BIOTECH

Application Note

USD 3476[1]

Re-Use of Sterilizing Grade Filters – Considerations and Risk Assessments

Technical Rationale

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Contents

1 Summary

Filters designed to sterilize liquids and gases have had a successful history of performance in a broad range of process applications. To reduce manufacturing costs, re-use of sterilizing grade filters in some processes may be considered. While sterilizing-grade filters have been thoroughly validated by their manufacturers for quantitative bacterial removal when integral and tested under standard conditions, the risk of undetected failure under re-use and non-standard conditions should be evaluated and mitigated prior to implementing filter re-use.

It is generally accepted that a non-destructive physical integrity test of a sterilizing grade filter, such as a forward flow (diffusion) test, is correlated to bacterial retention. If re-used filters continue to meet integrity test specifications upon repeated testing, they can be relied on to provide a sterile effluent. Forward flow and bubble point-type test methods are capable of detecting filter manufacturing defects such as bypass of membrane cartridge seals. However, filter re-use could cause changes to the membrane such as degradation, that cannot be detected by integrity testing but are enough to compromise the filter's bacterial retention properties.

The purpose of this document is to:

- describe the factors to consider for filter re-use,
- define the potential risk of filter re-use, and
- outline a strategy for end-users who wish to justify re-use of sterilizing grade filters in liquid services.

More detailed information is provided in the publication "Considerations on Re-Use of Sterilizing-Grade Filters" (2008) [1].

2 Strategies for Filter Re-Use in Liquid Services

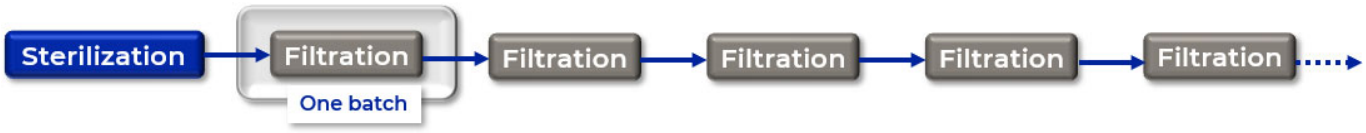
There may be variations as to what is interpreted as re-use. Filters can be considered re-used where they are employed for > 1 batch.

2.1 Without Removal, Rinsing, Cleaning, Sanitization or Re-Sterilization

The filters are initially sterilized then left in place with no interference as multiple batches of fluid are passed through them.

Figure 1

Schematic process diagram



While additional stress on the filter from re-use is minimal with this approach, retained bacteria may remain viable during the re-use cycles, possibly producing smaller cells while dividing and migrating through the largest pores of the filter media. This risk becomes even greater if the filters are allowed to stand unused for additional time between processing of consecutive batches while wet with fluid. There is also the additional risk of downstream contamination with bacterial by-products such as endotoxins.

Table 1

Summary of risks by filter re-use

Low Risk	Higher Risk
Physical stress on the filter (one sterilization only)	Remaining viable bacteria producing smaller cells while dividing and migrate through larger pores
	Development of biofilm during time of no use while wet with fluid
	Downstream contamination with bacterial by-products and endotoxins
	Chemical batch-to-batch cross contamination

Risk of time-dependent bacterial penetration will not be detected by filter integrity testing because there may be no additional stress on the filter, and it may remain integral.

2.2 With Inter-Batch Rinsing Only

The filters are subjected to water or other solvent rinse between each use to minimize carryover of process fluid components.

Figure 2

Schematic process diagram

While this type of re-use may reduce the ability of retained bacteria to multiply, the risk of time-dependent bacterial penetration from bacteria retained on the filter will remain. This is because retained viable bioburden can continue to divide even under starvation conditions. Again, there is also the additional risk of downstream contamination with bacterial by-products such as endotoxins.

Table 2

Summary of risks by filter re-use

Low Risk	Higher Risk
Physical stress on the filter (one sterilization only)	Remaining viable bacteria producing smaller cells while dividing and migrate through larger pores
	Downstream contamination with bacterial by-products and endotoxins
	Development of biofilm during time of no use while wet with fluid

2.3 With Inter-Batch Rinsing and Re-Sterilization

The filters are sterilized prior to every new process filtration.

Figure 3

Schematic process diagram

This can limit the risk of extended time-dependent bacterial penetration, as well as control possible development of biofilm. However, the re-sterilization can degrade retained bacteria and cause increased levels of leached bacterial endotoxins and other cellular by-products into the subsequent processed batch.

This type of re-use also imposes additional physical stress on the filter during the re-sterilization cycle. Most sterilizing grade filters are qualified by their supplier to withstand several steam autoclave or steam-in-place (SIP) cycles without compromising integrity or bacterial retention capability. However, filter supplier qualifications are typically conducted on intact filters wet only with water, subjected to multiple laboratory steaming cycles, and then tested.

While indicative of filter robustness, this does not necessarily model the additional chemical degradative stresses on the filter that may occur where residual product is insufficiently rinsed out prior to subjecting a filter to steaming conditions. It also does not preclude that any particular end-user sterilization cycle may be more stressful to the filter than the controlled laboratory sterilizations conducted to support product claims.

Table 3

Summary of risks by filter re-use

Low Risk	Higher Risk
Time-dependent bacterial penetration of smaller cells through larger pores	Downstream contamination with bacterial by-products and endotoxins caused by re-sterilization
Development of biofilm	Physical stress during re-sterilization cycle
Chemical batch-to-batch cross contamination	Chemical stress during re-sterilization due to insufficiently rinsed out residual products or rinsing agents

2.4 With Inter-Batch Rinsing, Cleaning and Re-Sterilization

An additional cleaning step is introduced post rinsing the filter prior to the next sterilization.

Figure 4

Schematic process diagram

While further reducing the risk of cross contamination or leaching of retained bacterial by-products by the rinsing and cleaning steps, the risk is due to potential stress to the filter and risk of filter damage that may not be detectable by routine integrity testing.

This type of re-use differs from the previous one as in addition to rinsing out the process fluid with a suitable solvent, the filter is subjected to an aggressive cleaning fluid intended to dissolve or degrade retained contaminants. In addition, residual cleaning agents retained within the filter due to inadequate rinsing after

cleaning and prior to steam exposure for re-sterilization, can be even more aggressive at the elevated temperature conditions of the re-sterilization process.

Table 4

Summary of risks by filter re-use

Low Risk	Higher Risk
Time-dependent bacterial penetration of smaller cells through larger pores	Physical stress during aggressive cleaning and re-sterilization cycle
Development of biofilm	Chemical stress during re-sterilization due to insufficiently rinsed out residual cleaning agents
Chemical batch-to-batch cross contamination	
Downstream contamination with bacterial by-products and endotoxins caused by re-sterilization	

2.5 Intermittent Use with Inter-Batch Drying

The filters are subjected to a drying procedure post rinsing.

Figure 5

Schematic process diagram

The filter entails a different form of stress incurred by drying of the membrane between batches. Some membranes may be damaged by repeated drying cycles, particularly if dried in hot air ovens. Residual contaminants or cleaning fluid or residue can be locally concentrated within the filter during drying, which can exert further chemical stress on the membrane. This may be sufficient to compromise the membrane's functionality, without being detected by routine integrity tests.

Table 5

Summary of risks by filter re-use

Low Risk	Higher Risk
Time-dependent bacterial penetration of smaller cells through larger pores	Downstream contamination with bacterial by-products and endotoxins caused by re-sterilization
Development of biofilm	Physical stress by drying (especially in a hot air oven)
Chemical batch-to-batch cross contamination	Physical stress during re-sterilization cycle
	Chemical stress during re-sterilization due to insufficiently rinsed out residual cleaning agent or contaminants and concentration on the membrane during drying

In each of these cases, where an end-user considers re-use to economize on filtration costs, it is essential that all process and re-use conditions be properly validated to not compromise the filter's ability to retain bacteria or the filter integrity test's ability to predict filter integrity.

3 Cleaning of Filter Cartridges

Cleaning is a complex issue and is not just a simple rinse and re-use. Cleaning means the removal of all prior batch residual materials from the entire system. This includes all piping, tanks, valves, filters, etc. A water for injection (WFI) flush (or pure solvent flush) following the final rinse, must show that the system is clean to a pre-defined level of cleanliness, using validated analytical methods. Furthermore, if any clean in place (CIP) material is used, this also must be removed and rinsed out completely.

It is important to keep in mind that cleaning may mean that material from the upstream tanks and pipes may be removed by the filters and remain on them. This can result in leaching into the next batch and even into the cleaning solutions. It is the responsibility of each user to develop a proper cleaning method and to validate the system suitability after cleaning. Users should consult with filter manufacturers on suitability of intended cleaning protocols.

4 Application of Re-Use in Liquid Service

In addition to process conditions, the criticality of the filtration process should form part of a risk assessment. On a risk-assessment basis, some processes may be considered less critical than others and may not require the highest levels of sterility assurance.

Table 6

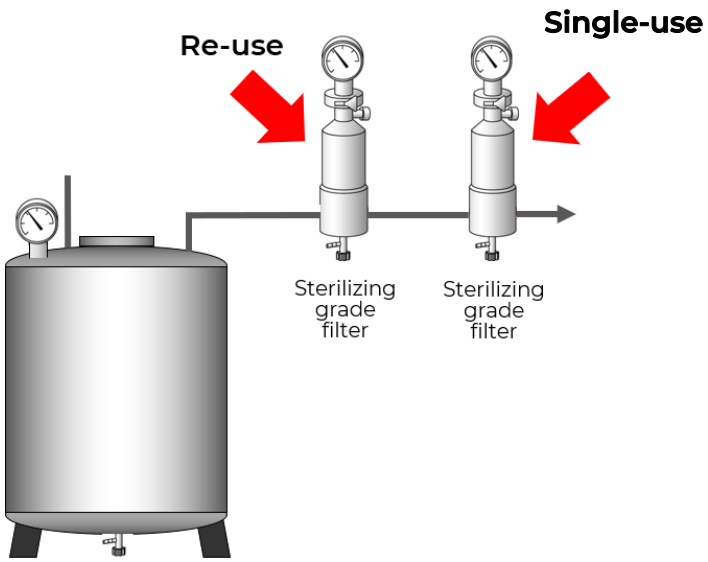
Required level of sterility assurance

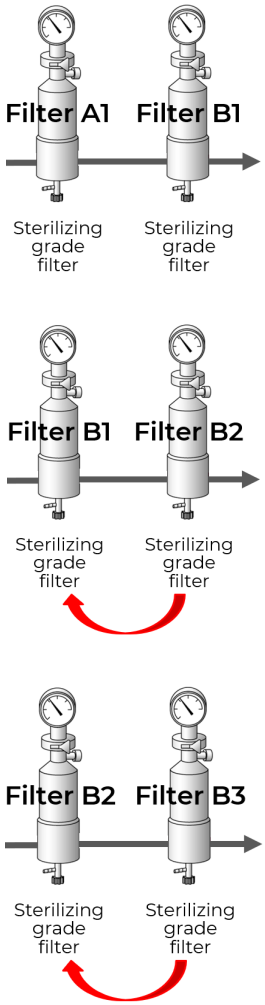
Low Level	Higher Level	Highest Level
Terminal sterilization performed	Non-critical applications	Critical applications
Use of sterilizing grade filters	Use of sterilizing grade filters	Use of sterilizing grade filters
Particulate and/or bioburden control	Sterile effluent required	Sterile effluent required
No claim for sterility of the effluent	Product can be flushed out easily	Use of bioburden control filters (0.45 µm or 0.2 µm) followed by sterilizing grade filter (0.2 µm) or redundant sterilizing grade filters
↓	↓	↓
Filter re-use may be considered	**Greater risk in re-use**	**Filter re-use not recommended**

Strategies for re-use of filters for critical applications are use of double or redundant sterilizing grade filters (0.2 µm or 0.1 µm).

Table 7

Re-use options for critical applications with redundant filters

Option 1	Option 2
Re-use of upstream filters and single use of final filters	Re-purposing of prior batch final filters as upstream filters for subsequent batches.
Note of caution: upstream filters may see the highest level of bioburden and may be difficult to return to a pre-use state.	
	Batch 1 Batch 2 Batch 3 .....and so on.....



In each case, any perceived economic advantage to re-use of the filters should be balanced against the risk of failure due to:

- premature plugging
- loss of integrity
- bacterial penetration

5 Considerations for Risk Assessment

Cleaning/re-use of a filter in a pharmaceutical application requires a risk assessment of at least the following factors besides excessive process parameters and the filter's chemical compatibility:

- Bioburden levels in the feed
- Growth-supporting activity of the product
- Extent of fouling of the filter
- Biological activity of the product, product components or by-products
- Resistance of the product, product components or by-products to solubilization
- Adherence of the product, product components or by-products to filter materials
- Difficulty of selecting an aseptic or growth-inhibiting filter storage method compatible with product
- Any impact on product Critical Quality Attributes (CQA)

These risks are the rationale for the recommended single use of disposable filters. Often, when taken into proper consideration of risks and the considerable efforts required to validate filter re-use, the drug product or process fluid is significantly more expensive than the filter and the risk to product quality is too high to make filter re-use an attractive option.

6 Regulatory Guidance on Re-Use of Sterilizing Grade Filters

The US FDA [2], EU guidelines [3], ISO 13408-2 [4], and PDA recommendations [5] all state that re-use is not recommended, but could be accepted, if sufficient justification exists, and if properly validated.

In addition, the leaching of contaminant or cleaning residue from used filters prior to re-use should be considered and absence of any such effects should be validated.

7 Validation of Filter Re-Use in Liquid Sterilizing Filtration

Following PDA, ISO and FDA recommendations, a multiphase bacterial retention study program is required for validation of sterilizing filtration with re-used filters. PDA Technical Report 26 and FDA aseptic processing guidance [5] currently call for 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, including one which represents a potentially least retentive membrane).

While a study of this extent is sufficient to demonstrate the filter membrane's capability to sterilize the drug product or process fluid on a single usage, it does not predict filter performance after multiple cleaning, sterilization and re-use cycles. Bacterial challenge testing should also be conducted on production filters subjected to actual, or preferably worst-case process conditions incorporating the full extent of multiple cleaning/sterilization and re-use cycles.

Table 8

Validation approach for re-use processes with only one sterilization cycle

Re-Use Processes Entailing Multiple Batches	
Without inter-batch rinsing 	Processes can often be scaled down and modelled as disc challenge tests at the bench.
With only solvent rinsing between batches 	

Table 9

Validation approach for re-use processes with multiple cleaning and sterilization cycles

More Complex Re-Use Processes	
Entailing multiple cleaning and re-sterilization cycles  	Processes are difficult to simulate in the laboratory with filter discs, capsules or even cartridges. Supplement the single batch disc challenge tests with bacterial challenges conducted on at least three used production filter cartridges.
Drying between campaigns 	

For complex re-use processes, 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, re-sterilization 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 if a filter's sterilizing properties remain unaffected by the multiple re-use process cycle conditions.

Alternatively, it is advisable to additionally test some used filters which have been subjected to fewer re-use cycles if the worst-case filters do not pass. If the filters subjected to fewer re-use cycles do pass, then it may be possible to release those earlier production batches. Because of the complexities of validating filter re-use, it is recommended to contact Pall for technical consultancy prior to re-using a filter intended for single-use applications.

8 Discussion

Re-use of any disposable equipment is subject to risks and hazards that must be controlled to assure the equipment remains safe, effective and continues to meet the 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.

Regulatory guidance discourages re-use of sterilizing grade filters. 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 regulatory guidelines [2,3] and the PDA

Technical Report 26 [4], validation of re-used sterilizing filters should include thorough testing of process filters exposed to the maximum specified number of cleaning, re-sterilization, drying and re-use cycles. Such testing should include bacterial challenges as well as filter integrity tests to assess chemical compatibility of the filter to process fluids and re-use cycle conditions, as well as chemical analysis of rinse effluents to identify 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. Nevertheless, Pall recommends implementation of performance of integrity tests pre and post product filtration cycles. Finally, users should consider carefully the level of risk and cost involved in validating re-use of sterilizing grade filters versus the apparent economy of re-use when designing and qualifying sterilization filtration processes.

More detailed information is provided in the publication "Considerations on Re-Use of Sterilizing-Grade Filters" (2008) [1]

9 References

1 J. Martin, "Considerations on Re-Use of Sterilizing-Grade Filters", 2008 *Pharmaceutical Technology, Sterile Manufacturing, Aseptic Processing*: 6 – 15.

2 US FDA Guidance for Industry: Sterile Drug Products Produced by *Aseptic Processing: Good Manufacturing Practice*, FDA 2004

3 EU Guidelines to Good Manufacturing Practice - Medicinal Products for Human and Veterinary Use - Annex 1 - *Manufacture of Sterile Medicinal Products* 2008

4 ISO 13408-2:2018 *Aseptic processing of Healthcare Products – Part 2: Sterilizing Filtration*

5 PDA, "Sterilizing Filtration of Liquids," *Technical Report No. 26, PDA* 2008

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