

Single-Use Systems Advance Filtration

Many Recently Launched Products Feature Disposable Modules that Help to Reduce Costs

K. John Morrow Jr., Ph.D.

Disposables for upstream and downstream processing were among the lead topics at IBC's recent "BioProcess International" meeting held in Raleigh, NC. In addition to their convenience and cost-reduction contributions, their use has been shown to result in reduced exploitation of water and electrical requirements. A number of presentations at the meeting dealt with new filtration technologies, many of which take advantage of disposable modules.

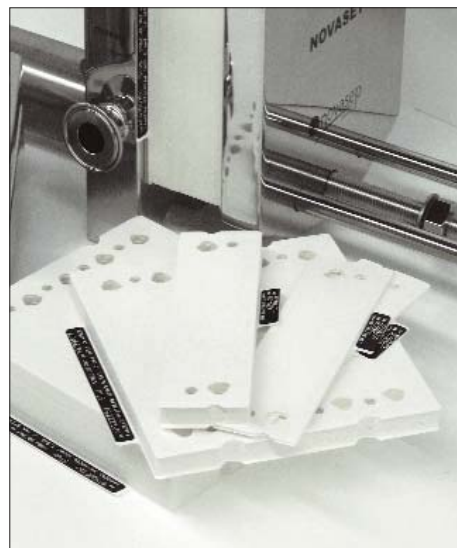
Single-pass tangential flow filtration "is a patented technology that enables high concentration factors in a single pass and delivers the performance of tangential flow filtration with the simplicity of direct flow filtration," stated Steven Pearl, vp for biopharmaceutical R&D at **Pall Life Sciences** (www.pall.com). "The technology results in more compact systems due to its reduced flow-rate requirements and simple control scheme."

According to Pearl, the configuration of Pall's single-pass system is much more straightforward than conventional tangential flow filtration, substituting a flow ratio

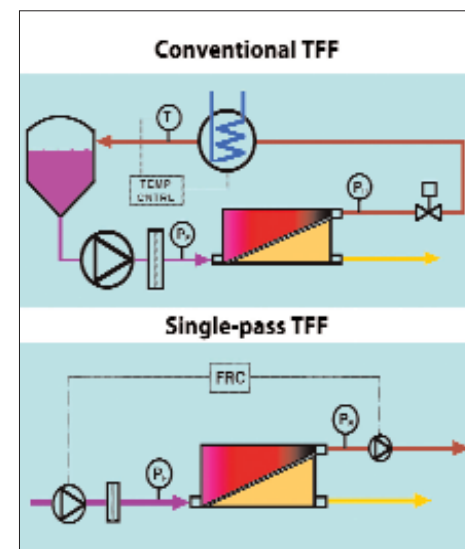
meter controller for a recirculation loop, thus allowing a lower working volume without risk of foaming. The fluids are passed directly through the system, so there is no need for a reservoir to accumulate batches.

Pearl described a number of advantages of the technology, including preassembled, easy-to-install modules, whose optimized flow path permits smaller pumps and tubing. The short resident time means shear forces and viscosity of exposure of the solution will be less. Moreover, process control is reportedly tighter, there is a higher total recovery while at the same time flush volumes are reduced. In addition, single-pass cleaning is purported to save materials and labor.

"The fact that we can work with reduced volumes means that we avoid having to install larger tanks, slow down the process, or split the batches," Pearl noted. "We can employ a simple in-line regulator module with the ability to concentrate our volumes by as much as 10-fold. We can also adjust salt concentrations during processing to improve the performance of the ion-exchange chromatography steps without dilution. This takes into account the fact that cation exchange requires higher



Sius is a presanitized disposable TFF cassette purposely designed for single use. The Sius TFF cassette is also suitable for use with traditional holders and hardware, Novasep reports.



Single-pass tangential flow filtration provides a direct flow path with simple flow ratio control, using a 1/10 smaller feed pump and eliminating the recirculation loop and need to accumulate the batch. Pall

salt concentrations than anion exchange."

Membranes

The gleam of stainless steel is much less in evidence in today's bioprocessing facilities as disposable aseptic filtration units replace the traditional reusable equipment, according to Michael Labreck, sales manager at **Novasep** (www.novasep.com). The company has developed disposable units for tangential flow filtration that are presanitized and prepacked in 0.2M NaOH, ready to use. The modified polysulfone membranes are available in a wide range of molecular weight sizes and are designed for low protein binding.

"The performance of our Sius Single Use TFF cassettes will meet or exceed the performance of traditional, reusable TFF cassettes," Labreck said. "We have engineered features for additional labor savings and better process economics."

Michael Xenelis, senior development associate at **EMD Serono** (www.emdserono.com), reported on his company's use of Sius TFF disposable units. EMD has replaced the step requiring an anion-exchange column with a membrane, and traditional tangential flow filtration cassettes have been replaced with disposable Sius membranes at the initiation and conclusion of the run.

Replacing the anion-exchange column with a Q membrane generated a myriad of benefits, according to Xenelis, including reduction in buffer usage, set-up time, amount of documentation, and maintenance requirements. The membrane comes ready to use from the box, avoiding laborious column packing, and water saving are significant—60 L of innocuous buffer per run in the disposable situation, as opposed to 350 L in the case of the reusable units.

"The final UF/DF tangential filtration step had previously been the longest and most problematic," explained Xenelis.

"This was a major source of frustration for operators, since flux recovery was poor, buffer demand high, and presumably reusable membranes had to be discarded after a single-use cycle."

Use of Novasep Sius membranes for tangential flow filtration, Xenelis explained, allowed the elimination of many steps, much attendant time, and resulted in consumables savings. Total process time was cut from 10.4 hours to 5.1 hours, including installation. Additionally, reductions in the protein A column size allowed a savings of \$37,000 in protein A resin and buffer costs.

"Through the implementation of the Sius TFF disposable cassettes we were able to reduce costs of buffer, bags, labor, and materials by half or more. For these reasons they are now our standard choice for all new projects."

Confronting Challenges

Synthesizing industrial-scale quantities of biologicals, especially antibodies, can introduce unwanted changes into these fragile molecules. The main sources of damage result from sheer stress due to drag as the liquid flows through pipes and tubing, cavitation or vapor bubbles formation, and grinding, when solid parts of the instrumentation impinge against one another.

At the meeting, James Colandene, Ph.D., associate director of drug production at **Human Genome Sciences** (www.hgsi.com), talked about physical and chemical stresses that occur during the filtration process. "We perform small-scale studies to determine V_{max} and flow rate through a given surface area of the filter, taking into

See Filtration on page 45

K. John Morrow Jr., Ph.D. (jmorrow@genengnews.com), is president of Newport Biotech and a contributing editor for GEN. Web: www.newportbiotech.com.

News Bioprocessing Highlights

Genmab to Sell Manufacturing Facility

Genmab (www.genmab.com) is selling its manufacturing facility in Brooklyn Park, MN, and has cut about 300 jobs worldwide as part of an approximately DKK 300 million (about \$445.74 million) cost-cutting exercise. The overall projected savings will include noncash items of approximately DKK 60 million, or about \$89.16 million.

Genmab says that it will continue to focus on the development of antibody therapeutics for cancer and has no plans to drop any of its ongoing projects. As part of its drive to build what it describes as a more flexible model, however, the firm has decided to meet future manufacturing requirements through outsourcing. The Brooklyn Park facility, which is now ready for sale, will operate on a maintenance-only basis until a buyer has been found.

Lonza to Manufacture Piece of Prochon's BioCart System

Prochon Biotech (www.prochon.com) selected Lonza's (www.lonza.com)

Hopkinton, MA, facility to manufacture its fibroblast growth factor variant (FGF2v) in the U.S.

FGF2v is a key regulator of cellular processes involved in blood-vessel formation, wound healing, and the remodeling of bone and cartilage. It is a critical component of Prochon's BioCart™ cartilage regeneration system, which enhances a patient's cells to grow more predictably, according to the company. Prochon also says the cells grow in only 10 to 14 days, compared to up to 6 weeks with other technologies.

DSM Pharmaceutical Inks Manufacturing Alliance with Galenix

DSM Pharmaceutical (www.dsmpharmaceuticals.com) entered into a manufacturing alliance with Galenix (www.galenix.fr). It will now be the preferred commercial-scale manufacturing partner for Galenix' commercial products on a global basis.

In addition, DSM and Galenix will collaborate on business-development opportunities co-marketing Galenix' drug-delivery technologies. n

Filtration Continued from page 42



Disposables avoid cross contamination, allow more flexibility, and usually represent an economical alternative, according to Sartorius Stedim Biotech.

account a greater than 50% safety margin. These studies ensure maximum batch capacity and maximum fill speed.”

At filtration pressures of up to 50 psi, Dr. Colandene’s team observed no adverse effects on product quality. Given the wide range of parameters under which they can perform their operations, Dr. Colandene and his colleagues do not consider filtration pressure to be a key parameter. He did, however, warn against extensive foaming, which denatures biological molecules.

“In our small-scale characterizations we determined that the only significant physical stress on our product was cavitation, which can be avoided with the right equipment.”

More Benefits

Millipore (www.millipore.com) has a long history of filtration technology development. Andrew Bulpin, Ph.D., vp for upstream processing, and Paul Chapman, Ph.D., vp for downstream processing, discussed their company’s commitment to disposable technologies. “Our market for single-use devices is \$400 million, which we predict will grow to \$1.4 billion in the next 10 years,” said Dr. Chapman. “This growth in our product line will be driven mainly by the expansion of antibody therapeutics.”

Indeed, membrane absorbers have shown phenomenal growth, quadrupling in sales between 2005 and 2008. Drs. Bulpin and Chapman stressed that single-use supports sustainability initiatives while lowering costs. Millipore’s results with the application of single-use technology reflect the positive numbers obtained by other firms. Its studies comparing single-use versus stainless steel found that the former required 87% less water, 21% less labor, 38% less space, and 29% less energy for a purification protocol.

In order to deal with validation and regulatory concerns, the company has also initiated an active program for minimiza-

tion of waste associated with single-use technology. The primary aim of this agenda is to drive home even deeper savings. Salient features include monitoring of extractables and leachables in purification protocols using customers’ feeds, comprehensive validation and testing packages for single-use containers, a complete bioreactivity safety profile for all components of single-use containers, and a flexible filtra-

tion concept to reduce waste and enhance operational flexibility.

Affordability Issues

“In bioprocessing, affordability figures into an equation in which we balance the cost of an innovative product versus the efficiency that it delivers,” Uwe Gottschalk, Ph.D., vp for purification technology at Sartorius Stedim Biotech ([www.sartorius](http://www.sartorius-stedim.com)

www.sartorius-stedim.com), explained.

“Consumers have seen how rapidly semiconductor technology has gone down in price over the years, while delivering more rapid performance. The biotech community expects to see the same dynamics in bioprocessing tools. The extent that we can deliver such improvements will go a long way toward the goal of making biotherapeutics affordable.” **GEN**

Say hello to integrated

flexible, single-use systems

Say goodbye to inflexible system design

Achieve maximum process performance with Allegro™ single-use systems

Allegro single-use systems are engineered to meet your specific process requirements.

Working with the Allegro systems team you will benefit from:

- ▶ Unparalleled process knowledge
- ▶ Exceptional engineering experience
- ▶ Wide range of products and technologies
- ▶ Excellence in technical support and validation

To learn more about Allegro single-use systems contact your local Pall representative, or email Allegro@pall.com

Providing Flexible Solutions

PALL Life Sciences

www.pall.com/allegro

© 2009 Pall Corporation. Pall, Allegro and the Allegro Design are trademarks of Pall Corporation. Pall is a registered trademark of Pall Corporation.