PALL

Life Sciences

Considerations on Re-Use of Sterilizing-Grade Filters

Contents

PALL Life Sciences

1.   Introduction

Membrane filters designed to sterilize liquids and gases have performed successfully in a broad range of process applications. As economic and market conditions lead pharmaceutical, biotechnology and vaccine manufacturers to search for ways to improve profitability by decreasing process costs, re-using sterilizing-grade filters may be considered. Although liquid sterilizing-grade filters are generally developed and recommended for single batch or campaign use, there are many applications where they may be subjected to multiple usages (i.e., re-use). This Application Note focuses on the re-use of hydrophilic or hydrophobic-membrane sterilizing-grade filters applied in liquid-sterilizing applications. It reviews different approaches that may be defined as re-use, discusses factors to consider when deciding whether to re-use sterilizing-grade filters and provides a case study that highlights potential risks and considerations for process validation in filter re-use applications. Suitability of re-use of sterilizing-grade filters in liquid sterilization applications ultimately depends on the requirements of the specific application, the supplier's core filter product-validation studies and the end user's filtration process validation. This evaluation includes assessments of re-use risk and effects that may compromise the filter's ability to completely retain bacteria and thus sterilize the process fluid.

It is generally accepted that when a nondestructive physical integrity test (e.g. a forward flow diffusion test or bubble point-type test) of a sterilizing-grade filter is correlated to bacterial retention, re-used filters can be relied on to provide a sterile effluent as long as they continue to demonstrate integrity upon repeated testing. Both forward flow and bubble point-type test methods are highly capable of detecting filter manufacturing defects such as holes in membranes or bypass of membrane cartridge seals due to inadequate installation. It is often overlooked, however, that membrane degradation can occur under incompatible re-use conditions that may compromise the filter's bacterial retention properties. Such cases of membrane degradation are not modeled by filter manufacturers' core validation studies and may not be detectable by common production integrity tests correlated to retention under those model conditions. The case study provided in this Application Note illustrates this point.

The use and re-use of sterilizing grade membrane filters, rated at 0.2 µm and even 0.1 µm, occurs often in nonsterilizing liquid-service applications such as those carried out for bioburden or particle reduction or control. In these applications, the filters may or may not be integrity tested because they are not necessarily expected to remove 100% of incident bacteria with validated assurance (i.e. sterilize) and their filtrates are not claimed to be sterile. They may be used as prefilters or as final filters to control bioburden that may already be very low in the influent fluid. Although such filters have been validated by their manufacturers for quantitative bacteria removal when integral under standard conditions, the risk of marginal, or in some cases, gross failure, carries much less consequence than a risk of nonsterility in the production of a sterile drug or maintenance of a sterile process. Despite the less critical nature of these applications, many of the risks that come with the use of sterilizing-grade filters in sterilizing processes may be applicable and can be used in risk assessment. Hydrophobic sterilizing-grade membrane filters for air, gas or vent service, typically manufactured with 0.2 µm pore-rated polytetrafluoroethylene (PTFE) or polyvinylidene fluoride (PVDF) membrane, have also traditionally been re-used in multiple batch service with autoclave or *in-situ* steam (i.e. steam in place, SIP) sterilization between batches or campaigns. Because this note focuses on liquid-sterilizing filtration applications, the re-use of air, gas and vent filters will not be addressed.

2.   Definitions of Re-use in Liquid Service

In general, one can consider re-use of sterilizing-grade filters as applying to filtration of multiple batches of product or other process fluid. This approach is consistent with applications of re-use of air, gas and vent sterilizing filters in multiple batches or campaigns. However, in the case of liquid sterilizing filtration, there are many interpretations of re-use. Each interpretation has different implications on filter performance. Filters can be considered reused when they are employed for multiple batches in the following instances:

- Without removal, rinsing, cleaning, sanitization or resterilization
- With inter-batch rinsing only
- With inter-batch rinsing and resterilization
- With inter-batch rinsing, cleaning and resterilization
- Intermittent use with inter-batch drying.

Without Cleaning or Resterilization

In the first case of re-use, defined as "without removal, rinsing, cleaning, sanitization, or resterilization" the filters are initially sterilized and left in place with no interference as multiple batches of fluid pass through them. Although additional stress on the filter from re-use is minimal with this approach, a significant risk factor is that bacteria from the first batch and subsequent batches may remain viable on the membrane during the re-use cycles. These bacteria could potentially produce smaller cells while dividing and migrating through the largest pores of the filter media until they contaminate the filtrate and compromise the sterility of later batches. This time-dependent bacterial penetration, sometimes referred to as "grow-through," has been reported for integral 0.2 μm-rated sterilizing-grade filters even for single batches that are run for extended periods of time (> 8 hours). The results would be no different if a single batch were simply subdivided into multiple batches of product, each processed through the same installed filter in shorter consecutive periods of time. This risk becomes greater, however, when the filters are allowed to stand unused for additional time between processing of consecutive batches. Risk of time-dependent bacterial penetration cannot be assessed by filter-integrity testing because there is no additional stress on the filter.

With Inter-batch Rinsing

A second and similar process of sterilizing-grade filter re-use occurs when the filters are subjected to water or other solvent rinse between each use to minimize carryover of process fluid components from one product to the next, or one batch to the next. While this type of re-use benefits from reduced batch-to-batch cross-contamination of process fluid components and may slow the ability of retained bacteria to multiply by removing some process fluid-derived nutrients, the risk of time-dependent bacterial penetration remains. This is because retained viable bioburden can continue to divide even under starvation conditions, forming biofilms comprised of cells and cell-derived adhesive secretions that are difficult to rinse away. If the bioburden load from the previous batch is significant, or a biofilm develops on the filter membrane, there is additional risk of downstream contamination with bacterial byproducts such as endotoxins, where the rinse fluid can stress the retained bacteria.

With Inter-batch Rinsing and Resterilization

The third type of re-use (inter-batch rinsing and resterilization) can limit the risk of extended time-dependent bacterial penetration beyond a single batch processing time and control possible development of biofilm. If the filter is not sufficiently rinsed after each re-use cycle before resterilization and introduction of the next batch, however, the resterilization can degrade retained bacteria and leave increased levels of leachable bacterial endotoxins and other cellular byproducts that can contaminate the subsequent processed batch. This type of re-use also imposes additional physical stress on the filter during resterilization. Most sterilizing-grade filters are qualified by their supplier to withstand several steam autoclave or SIP cycles without compromise to integrity or bacterial retention capability. It should be noted, however, that filter-supplier qualifications are typically conducted on intact filters wet only with water, subjected to multiple laboratory steaming cycles and then tested. Although indicative of filter robustness, these tests do not necessarily model the additional chemical degradative stresses on the filter that may occur when residual product or cleaning agent is insufficiently rinsed out before subjecting a filter to steaming conditions. The tests also do not take into account that a particular end-user sterilization cycle may be more stressful to the filter than the controlled laboratory sterilizations conducted by the filter manufacturer to support product claims.

PALL Life Sciences

With Inter-batch Rinsing, Cleaning and Resterilization

The fourth type of re-use (incorporating inter-batch rinsing, cleaning and resterilization) further reduces risk of cross contamination or leaching of retained bacterial byproducts during rinsing and cleaning. Despite the reduced contamination risk, this type of re-use becomes more severe in terms of potential stress to the filter and risk of filter damage that may not be detectable by routine integrity testing.

In addition to rinsing out the process fluid with a suitable solvent, this type of re-use subjects the filter to an aggressive cleaning fluid intended to dissolve or degrade retained contaminants. Compatibility of the filter membrane and other component materials must be determined beyond only the batch process fluid in this situation to also consider the cleaning fluids and regimens, cumulative contact time and so forth. Residual products or cleaning agents retained within the filter due to inadequate rinsing after cleaning and before steam exposure for resterilization can be more aggressive at the elevated temperature conditions of the resterilization process. An example of the potential impact of such conditions is provided in the case study discussed later in this article.

Intermittent Use

The fifth category of re-use entails a different form of stress incurred by drying the membrane between batches. Some membranes may be damaged by repeated drying cycles, particularly if dried in hot-air ovens. Residual contaminants, cleaning fluid, or residue can be concentrated within the filter during drying, exerting further chemical stresses on the membrane and compromising its functionality without being detected by routine integrity tests. In each of these cases where an end user considers re-use to economize on filtration costs, it is incumbent that all process and re-use conditions be properly validated for filter performance and leachables. It is critically important that the filter's ability to retain bacteria and the filter integrity tests' ability to predict filter integrity not be compromised.

3.   Applications of Re-use in Liquid Service

In addition to process conditions, the risk of re-use, including the criticality of the filtration process, should be assessed for each application. Some processes may be considered less critical than others and may not require the highest levels of sterilization assurance. Such processes use sterilizing-grade filters for particulate and/or bioburden control but do not claim sterility of the effluent. In these applications, a user may consider re-use of those filters more aggressively. Other processes require a reasonable level of sterilization assurance, suggesting greater risk in re-use. The most critical applications require the highest levels of sterilization assurance achievable and are often done by combining sterilizing-grade filters with effluent from bioburden control filters and, in some cases, use of serial filtration with double 0.2 µm, 0.2 µm to 0.1 µm, or double 0.1 µm sterilizing-grade filters. With such redundancy, there may be a balance between re-use of upstream filters and single use of final filters, or re-purposing of prior batch final filters as upstream filters for subsequent batches.

In each case, any perceived economic advantage to re-use of the filters should be weighed against the risk of failure, which can be caused by premature plugging, loss of integrity, increased leachable contamination or bacterial penetration.

Examples of applications for sterilizing-grade filters used as either nonsterilizing particle or bioburden control filters or as sterilizing filters, or both, include filtration of:

• Fermenter or cell-culture bioreactor culture media

• Fermenter or bioreactor additives

• Serum for cell culture media

• Process water

• Chromatography buffers

• Diafiltration buffers

• Solvents

• Disinfectants

• Intermediate product hold

- Nonsterile active pharmaceutical ingredients (APIs)
- Final bulk sterile APIs
- Sterile culture media for aseptic filling validation
- Terminally sterilized injectables
- Aseptically filled sterile injectables
- Aseptically filled sterile topicals and ophthalmics.

Each of these applications has its own requirements and risk factors for bioburden control and/or sterilizing filtration. In addition to the conditions of re-use (rinsing, cleaning, resterilization, drying), each application for re-use should be considered independently based on its criticality for sterilization assurance and any other influence on the filtered effluent.

4. Regulatory Guidance on Re-use of Sterilizing-grade Filters

FDA and ICH Guidelines

A review of API and nonsterile drug manufacturing guidance from the US Food and Drug Administration and European Medicines Agency (EMEA) indicates that neither use nor re-use of sterilizing-grade filters is specifically covered for nonsterile APIs or nonsterile finished drug products[1–2]. Such guidance would also apply to use of sterilizing-grade filters in manufacture of nonsterile API and biotech APIs from fermentation to downstream purification, including sterile-filtered media, additives, buffers and process intermediates. Although use of sterilizing-grade filters in nonsterile API and nonsterile drug manufacturing (e.g. for bioburden control) may be considered current good manufacturing practice (CGMP), specific guidance for use and re-use of sterilizing-grade filters is only provided under guidance for sterile drugs.

There is one aspect of ICH Q7A: Good Manufacturing Practice Guide for Active Pharmaceutical Ingredients that can be considered applicable to the re-use of sterilizing-grade filters even with nonsterile APIs. ICH Q7A states, "Equipment should be constructed so that surfaces that contact raw materials, intermediates, or APIs do not alter the quality of the intermediates and APIs beyond the official or other established specifications"[2]. Under this guidance, the potential impact of sterilizing-grade filters on the API, including extractables data that may be provided by the filter manufacturer, in cases where filters are re-used in API manufacturing, the end user should also consider the potential impact on the product of retained bacteria and insufficiently removed product or cleaning agent residues on the filter surface. With regard to sterile drug manufacturing, a corresponding statement can be found in 21 CFR 211.65(a) on CGMP for finished pharmaceuticals, which states,

"Equipment shall be constructed so that surfaces that contact components, in-process materials, or drug products shall not be reactive, additive, or absorptive so as to alter the safety, identity, strength, quality, or purity of the drug product beyond the official or other established requirements"[3].

The same consideration for potential impact of surfaces of re-used filters would apply.

FDA's Guidance for Industry on Sterile Drug Products Produced by Aseptic Processing — Current GMP presents two views with regard to use and re-use of sterilizing filters. For sterile drug products, the guidance states, "Sterilizing filters should be routinely discarded after processing of a single lot"[4]. Although this statement appears nonsupportive of re-use of sterilizing filters, it is followed by the statement, "However, in those instances when repeated use can be justified, the sterile filter validation should incorporate the maximum number of lots to be processed." This allowance indicates that where sterilizing-grade filters are to be re-used, the sterilizing filtration process validation should assess the impact of cleaning and resterilization in the end-user's process. The guidance goes on to state, "It is important that integrity testing be conducted after filtration to detect any filter leaks or perforations that might have occurred during the filtration." This guidance applies to individual batches and campaigns of batches.

Of critical interest is that the guidance suggests that filter leaks or perforations presumably capable of compromising sterilizing performance will be detected by integrity testing.

PALL Life Sciences

European Guidelines

The European Commission's Guidelines to Good Manufacturing Practice for Medicinal Products for Human and Veterinary Use (Annex 1 on Manufacture of Sterile Medicinal Products) states, "The same filter should not be used for more than one working day unless such use has been validated"[5]. While this statement seems to allow extended use and potential re-use of filters, process validation should include consideration of any re-use effects on the filter. The guidance goes on to state, as in the API guides, that, "The filter should not affect the product by removal of ingredients from it or by release of substances into it." Here again, the leaching of contaminant or cleaning residue from used filters before re-use should be considered and absence of any such effects should be validated.

PDA Recommendations

Industry recommendations on re-use of sterilizing-grade filters have been limited to date. The first edition of the Parenteral Drug Association (PDA) Technical Report 26, "Sterilizing Grade Filtration of Liquids" in 1988 focused exclusively on final drug sterilization and did not address re-use of sterilizing-grade filters[6]. The 2008 revision of this document considers applications of sterilizing-grade filters in biotechnology and pharmaceuticals manufactured outside the US and states, "Sterilizing filters should be routinely discarded after processing of a single lot." But the revision also elaborates on FDA's aseptic processing guidance on re-use by stating, "However, in instances where repeated use can be justified, the sterile filter validation, including integrity testing, bacterial challenge and cleaning should incorporate the maximum number of lots to be processed"[6].

FDA Enforcement

FDA has actively enforced its guidance on reuse of filters under GMP. An FDA Warning Letter to a sterile pharmaceutical manufacturing facility has stated, "Failure to validate the extended re-use period of the (redacted) filters used for many different injectable product formulations and batches. Validation rinse data was inadequate to support that ingredient residues from the previous batch are removed… Your response (to the 483) failed to ensure that products (redacted) do not contain unacceptable residues from prior batches of different products that used the same filters. The inspection found inadequate validation rinse data to support that drug residue from the previous batch was removed. We are concerned of the possibility of cross-contamination"[7].

Another FDA Warning Letter to a sterile ophthalmics manufacturer stated, "According to the establishment inspection report you re-use sterilizing filters as long as they perform to the manufacturer's filter integrity standards of (redacted) or for a maximum of your internal specification of 50 re-uses. We are concerned about the effectiveness of your filters after being re-used and autoclaved 50 times. We understand that you conduct a filter integrity test by the (redacted) method before and after each batch. However, in order to justify 50 re-uses, we would like to see bacterial retention validation studies using product both upon the initial use of the filter and after the 50th re-use. Further, it is unclear to us whether you have conducted filter extractable and leachable testing with product. If you have this data, provide it to us. If not, let us know when you will be able to provide it to us"[8].

An FDA reviewer has stated publicly that reuse of sterilizing filters is "discouraged for sterile drug product," while simultaneously recognizing that sterilizing-grade filter re-use is "common for API production"[9]. The reviewer recommended, "Microbial retention validation should incorporate multiple filtration and sterilization processes" and "correlate microbial retention validation, filter integrity testing following multiple sterilization/filtration cycles and sterility of API/product"[9]. FDA is now requesting that batch records indicate when sterile filters have been previously re-used, as stated in an October 2008 483 observation[10].

5.   Validation of Filter Re-use

Following PDA and FDA recommendations, a multiphase bacterial retention study program is indicated for validation of sterilizing filtration with re-used filters. PDA Technical Report 26[7, 8] and FDA's aseptic processing guidance[4] currently call for preliminary bioburden studies of product or process fluid to determine suitability of conducting bacterial retention studies on production filter membrane discs using either the standard bacterial challenge organism *Brevundimonas diminuta* (ATCC 19146) or a bioburden

isolate under worst-case product and process conditions. These bacterial challenge tests should include multiple filter membrane lots (typically three) and "at least one of the three membrane lots used for the bacterial retention validation study should have a pre-study or pre-use physical integrity test value at or near the filter manufacturer's test specification" (i.e. representing the least retentive membrane)[6].

A study of this extent would be sufficient to demonstrate the filter membrane's capability to sterilize the drug product or process fluid on a single usage. The study would not, however, predict filter performance after multiple cleanings, resterilizations and re-use cycles. Bacterial challenge should be conducted on production filters subject to actual, or preferably, worst-case process conditions incorporating the full extent of multiple cleaning, rinsing, or resterilization and re-use cycles. Re-use processes entailing multiple batches, either without inter-filter batch rinsing or with solvent rinsing between batches, can often be scaled down and modeled at the bench. More complex re-use processes, however, such as those entailing multiple cleaning and resterilization cycles, or drying between campaigns, are difficult to simulate in the laboratory with filter discs, capsules or even cartridges. In such cases, it is preferable to supplement the single batch disc challenge tests with a series of bacterial challenges conducted on production filter cartridges that have been exposed to the full extent of actual process use, cleaning, resterilization and re-use cycles. Typical production cartridges are appropriate for this second phase as "worst-case membrane" is assessed in the initial disc study and testing of used production cartridges serves to confirm process compatibility as measured by maintenance of bacterial retention properties. Such tests may be the only means to determine whether a filter's sterilizing properties remain unaffected by the multiple re-use process cycle conditions. Integrity tests may be insufficient as demonstrated by the following case study.

6.   Case Study: Risk of Re-use

The case study described here highlights an example of the risk of re-use of sterilizing filters without conducting a full re-use process-scale validation. Specific process details are excluded to maintain confidentiality. In this case, a pharmaceutical company was using a high-area, pleated, sterilizing grade membrane filter cartridge assembly to prepare a bulk sterile API antibiotic in a solvent for which the selected filter membrane had some limited compatibility. The limited capability was deemed acceptable and unrelated. Filters were rinsed with water after each use, followed by cleaning with a caustic solution. The caustic was rinsed from the filter with water (the degree of removal was not quantified or validated). The filter was then subjected to an SIP cycle between each batch for which it was re-used. The filter was integrity-tested before and after each batch and consistently passed its recommended integrity test limit for the maximum number of re-use cycles specified. Sterility tests of each filtered batch were unremarkable and there were no reports of product nonsterility. To supplement the level of confidence provided by the filter integrity tests and batch sterility tests, the drug manufacturer conducted a bacterial challenge on a filter that had reached its maximum specified re-use life. Following challenge conditions based on the ASTM Standard Test Method for Determining Bacterial Retention of Membrane Filters Utilized for Liquid Filtration[11], bacterial penetration of the filter was demonstrated. It was determined that the used filter no longer met the definition of a sterilization grade filter (i.e., 100% retention of *B. diminuta* bacterial at a challenge level of $>10^7$ cfu/cm^2 effective filtration area[4].

The bacterial retention test of the reused filter failed despite the fact that the filter continuing to pass integrity tests correlated to 100% bacterial retention under comparable challenge conditions performed on previously unused filters by the filter manufacturer. Several key observations were made from this study. First, after re-use, the filter still showed high bacterial retention efficiency, but was no longer capable of meeting its 100% *B. diminuta* retention claim and the regulatory definition of a sterilizing-grade filter. Second, the controlled low bioburden in the product, coupled with the reduced but still significant retention properties of the filter, was sufficient to prevent detectable bacterial penetration in the process, as evidenced by the successful sterility tests and absence of product nonsterility events. Third, the damage to the filter from the re-use process was not detectable by a standard filter integrity test. This third observation may seem contradictory to those who believe that filter integrity tests can

PALL Life Sciences

detect any oversized pores, leaks or defects that can compromise sterilizing filter performance. The correlation of such tests as forward flow or bubble point is based on bacterial challenges of intact filters and those with actual membrane or cartridge damage or defects incurred during filter manufacturing, handling and installation. The population of filters subjected to the filter manufacturer's bacterial retention validation and integrity test correlation studies does not include filters with damage caused by end-user re-use process incompatibilities. These incompatibilities can occur with unvalidated, cleaning, resterilization and re-use.

7.   Limitations of Integrity Tests

Filter membranes are often thought of as multiple cylindrical capillaries, in which bacterial retention is governed solely by size exclusion of incident bacteria that are larger than the largest pores in the membrane. Under such a model, bubble point-type tests can indicate the presence of excessively large pores or defects (i.e., holes, seal bypass) in the membrane and forward flow tests can provide a quantitative measurement of flow that demonstrates the absence of excessively large pores or defects. Retention of bacteria through microporous membranes, however, is not solely a function of size exclusion by cylindrical pores smaller than the incident bacteria. Other properties of membranes can contribute to retention such as the shape and tortuosity of the porous structure, thickness of the membrane (i.e., length of the flow path through the membrane pores from upstream to downstream) and adsorptive forces, which may occur between the bacteria and the walls of any pores large enough for bacteria insertion. Neither forward-flow nor bubble point-type tests are fully capable of detecting changes to these secondary retention factors.

Degradation of these conditions typically does not occur in a compatible validated membrane manufacturing process and the limitation of integrity tests to detect deviations in these retention variables can be underappreciated.

Failure analysis of the re-used pleated filter cartridge ultimately identified the root cause of the filter penetration. The damage incurred during the multiple re-use cycles was manifested by chemical degradation of the membrane, resulting in a thinning that was localized at the pleat crests of the filter cartridge, as shown in Figure 1. Localized chemical damage and thinning at pleat crests is typically indicative of partial drying of the filter whereby fluid components capable of chemically attacking the membrane under hot steam conditions are concentrated at the pleat crests during evaporation from those points.

Figure 1

Diagrammatic Cross-section of a Pleated Membrane Filter showing Locations of Partial Thickness Membrane Degradation at Pleat Crests Incurred during Inadequate Cleaning and Resterilization
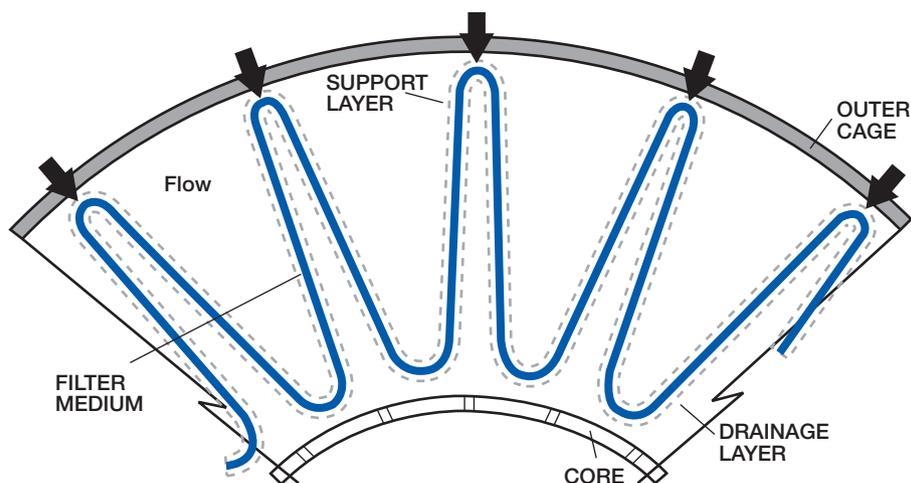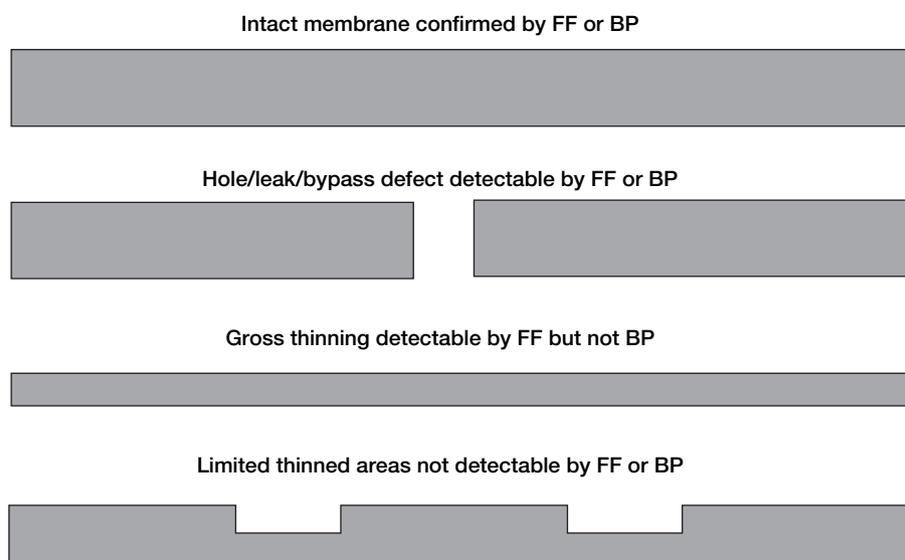

In this case, the partial degradation of the membrane's thickness was attributed to exposure to hot caustic during the SIP resterilization phase of the re-use cycle. The presence of residual caustic prior to

SIP was attributed to insufficient rinse-out of the caustic cleaning agent, whereby subsequent evaporation of water from the cartridge before resterilization caused increased concentration of caustic at the pleat crests during the SIP resterilization phase of the re-use cycle. The elevated temperature from the steam on the residual concentrated caustic at the pleat crests then caused accelerated chemical degradation of the membrane face surface at the aforementioned locations. The compromise in membrane thickness in these localized regions was sufficient to enable bacterial penetration. However, because the damage did not go all the way through the membrane (no holes or oversized pores) and the thin areas were limited to a very small total area at the pleat crests, neither the bubble point-type test nor the forward-flow test measurements exceeded their pass/fail limits.

As illustrated in Figure 2, the bubble point-type test can only detect full-thickness hole defects. Forward flow diffusion-type tests can provide values that relate, in principle, to membrane thickness, but they were unable to detect the limited thin areas isolated at some of the pleat crests in this case. The thin areas were not detected because they did not elevate the forward flow in excess of the flow test limit.

Figure 2
Membrane Damage During Re-use may be Detectable or Nondetectable by Forward Flow (FF) or Bubble Point-type (BP) Filter Integrity Tests

Intact membrane confirmed by FF or BP

Hole/leak/bypass defect detectable by FF or BP

Gross thinning detectable by FF but not BP

Limited thinned areas not detectable by FF or BP

8. Cleaning Filter Cartridges

Cleaning is a complex issue that goes beyond simple rinse and re-use. Cleaning involves the removal of all prior batch residual materials from the entire system, including all piping, tanks, valves and filters. A water-for-injection (WFI) flush (or pure solvent flush) following the final rinse must show that the system is clean to a predefined level of cleanliness using validated analytical methods. If any clean-in place (CIP) material is used, it also must be rinsed out completely. Keep in mind that cleaning may lead to material from the upstream tanks and pipes being filtered out and remain on the filters. This retention can result in leaching into the next product batch. It is the responsibility of each user to develop and validate a proper cleaning method. Users should consult with filter manufacturers on suitability of intended cleaning protocols. Regarding CIP of a filter used for liquid processing, there are several additional points to consider:

• Some process fluids can support bacterial growth, which may lead to pyrogenic bacterial endotoxins on the filter as a degradative byproduct of the retained bacterial cells. Endotoxin levels must be kept low. Therefore, carryover of any bacterial growth-supporting fluid from one product cycle to the next is problematic.

• Once a filter has any appreciable amount of plugging (i.e. lower flow rate or higher pressure differential), the plugged pores do not allow easy flow of fluids and therefore prevent access of cleaning solutions to the plugged pores.

PALL Life Sciences

- The cleaning fluid will preferentially flow through cleaner pathways, leaving the "dirtier" plugged pathways virtually unaffected.

- Some product residues and cleaning-solution components always stay on a filter to some extent. Any cleaning process needs to be defined in terms of acceptable limits of residual leachable material detected by a defined validated test.

Cleaning and re-use of a filter in a pharmaceutical application can be more or less difficult depending on the magnitude of the following factors:

- Bacteria bioburden levels in the feed

- Growth-supporting activity of the product

- Plugging of the filter

- Biological activity of the product, product components or byproducts

- Resistance of the product, product components or byproducts to solubilization

- Adherence of the product, product components or byproducts to filter materials

- Difficulty of selecting an aseptic or growth-inhibiting filter storage method compatible with product.

These risks provide a rationale for single-use of disposable filters. Often, when taking risks into consideration, the drug product or process fluid is significantly more expensive than the filter and the risk to product quality and patient safety is too great to make filter re-use attractive.

9.   Conclusion

Re-use of any disposable equipment is subject to risks and hazards that must be controlled to ensure the equipment remains safe and effective and continues to meet its manufacturer's specifications and requirements for use. The following considerations are intended only to identify some of the risks associated with the re-use of sterilizing-grade filters. These concepts should not be construed as universally applicable in all circumstances, nor do they relieve the user of complete responsibility for multiple re-use of these products. Reprocessing systems for sterilizing-grade filters may include equipment to flush, clean and re-sterilize the filters. Each piece of equipment used for reprocessing must be appropriately designed, constructed and validated. Grades of water and other fluids used in reprocessing should be specified in the master record. All chemicals used in reprocessing and all filter effluents, including drug product residues, must be handled and disposed of in compliance with local, regional and national requirements for operator and environmental safety. Documentation should accurately record the processes carried out and the results of tests for filter performance and safety.

Testing of validated filters for integrity, non-pyrogenicity and removal of prior fluid residues or byproducts should be conducted before re-use. Validation testing is performed to establish performance and time limits for re-used sterilizing filters in each manufacturing process. Validation should follow FDA guidelines for aseptic processing in that factors such as pH, viscosity, flow rates, pressure, temperature, chemical compatibility and effects of hydraulic shock should be considered when establishing limits for multiple re-use of filters. In addition, controls must be instituted and documents maintained to ensure that filters containing residues of product or cleaning agents that could adversely affect effluent drug product quality, safety, or efficacy are not used in subsequent lots. Unlike data from the filter manufacturer, data on re-used filter retention properties, pyrogenicity and leachable residues are specific to each user process and conditions of use. Despite these cautions and the risks involved, re-use of sterilizing filters is currently practiced by some pharmaceutical companies who have developed product and process-specific re-use protocols.

Regulatory guidance discourages re-use of sterilization filters, particularly for sterile drug products. Where justified, sterilizing filters may be re-used in some cases, but their re-use must be validated to not compromise filter sterilizing performance or filtrate quality. In addition to basic sterilizing validation studies, as recommended in PDA Technical Report 26 and FDA's aseptic processing guidance, validation of multiply re-used sterilizing filters should include thorough testing of process filters exposed to the maximum specified number of cleaning, resterilization, drying and re-use cycles. Such testing

should include bacterial challenges as well as filter-integrity tests. These tests should assess chemical compatibility of the filter to process fluids and re-use cycle conditions, validity of the integrity test limits under re-use conditions and include a chemical analysis of rinse effluents to qualify any leaching of bacterial, product or cleaning agent residues.

Integrity testing alone cannot be relied on to predict sterilizing performance of re-used filters without adequate bacterial challenge validation employing used filter cartridges. Finally, users should consider carefully the level of risk and validation costs involved in satisfactory re-use of sterilizing filters versus the seemingly apparent economics of re-use when designing and qualifying sterilization filtration processes.

10. References

1. FDA, Q7A: Guidance for Industry: Good Manufacturing Practice Guidance for Active Pharmaceutical Ingredients (Rockville, MD, August 2001).

2. EMEA, Note for Guidance on Good Manufacturing Practice for Active Pharmaceutical Ingredients (London, November 2000).

3. "Current Good Manufacturing Practice for Finished Pharmaceuticals: Equipment Construction" in Code of Federal Regulations, Title 21, Food and Drugs (Government Printing Office, Washington, DC), Part 211, Subpart D, Section 211.65.

4. FDA, Guidance for Industry: Sterile Drug Products Produced by Aseptic Processing: Good Manufacturing Practice (Rockville, MD, Sept. 2004).

5. European Commission, EU Guidelines to Good Manufacturing Practice—Medicinal Products for Human and Veterinary Use, Annex 1, Manufacture of Sterile Medicinal Products (Rev., Brussels, Feb. 2008).

6. PDA, "Sterilizing Filtration of Liquids," Technical Report No. 26 (1998), Revised, 2008, in press.

7. FDA, CDER Warning Letter, Sept. 24, 1999, accessible at www.fda.gov/foi/warningletters/archive/M3132n.pdf, accessed Oct. 20, 2008.

8. FDA, CDER Warning Letter, Aug. 16, 2005, accessible at www.fda.gov/foi/warning_letters/archive/g5463d.htm, accessed Oct. 20, 2008.

9. N. Sweeney, "Sterility Assurance: Optimization of Sterility Assurance Submissions," presented at the Generic Pharmaceutical Association (GPhA) Fall Technical Conference, Bethesda, MD, Oct. 11, 2007.

10. Personal communication.

11. ASTM, "F838-83 Standard Test Method for Determining Bacterial Retention of Membrane Filters Utilized for Liquid Filtration" (Reissued as F838-05), ASTM Book of Standards 11.02 (1983).

PALL Life Sciences

PALL Life Sciences

United States
800.717.7255 toll free (USA)
516.484.5400 phone
516.801.9548 fax
biopharm@pall.com E-mail

Europe
+41 (0)26 350 53 00 phone
+41 (0)26 350 53 53 fax
LifeSciences.EU@pall.com E-mail

Filtration. Separation. Solution.sm

Visit us on the Web at www.pall.com/biopharm
E-mail us at biopharm@pall.com

International Offices
Pall Corporation has offices and plants throughout the world in locations such as: Argentina, Australia, Austria, Belgium, Brazil, Canada, China, France, Germany, India, Indonesia, Ireland, Italy, Japan, Korea, Malaysia, Mexico, the Netherlands, New Zealand, Norway, Poland, Puerto Rico, Russia, Singapore, South Africa, Spain, Sweden, Switzerland, Taiwan, Thailand, the United Kingdom, the United States, and Venezuela. Distributors in all major industrial areas of the world.

The information provided in this literature was reviewed for accuracy at the time of publication. Product data may be subject to change without notice. For current information consult your local Pall distributor or contact Pall directly.

11/09, PDF, UK GN09.3873   USTR 2660