

# Disposable Filtration Lightens Cleaning and Validation Load

Pharmaceutical Makers See Multiple Advantages of Single-Use Systems

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Single-use filtration technology is becoming increasingly popular as manufacturers seek to cut costs and minimize processing times.

**T**he latest components in sterile filtration technology are not made to last. In fact, pharmaceutical manufacturers are throwing them out after every batch filtered. Tossed out with them, however, are the expense and time of cleaning, cleaning validation, and maintenance as well as the concerns of cross-contamination associated with multi-purpose production lines.

Single-use systems are earning double takes from manufacturers impressed with the results from disposable assemblies designed specifically for drug development. But the plastic reconfigurations of pharmaceutical processes are doing more than trimming timelines and fattening revenues. Disposable manufacturing has triggered a new approach to risk management

and safety—aspects that have made it an appealing choice for contract service providers and manufacturers of both conventional and biotech pharmaceuticals.

Before manufacturers can consider switching to single-use filtration systems, however, they must have an understanding of their design and performance characteristics as well as their potential effect on manufacturing, testing, and validation procedures.

## Evaluating alternatives

Single-use filter capsules consist of disposable filter cartridges encapsulated in disposable housings typically constructed of gamma-stable polypropylene or polyetherimide. Although several filter capsule models are available, they share many



Example of a disposable capsule filter for single use in biomanufacturing (UltraCap, Meissner Filtration).

essential characteristics (see sidebar, “Ideal attributes of single-use filter capsules”). And, as explained by Holly Haughney, PhD, vice-president of BioPharmaceuticals Marketing at Pall BioPharmaceuticals (East Hills, NY), “All capsules must provide the same particulate retention and media flow as reusable systems as well as have the same form, fit, and function as a traditional system.”

Features such as ease of use, reduced process times, increased personnel safety, and tighter risk-control management have all helped make disposable units an attractive alternative for many

applications, and most filtration companies have broadened their product lines to include both stainless steel and disposable designs. As observed by Steve Tingley, director of biopharmaceutical manufacturing at Millipore Corporation (Bedford, MA), “if an application demands a more-retentive, less-expensive,

or faster-flowing membrane, that need will have to be met in both reusable and disposable configurations.” Choosing the right components then becomes more of a process rather than a selection by rote. Says Tingley, “This provides the end user much more freedom to choose a filter pore size, membrane, and filter device type.”

Although the most noticeable impact of switching to disposable systems is the avoidance of the cleaning and cleaning validation requirements associated with reusable components, the incorporation of a disposable system into an existing fluid path does require a re-evaluation of cleaning procedures, sterilization methods, and connections to other components in the filtration line. Manufacturers must also reconsider their approaches to complying with regulatory testing and validation requirements.

### Sterilization

Stainless steel systems are sterilized by following either autoclave or steam-in-place (SIP) procedures. However, most polymer-based housings are not designed for the conditions of in situ steam sterilization because of the high differential pressures (typically 15 psi) that can develop at the elevated temperature for steam sterilization (typically between 121 and 140 °C). Thus, most disposable filter capsules must undergo autoclave sterilization and be connected under aseptic conditions or be purchased as presterilized units or as part of larger configurations.

If filter capsules are to be used with other disposable components such as disposable bags, tubes, and connectors, the entire system can be sent to a contract sterilizer. However, as Tingley observes, “a presterilized component cannot simply be dropped into a stainless steel process.” Operators must have a procedure for connecting that presterilized component with other components of the sterilization process, which may or may not be disposable units (e.g., stainless steel tanks). “In situ steaming is not a good option, so people are looking toward other technologies,” says Tingley, “including filters that are validated for irradiation sterilization, gamma irradiation being the method of choice at the moment.”

Choosing filtration assemblies that have been sterilized by gamma irradiation eliminates the need for on-site sterilization and sterilization validation. However, manufacturers must ensure that the materials are suitable for gamma sterilization. Such materials include polyvinylidene fluoride, stabilized polypropylene, nylon, and polyethersulfone. Unstable polypropylene and PTFE cannot undergo sterilization by gamma irradiation. Hydrophobic PTFE filters are used for air or gas filtration and

### Ideal attributes of single-use filter capsules

- 2–3 year shelf life
- scalable
- easy hook up to integrity test equipment (convenient placement of vent and drain ports)
- low hold up design
- ease of use (in-line and T-style designs available, multiple inlet/outlet options, various mounting configurations)
- compatible with various filtration media and membranes
- can be used with existing stainless steel components or with other disposable units with appropriate connections.



A small-valve connector for use between presterilized disposable assemblies and stainless steel systems (Lynx ST connector, Millipore Corp.).

vent filtration applications. For disposable systems, hydrophobic PVDF filters can be used because they can be sterilized by gamma irradiation.

### Connections

Regardless of the sterilization method, sterility can only be maintained through the use of appropriate connection devices under aseptic conditions. Because of the range of applications for which disposable systems can be used, there has been an increased demand for complex, specialized configurations customized to particular applications.

According to Pall's Haughney, pharmaceutical manufacturers are increasingly interested in coupled, manifolded systems. "We've seen tremendous interest in terms of the size and the flexibility that these give," says Haughney. "We've also seen more and more companies having multiple steps in their filtration process," she adds.

For example, a polypropylene prefilter can be coupled to a 0.2- $\mu$ m filter, which is then coupled to a virus filter. These filters can be coupled together in one disposable unit that can also include supplemental equipment such as tubing, aseptic connectors, and bags. The entire assembly can be packaged and then subjected to gamma irradiation so that it is ready for use directly upon receipt. Multiple 10-in. filters also can be coupled together in systems that have integrated disposable polypropylene valves, pressure gauges, and flow detection devices.

In some cases, a connection between a stainless steel unit such as a tank and a disposable filter capsule is required. For example, Millipore has designed a small-valve connector for use between presterilized disposable assemblies such as plastic tubing or filters and stainless steel systems. The Lynx ST connector can be preassembled to

the disposable fluid path and gamma sterilized. SIP procedures can then be used to sterilize the stainless steel equipment, piping, and the connector interface before fluid is transferred or sampled. Because the connector is a closed valve, no steam gets into the line, thereby preventing damage to the plastic tubing or filter.

Haughney says disposable connectors are also eliminating the need for bulky laminar-flow hoods where many aseptic connections must currently be made. Pall, for example, recently introduced an aseptic connector that doesn't require a hood or other capital equipment to maintain sterility. The Kleenpak connector can be used in cases in which two pieces of flexible tubing need to be aseptically connected in an uncontrolled environment.

Colder Products Co. (St. Paul, MN) has also introduced a disposable connection device for making sterile connections without the need for a laminar hood. Its Steam Thru device allows sterilization of a biopharmaceutical flow path and initiates connections between a bioreactor and media bag without plumbing connections.

### Validation

Validation and compliance remain top concerns for those responsible for ensuring sterile filtration lines. "Disposable manufacturing does not significantly change the science and technology of sterile filtration," says Millipore's Tingley, "but it does change the philosophical approach to the process that you put together and end up assembling and running." For example, Tingley points out that although the use of presterilized disposable systems removes the need to worry about steam sterilization of the filter element, the end user will still have to question the supplier. "Does the supplier have a certificate of sterilization from the irradiator? Can they prove that your product is sterile? That's a shift in the burden from the manufacturer to the supplier."

In addition, although the integrity test requirements for a disposable system are the same as for a traditional system, the user will have to work out a procedure for testing the filter once it's in a disposable format. Similarly, procedures for the validation of extractables will have to be developed. "Again it's a custom validation," explains Tingley. "In disposable manufacturing, more plastics may be involved. In addition to the tubing, you may have the bag, the containment, and perhaps the valves. So the extractables validation is still done. It's done in exactly the same way but instead of being done on the filter, it's done on the entire fluid path" (see sidebar "Validation comparisons").

Filter-capsule qualification, which includes product-material challenge testing as well as extractables and leachables testing, is typically conducted at the filter company. For example, Maik Jornitz, group vice-president of global product management bioprocess at Sartorius Corporation (Edgewood, NY), says validation at Sartorius can be conducted using two methods: “one that includes a choice of using model solvents, depending on the base solvent used within the process, or testing with the client’s actual drug product under the client’s process conditions.”

In either case, the type of filter capsule must be carefully considered. “One of the major problems I see in the industry,” says Jornitz, “is that clients don’t take into account scalability factors.” For example, he points out that when filterability studies are performed, one can use flat filter composites; however, these results can’t be used to scale-up linearly because the flow dynamics are different. “If you go through the clinical phases with small-scale volumes, you don’t want to revalidate the entire process when you scale up to process batches. That’s why we not only scale up these 10-, 20-, and 30-in. filters, but we also scale down from 300 cm<sup>2</sup> to 150 cm<sup>2</sup>.”

### Time and cost

Depending on the complexity and scale of the application, disposable systems can often lead to significant time and cost savings by eliminating the need for preparation and installation of the filter element, cleaning, sterilization, and maintenance. In reusable configurations, each of these steps must be documented and records must be kept to ensure proper procedures have been followed. But, as pointed out by Pall’s Haughney, “With preassembled disposable capsules, the time and labor for assembly, and the documentation associated with that, goes away.”

Barry Bardo, director of business development at Meissner Filtration Products (Camarillo, CA), agrees. “Manufacturers want to condense the time requirements associated with the acquisition, installation, and maintenance of more capital-intensive stainless steel filter systems.” Because single-use filter capsules are packaged as off-the-shelf units, the time required to prepare and set up the filter assemblies is dramatically reduced. Says Millipore’s Tingley, “What you gain going to ready-to-use manufacturing is a reduction in validation burden—no CIP validation, minimized sterilization validation burden, and significant time savings. The end user just unpacks and assembles the components.”

Although the cost of a single-use filter capsule is typically higher than stainless steel cartridges,



Bardo says the operating-expense savings more than overcome the additional per-unit costs. Tingley agrees. “The premium of a high-capacity capsule over a regular cartridge is not that high, and there’s clear evidence that this initial cost is offset by the overall savings from implementing disposable systems. End users need to look at their total processes and value all of their costs.” Tingley observes that cost considerations should include more than just time saved in cleaning, maintenance, and assembly. “Every time you run that steam clean generator, there’s electricity, waste water, waste chemicals, and power. A company must look at all of that.”

A manifold system may consist of a prefilter to a final filter (shown above: Pall’s Kleenpak Nova capsules. Courtesy of Pall Life Sciences).

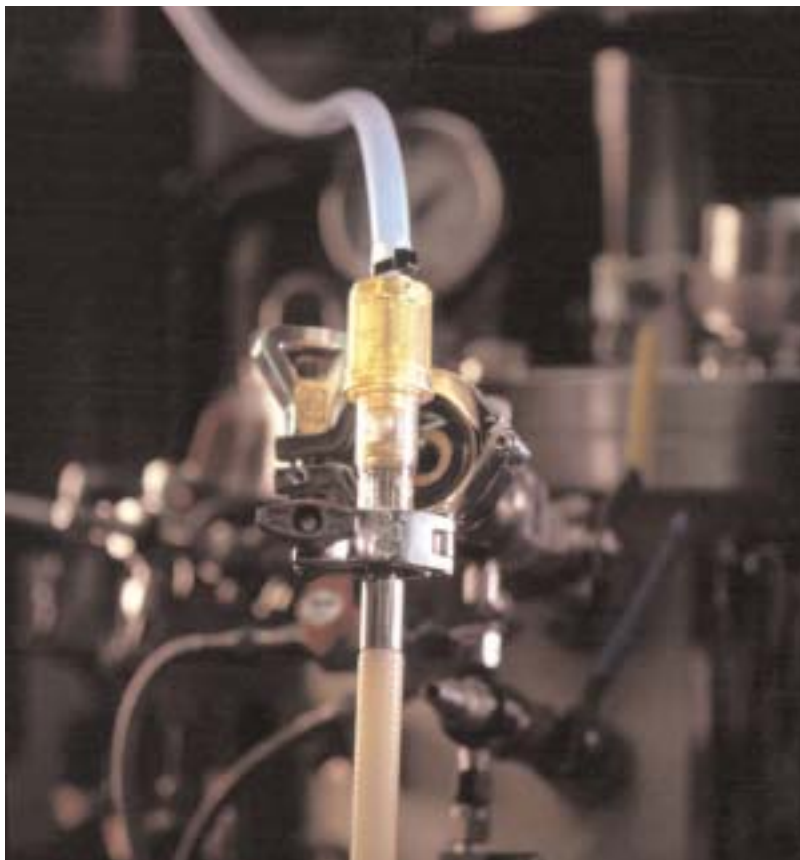
### Validation comparison

#### Stainless steel system

- validate sterilization process
- validate cleaning system
- integrity test before and after use
- bacterial retention validation
- validation of the extractables

#### Disposable system

No SIP. Can be autoclaved and aseptically connected or purchased presterilized (gamma irradiated)  
 No CIP validation necessary  
 Same requirements, commonly available as a service from supplier  
 Same requirements  
 Required, though may be done on the entire assembly, including bags, tubings, connections, and valves.



Example of a disposable connector for steam-in-place biopharmaceutical processes (Steam-Thru Connection, Colder Products Co.).

### Risk control and safety

Another prevalent concern for pharmaceutical manufacturers is ensuring minimal contact between personnel and product. “The beauty of disposability,” says Sartorius’ Jornitz, “is that people don’t come into contact with potentially high-potent drug products.”

On the flip side, Tingley points out that contact with people is also the single greatest risk associated with final fill and finish. “Companies are going to extraordinary lengths to keep people out of the process, and disposable systems help with this because people don’t have to make aseptic connections or run SIP procedures. It’s like an extra barrier.”

### Biotech pharmaceuticals leading the way

Although the time and labor saved by eliminating cleaning validation can be compelling factors in deciding whether to use a disposable system, the major driving force propelling the trend to disposables has clearly been the development of biotechnology-derived drugs.

As described by Jerold M. Martin, senior vice-president and global technical director at Pall Bio-Pharmaceuticals, the manufacture of biological drugs has historically required the use of dedicated facilities and dedicated equipment where it

was reasonable to put in a stainless steel system because only a single drug product or vaccine was being handled. “In those days,” says Martin, “operators were primarily concerned that cleaning prevent lot-to-lot contamination, and insignificant levels of carryover were allowed.”

Today, however, the situation is different, with the potency of biotech drugs at such high levels that companies can manufacture a year’s supply in a very short period of time. As a result, biotech companies have begun to manufacture multiple products on the same line, which has in turn led FDA to place renewed pressure on them to develop exhaustive cleaning methods, prove the effectiveness of these methods, and prove that any residual cleaning agents are removed. “This became so burdensome,” says Martin, “that the industry began to look for ways to avoid it altogether. So, they looked to disposable technology.”

Biological entities are usually low-volume, high-value products. Sartorius’ Jornitz envisions that “at one point the industry will have a completely disposable facility for these products, which means a disposable upstream, feed stream system, into a disposable bioreactor, then into a disposable cell harvest, a disposable purification column, disposable final filtration, and even a disposable filling system.”

Although current applicability is best suited for these low-volume conditions, Jornitz predicts that it’s just a matter of time before completely disposable systems are available at the larger scale. “It will happen,” he says, “and there are already developments in the pipeline to achieve this goal, including bioreactors, tank linings, and filling systems.”

### Facing the viral clearance challenge

The threat of contamination from viruses such as West Nile and the virus believed behind severe acute respiratory syndrome as well as organisms such as mycoplasma has placed stringent demands on biotech pharmaceutical manufacturers to prove the purity of their products. As observed by Pall’s Martin, the concerns the industry faces about being able to validate their virus filtration systems and whether they have been properly re-cleaned and re-sterilized looms so large that many of these companies are abandoning reusable virus filters and incorporating disposable systems instead. To this end, some disposable filtration technology has been specifically designed for the biotech arena. But, there are still several concerns to be resolved.

Hazel Aranha, PhD, manager of bioprocess applications at Pall Corporation (East Hills, NY), observes that virus clearance today is “not an op-



Commercially available single-use filter capsules are manufactured in a range of sizes (shown above: Sartorius's fully scalable capsule designs from 150 cm<sup>2</sup> to 1.8 m<sup>2</sup>).

tion but a requirement for biopharmaceuticals and biotech-derived products." Any product that is made either directly from human plasma or has any kind of human or animal component in it must be validated for virus clearance.

Examples of products that must be validated for virus clearance include many of the tissue culture cell lines that are often supplemented with serum (e.g., bovine serum) and anything that uses serum during manufacture. According to Aranha, "theoretically you shouldn't have any virus in your product itself. If your product is plasma derived and if the plasma is contaminated with pathogenic viruses like HIV, Hepatitis B and C, the viral contaminants would be detected and the plasma quarantined as current regulations require that all blood be screened for these viruses." However, she adds, "it is possible that plasma may contain very low levels of infectious virus which cannot be detected by current detection systems."

Theoretically, the raw materials, whether plasma-derived or biotech, should not be contaminated with virus. "The primary reason that regulators require viral clearance steps in the process is essentially to document just in case virus has entered your systems," says Aranha, "and that your

processes are adequate to provide enough virus clearance." One example, notes Aranha, is the industry's concern last year over West Nile virus. "The industries and blood banks dealing with whole blood considered it as a major concern," she says. "However, manufacturers of plasma-derived products such as clotting factors and enzymes sourced from human plasma were less concerned."

Aranha explains that this was because plasma products are highly processed and their manufacturing operations include viral clearance steps that would clear West Nile virus. "Currently, validation studies conducted to document viral clearance, and thus a level of viral safety assurance, often include a virus belonging to the same family as West Nile virus," she says.

Filters that can completely remove 100% of the bacteria that are in a fluid have been developed. But, in the case of viruses, no test exists that can confirm that no viruses are present. "It is impossible to prove this," says Martin, "but you can remove this question by simply using several different [orthogonal] virus clearance methods."

Many steps in a protein purification process can also either remove or inactivate viruses. For example, notes Martin, "a chromatography column for purifying pro-

teins might also remove viruses, and you could elute the protein off the column in a way that some of the viruses still stay on the column. Or you may be able to stick the protein onto a column and wash viruses through." Martin also points out that FDA considers filtration to be an additional step in the purification process that further enhances the clearance factor and therefore increases the safety of the drug.

**Balancing flow and viral clearance.** Another challenge associated with viral clearance is finding ways to increase flow while maintaining or even improving filtration efficiency. Several approaches can be used to increase the flow, including modifying the physical characteristics of the filtration system such as increasing the area of membrane within a cartridge or making the membrane thinner. According to Martin, the objective is finding the right balance. "If you make the membrane thinner, then you need to narrow the pore-size distribution to maintain the same virus removal rate." However, as the pore-size distribution narrows, the filter is more liable to plugging. "So," says Martin, "there's a lot of R&D going on right now to develop next generation filters that will have the same or higher titer reductions while increasing the flow."

In addition, Meissner's Bardo says filter companies are increasingly called upon to provide 0.04- $\mu$ m polyethersulfone systems, usually in combination with other technologies, but also as a virus reduction step. To this end, the company provides a unit that can be used in conjunction with other systems and perform similarly to a prefilter (StyLUX 0.04- $\mu$ m filter).

"The trick there is that you're really reaching the edge of what so-called microfiltration technology can do," says Bardo. "The pores are getting so tight that it almost risks becoming a solid. You can't get the very smallest viruses, but you can remove some of the larger ones and still have a reasonable amount of flow through such a filter." However, if a membrane gets much tighter, warns Bardo, "the good news is that you remove everything, the bad news is that it flows very slowly. That's the trade-off—viral clearance versus flow. The goal is to improve the flow but maintain or if possible even improve viral clearance."

**Mycoplasma removal.** Unlike a virus, mycoplasma is a bacteria-like microorganism that has a characteristic called *pleomorphic*, which means that it will deform and ooze through structures like filters that would otherwise retain more rigid-walled bacteria. A mycoplasma infection can shut down production or development because the small size and absence of a cell wall of mycoplasma enables it to penetrate 0.2/0.22- $\mu$ m filters.

The presence of mycoplasma in the industry resulted in a new generation of filtration systems (e.g., Pall's Fluorodyne II 0.1 micron DJLP filter and Meissner's SC0.1 version of its StyLUX filter). "Combined with biotech demands on sterility, disposable systems would be best suited for this type of process as opposed to stainless steel systems," says Martin. According to Bardo, a company can have a sterilizing filter that sieves out all the bacteria, but the mycoplasma will still get through many of them. "So as manufacturers, we have to have validated mycoplasma retentive filters," he says.

**Future challenges.** Although much has been accomplished in the area of viral clearance, Martin recognizes the following three areas of concern yet to be fully resolved.

**Need for a rating system for virus filters.** Every filter manufacturer qualifies its filters in different ways, and they apply different rating standards. That has created some confusion because there is no standard system by which the filters are rated. There is a standard definition for bacterial removal filter, but there is no such standardized definition for virus filters. According to Martin, a PDA task force is working to develop a standard qualification protocol using a bacteriophage, which is a virus of bacteria. The committee also is writing a technical report that would be an industry-based study about how to select and qualify virus filters. The goal is to address the questions that challenge the users in terms of how best to select a virus filter. Jornitz adds, "viral filtration cannot be compared with bacterial filtration. It is by far more complex and requires evaluation, qualification, and validation of every single application. Often too much emphasis is put on retention ratings. Nevertheless, the true performance of the filter used

can only be measured by appropriate process validation."

**Streamlining virus-challenge testing methods.** Current FDA guidelines require that a biotech or biological manufacturer generate data with multiple different mammalian viruses to qualify a particular viral clearance step. Several viral clearance steps are involved in the process, which means that a drug manufacturer must challenge several steps, each with multiple different viruses. "Challenges with mammalian viruses are time consuming and expensive," says Martin, "and this can be a large burden on the drug manufacturer; first do to it once and then second if they wanted to change any step in the process, then they have to go through this whole procedure again." Martin explains that researchers have shown that for virus filters—which remove viruses by size exclusion—viruses of bacteria (i.e., a bacteriophage) can be used as models for the mammalian viruses and can then be applied in bacterial virus challenges. These challenges are very rapid and inexpensive to conduct and to predict what the filter performance is going to be with the mammalian viruses. In turn, this process enables a drug manufacturer to test out their process development steps quickly and inexpensively.

**Understanding the integrity-testing process.** The purpose of the integrity test is to confirm that the actual process filter is going to perform at the same level as filters that were used in a validation exercise. No one can take a full-scale process and challenge it with viruses to prove that it works, so filters usually are qualified using very small disks or modules. The integrity test that goes into the production process has to predict the same performance. Martin believes there is a growing need to have these integrity tests be sensitive enough to predict virus removal and to be practical and useful in a production environment. "Many of the integrity tests that have been applied on the lab-bench scale and seem adequate on small-scale filters end up being very problematic on the production floor," he says, "and that is something that actually doesn't get considered when a drug is submitted for approval by FDA. It doesn't come into play until the drug is approved and falls under GMP manufacturing."

### A permanent place in the industry

The extent to which disposables will successfully invade the pharmaceutical filtration arena remains to be seen. Millipore's Tingley says he can envision an all-plastic factory or a factory that would contain a manufacturing process all in plastic. "You would just take it out of a box, unroll it, do your processing, and throw it away." However, he adds that "in the shorter term, we're seeing end users with stainless steel in place that want to integrate these disposables with existing stainless steel systems."

Sartorius' Jornitz doesn't see disposable or single-use systems ever completely replacing stainless steel, but says that "they are definitely an alternative that's here to stay. They may perhaps be the solution of choice for biotech applications, and for start-ups, where they can help reduce the tremendous capital investments necessary."

Contract manufacturers, in particular, have seen the advantages offered by single-use filtration systems. "These companies have such a large number of different chemicals in their manufacturing," says Tingley, "that they either have to have a unique set of manufacturing equipment for each drug, or they have to have very clear validation for the cleaning processes, so that they can guarantee that they are not going to have cross contamination from one drug to another." Contract service providers also don't have a lot of time to change or develop new processes. "First and foremost, they are manufacturers," he adds, "so eliminating cleaning and cleaning validation saves them extensive amounts of time."

Whether disposable filtration will remain an alternative or become the predominant methodology, its multiple advantages are clearly already having a major effect on pharmaceutical manufacturing. As observed by Tingley, "anybody who's putting in a new process, anybody who's expanding a manufacturing facility, anybody who's putting in a new manufacturing facility, or anybody who's dealing with biohazard materials is a perfect candidate for this technology." **PT**