic and operational benefits achieved using production-scale disposable filtration, citing a representative example.

The traditional filtration solution to the challenge of large batches has been to use hydrophilic membrane filter cartridges — rated 0.2 µm, 0.1 µm, or 0.04 µm absolute — sized to accommodate batch processing requirements and installed in stainless steel filter housings. Major drawbacks to that method can include

- Capital expense: stainless housings and piping
- Energy costs: steam generation for sterilization of filters, housings, and piping
- Operating expense: total filtration costs, labor associated with installation, steam sterilization, integrity testing, monitoring, tear-down, cleanup, and disposal of filter systems
- System scalability: ensuring that filtration systems provide adequate performance when extrapolated from laboratory to full production scale
- Cleaning validation: hours of costly analytical and managerial time to formulate and implement a cleaning validation master plan to ensure that cross-contamination of reusable systems is eliminated and to comply with regulatory requirements
- Operational interruptions: production delays caused by flow slowing or stoppage because of foaming, partial airlocking, or unexpected plugging of prefilters as a result of biofluid batch variability or improper filter sizing
- Yield losses: use of multiple prefilters and final filter systems and related hardware, with filters typically oversized to prevent interruption of production, causing holdup of valuable biofluid in filter pleats, filter housings, and related hardware thereby decreasing yields of valuable bioproducts.

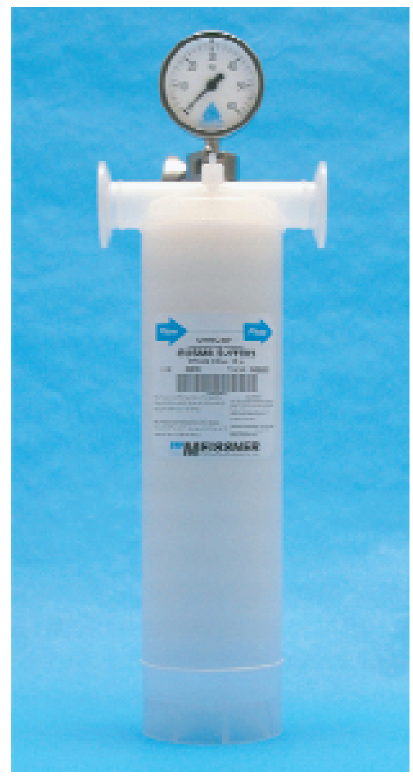

Photo 1: UltraCap® disposable filter assembly with gauge and vent valve
(COURTESY OF MEISSNER FILTRATION PRODUCTS, INC. AND ANDERSON INSTRUMENTS CO.)

THE DISPOSABLE SOLUTION

Throughout the biotechnology industry, in both large- and small-scale operations, disposable filtration is providing opportunities to reduce both capital and operating costs. The high value of biotechnology products has accelerated this trend to disposable manufacturing, even at production scale.

When high-capacity capsule filters are properly designed to replace hard-plumbed production filtration systems, many costs are reduced: the total cost of filters and related hardware, cleaning and cleaning materials, cleaning validation, production time lost to interruption of filtration, and time and energy associated with steam-in-place (**4**). In newer facilities, initial design of disposable filtration and related systems will minimize capital expenditures for water and steam plants and reaction vessels.

Implementation

At biofluid manufacturers — and in the manufacturing departments of numerous biopharmaceutical companies — legacy stainless housings are being removed and replaced with large-scale capsule filter based systems. Each company has its own justification and does its own return-on-investment calculations. High-volume producers of biofluids, such as serum manufacturers, are justifying the conversion on the basis of improved yields, reduced costs of filtration, increased efficiency, and reduced chance for batch-to-batch contamination. Biopharmaceutical companies appear to be most interested in cutting the time and costs of cleaning, eliminating filtration-related cleaning validation, increasing yields by cutting the loss of saleable product, improving production efficiency, and reducing labor costs.

Disposable Filtration

Disposable filtration systems use the same filter media in the same cartridge constructions as those found in stainless housings. That minimizes requalification time for companies converting to disposable systems from stainless steel. Scale-up is facilitated by using the same filtration media in laboratory-, pilot-, and production-scale systems. Disposable systems are available presterilized by gamma irradiation, eliminating concerns for validation, safety, and the energy associated with onsite sterilization. Disposability sharply cuts cleanup costs and protects operators from dangerous drugs and chemicals.

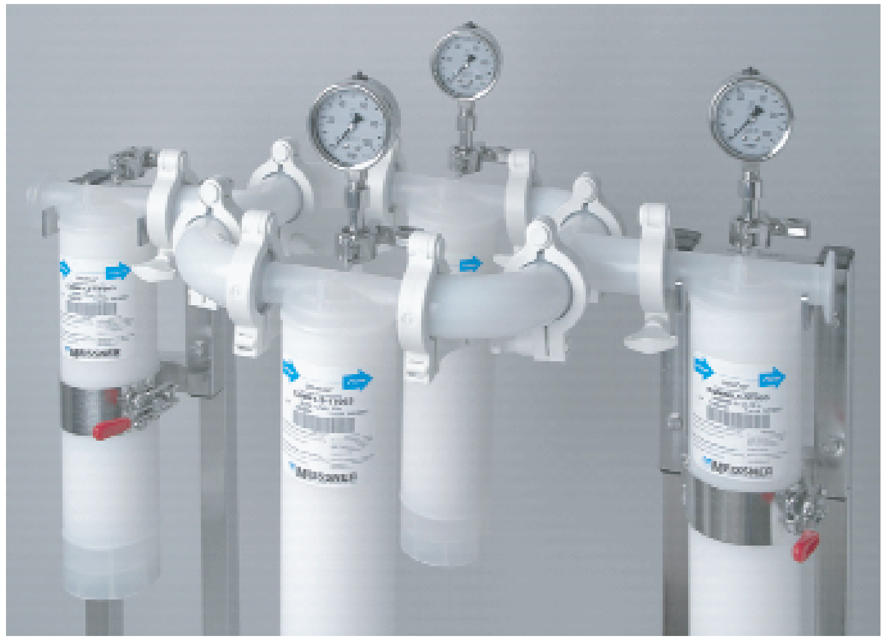

Photo 2: A high-capacity disposable filtration system can be sized and configured to process thousands of liters of biofluids. (Courtesy of Meissner Filtration Products, Inc. and Anderson Instruments Co.)

In an optimized high-capacity disposable system, disposable housings can be configured in series or in parallel, depending on fluid characteristics, flow, and batch requirements (**4**). Batch sizes processed by such systems can range from a few liters to several thousand liters.

A high-capacity disposable filter is the building block of a disposable process filtration system. It contains a 10-, 20-, or 30-inch long filter with T-style connections typically preferred (inline connections are also available), a vent and gauge port atop the polymeric housing, and a drain valve at the bottom of the housing. Low-holdup design is critical to eliminating holdup of valuable biofluid in the filter pleats and housing. Photo 1 depicts the UltraCap filter assembly.

Multiple disposable filter assemblies are sized and connected in series or in parallel in an optimized disposable system. An optimized production-scale disposable filtration system has the flow rate capacity, service life, and throughput capacity to process an entire batch without interruption.

Disposable housings can be configured in series OR in parallel, depending on fluid characteristics, flow, and batch requirements

Gauges on each housing allow monitoring of pressure differentials across each prefilter and final filter. Potential flow interruption caused by foaming or partial airlock can be seen through the translucent plastic housings and vented immediately to return to full flow.

Production-scale systems can incorporate duplexed or triplexed prefiltration. This permits a redundancy or backup capacity to be used only if unexpected batch variations cause premature plugging of prefilters. Such "prefiltration on demand" is made feasible by designing parallel-flow filtration into the system and valving over to backup prefilters in the event of flow reduction caused by unexpectedly high bioburden or particulate loading of prefilters in a given batch. A representative system design is shown in Photo 2.

The above-described operating control measures are designed to ensure continuity of operation during processing and permit immediate responses to flow interruptions. The opacity of stainless steel housings makes direct observation of foaming or airlocking impossible. And it is highly unlikely that stainless steel systems would be designed with redundant prefiltration because of their high capital and maintenance costs.

Table 1: Cost-savings (approximate) resulting from conversion from cartridge-and-stainless housing system to disposable system at a bovine serum manufacturer, for 3000-L batches

	Cartridge filters in metal housing	Single-use disposables
Filter component cost		
Number of prefilters per run	16	4
Number of final filters per run	6	3
Total filters per run	22	7
Total cost of filters per run	$8000	$2135
Labor schedule		
Installation	420	105
Preuse flush and integrity test	90	90
Changeover	30	30
Postuse flush and integrity test	30	30
Changeout (dismantle and clean)	280	70
Total time per run (minutes)	850	325
Labor cost per run at $35/hour	$496	$190
Lost product		
Unrecoverable product per run	450 L	60 L
Cost at $50/L	$22,500	$3000
Batch Filtration Costs		
Subtotal: filter costs per run	$8000	$2135
Subtotal: labor costs per run	$496	$190
Subtotal: lost product per run	$22,500	$3000
Total cost per run	$30,996	$5325
Percent savings		83%

Advantages of Disposable Filtration

The use of fewer filters cuts total filtration costs.

Total labor time and costs are reduced.

Production yields, especially in complex, expensive biological solutions, are increased.

Interruption or stoppage of production are prevented.

Installed backup capacity gives immediate responsiveness, flexibility, and system control.

Direct observation of foaming or partial airlock permits immediate correction.

Cleanup is minimized.

Cleaning validation of filtration system is eliminated.

Presterilization cuts energy cost of steaming, validation costs, and safety concerns.

Same prefiltration and final filtration media facilitate conversion from cartridges to disposables.

Biofluid batches are easily scaled from a few liters to thousands of liters.

Low holdup volume design facilitates high recovery of product fluids.

Disposability protects operators from cytotoxic drugs and dangerous chemicals.

Economic Comparison Case History

Among commercial manufacturers of sera and culture media, batches of thousands of liters are being successfully processed with optimized disposable filtration systems. One serum processor that converted from cartridge to disposable filtration systems had used a 22-cartridge (10-inch equivalents) and stainless steel system. It was replaced with a disposable system that accomplished the same batch filtration results without interruption.

Measurable cost reductions were greatest in yield improvement and total filtration costs. Results are summarized in Table 1. In this process, the total number of filters was cut drastically by adjusting the prefiltration grades and sizing and operating the system so the differential pressure across all filter housings was equal. That prevented premature plugging of the prefilters and provided completion of batches with far fewer filters. Cutting the total number of filters from 22 to seven reduced the total filtration cost by approximately 73%. The total labor cost per production batch run was reduced by approximately 62% through a substantial reduction in installation and dismantle times.

Yield improvement gave the largest payback. By saving some 390 L of wasted product per batch, the company's cost of lost product was reduced by about 87%, about $19,500, by conservatively applying a value of $50 per L. That is largely attributable to using fewer filters per batch, with a correspondingly lower volume of product held up in the filters and less fluid volume trapped in both cartridge filters and stainless filter housings.

Although the total cost reductions in this case were approximated at 83%, most biofluid manufacturers are unlikely to experience savings of such magnitude. At this manufacturer, the legacy filtration system had been substantially oversized to prevent premature plugging from stopping production of some very difficult-to-filter sera. However, the price was a sacrifice in yield that is no longer necessary.

MOVING TOWARD DISPOSABLES

The benefits created by production-scale disposable filtration systems are summarized in the "Advantages of Disposable Filtration" box.

For process-scale biofluid filtration, disposable filtration systems can provide better operating costs and yields than stainless filter housing and cartridge systems. Thus it appears likely that in production-scale biofluid manufacturing operations, many legacy stainless-steel housing and cartridge filter systems will eventually be retired in favor of optimized disposable filtration systems. Initial design of such disposable systems will provide even further cost-savings to biomanufacturers through reduced capital and operating costs.

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