Millipore®
Preparation, Separation,
Filtration & Monitoring Products

Technical Brief

Validation Master Plan

For Filtration Systems Used In Aseptic Processing

Introduction

Sterile filtration is a critical step in manufacturing of medicinal products produced by aseptic processing. Regulatory guidance provides a framework for aseptic processing that ensures patient safety.

Developing a sterile filtration process starts with selection of the appropriate filtration system and qualification of filter performance. It continues with good engineering and validation practices and the establishment of standard operating procedures (SOPs), training of operators and ongoing adherence to documented procedures.

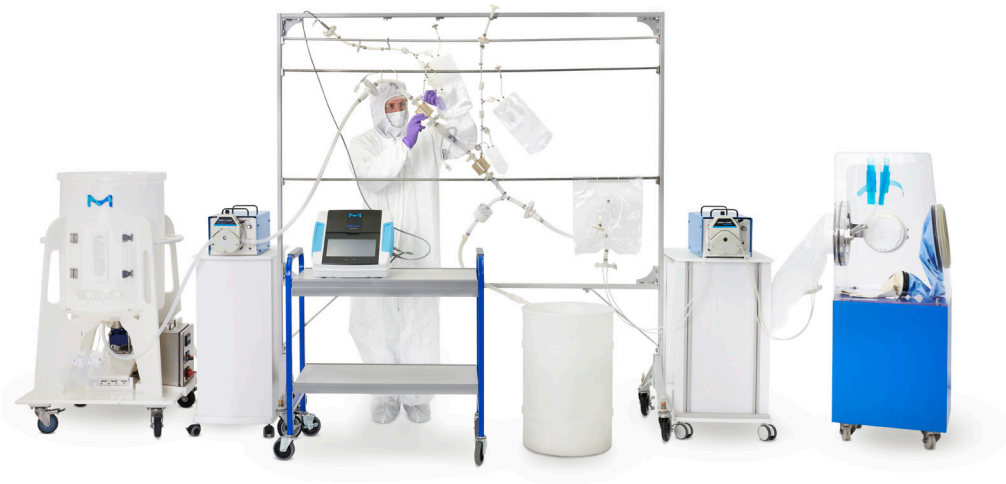
Our Validation Services team has developed a general master plan that summarizes best practices for validating performance of critical filtration systems used in aseptic processing. We provide support to medicinal product manufacturers on the various tests needed to meet global regulatory requirements.

Objectives of Filtration System Validation

Regulatory agencies require product and process specific validations to simulate the normal production process [1-4]. Typically, validation starts with risk assessments in early phases of clinical development and continues throughout development with comprehensive process validation before commercial scale manufacturing.

The objective of validating the filtration system is to provide a high level of assurance that the system performs reliably within the predefined process conditions:

- It must assure that the filter's bacterial retention is unaffected by the drug solution and processing conditions and that the filter provides sterilizing grade performance under actual processing conditions.
- Validation should assure that the filtration process does not affect the original drug product's attributes such as its quality, safety and efficacy. This is addressed by binding studies, extractables and leachables studies, and the patient safety evaluation.
- Validation should assure that neither the drug solution nor the process affects the filtration system's characteristics. This information covers chemical, physical and thermal compatibility and integrity testing.



Validation Master Plan

Before starting a filtration system validation, a general Validation Master Plan (VMP) is established to summarize the protocols and testing strategy. These pre-approved protocols, together with final test reports are collated into a summary report when the validation is completed[5].

Manufacturers of medicinal products, as the end-users, should ensure that the appropriate tests are performed and documented correctly and that the validation documentation is properly maintained[1-5]. Following the validation of filter performance, critical procedures such as filter-sterilization and integrity testing should also be validated. **Table 1** lists the responsibilities of the filter end-user and filter manufacturer.

Table 1. Responsibilities and contributions of the end user and filter manufacturer in sterilizing filtration systems validation

Activity	End-user	Filter Manufacturer
Certificate of Quality	-	✓
Qualification Dossier/Validation Guide	-	✓
Filter bacterial retention in drug product with simulation of worst-case processing conditions	✓	Service
Chemical compatibility verification	✓	Service
Extractables documentation (e.g. Emprove® Dossier)	✓	✓
Extractables/Leachables studies	✓	Service
Drug product interaction	✓	-
Patient safety evaluation	✓	Service
Transmission/binding studies of API and excipients	✓	Process simulation and sampling
Filtration system sterilization validation	Autoclave, Steam in Place	Ionizing irradiation
Filter integrity test limits with product	✓	Service
Particulate matter compliance	✓	-

Bacterial Retention Testing

A sterilizing-grade filter is defined as a filter which will produce a sterile effluent when challenged with *Brevundimonas diminuta* at a minimum concentration of 10^7 organisms per cm^2 of filter area. This bacterium was selected because it is non-pathogenic and consistently yields single-cell populations reproducible in terms of size and morphology. The operational procedure for challenge testing is registered as a standard method by the American Society for Testing and Materials, under designation ASTM F838. This standard test is used by filter manufacturers for qualification and quality assurance of sterilizing filters as listed in the filter's Certificate of Quality and other documents.

Typically, for a product and process-specific validation, the challenge bacteria is *B. diminuta*, cultured according to ASTM F838 standards to ensure organism viability, diminutive size and monodispersion. However, it is expected that end-users evaluate their process bioburden to justify selection of the challenge bacteria. If bacteria smaller than *B. diminuta* are identified in process bioburden, then this smaller bacterium, more representative of 'worst case' conditions, should be used for bacterial retention studies. **Table 2** outlines different considerations for bacterial retention testing.

Table 2. Bacterial retention testing: differences between the filter qualification and QA activities performed by a filter manufacturer and product-specific validation and process controls, that are the responsibilities of the end-user.

Test Parameters	Qualification and QA (ASTM F838)	Product-specific bacterial retention testing	Production and in-process controls
Time	1-2 mins.	Process-dependent	< Validated time
Pressure	2 bar maximum	Process-dependent	< Validated pressure
Flow Rate	2-4 mL/min.cm²	Process-dependent	< Validated flow rate
Test organism	*B. diminuta*	*B. diminuta* or process isolate	Size of bioburden > test organism
Challenge level	$>10^7$ cfu/cm²	$>10^7$ cfu/cm²	< 10 cfu/100 mL
Integrity test data	Correlation with bacterial retention	Use at least one membrane with a pre-use integrity test value at or near the acceptance specification	Relationship with integrity test used during validation

To validate the bacterial retention performance of a sterilizing-grade filter at small scale, the test protocol should be designed to simulate the large-scale process in terms of volume filtered per unit area, flow-rate per unit area, process time, differential pressure and temperature. Any filtration system operations such as PUPSIT (Pre-Use Post Sterilization Integrity Testing), final filter integrity test, and associated blow down steps or filter drying should be incorporated in the protocol design. Tests are conducted in triplicate on disc filters to minimize the volume of drug product fluid required and will include appropriate controls. These small-scale tests enable testing of the entire filter effluent for sterility. **Figure 1**.

Figure 1. Small scale filter test set-up.

The preferred approach for bacterial retention testing in filter validations is direct inoculation of challenge bacteria into the drug product. If the drug product or the process conditions are bactericidal to the test micro-organism, test filters can be preconditioned with the product before the challenge test; this approach is outlined in PDA Technical Report 26[6]. The selection of the appropriate validation test design is dependent on the results of preliminary viability and recovery tests shown in **Figure 2**.

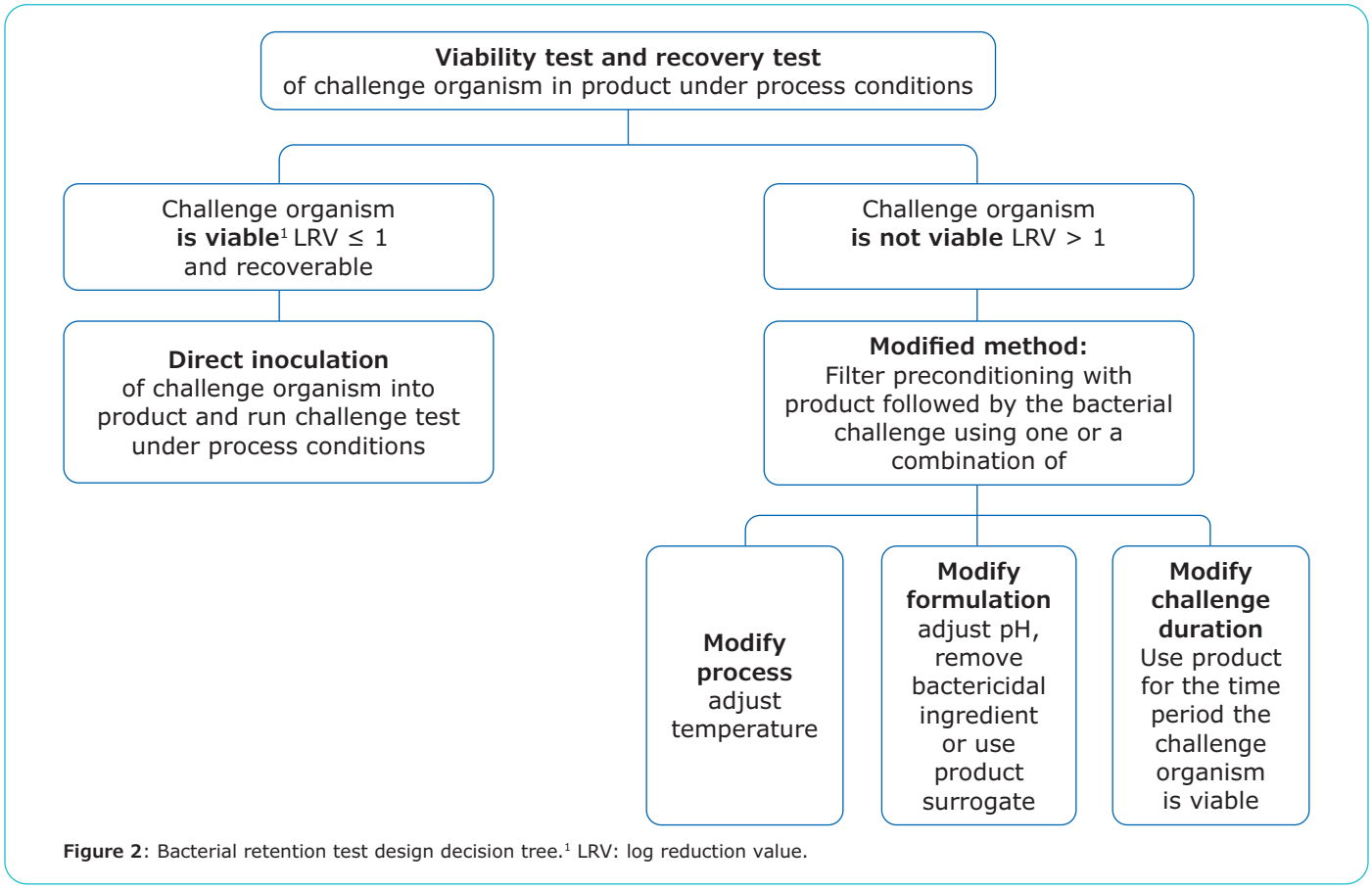


Figure 2: Bacterial retention test design decision tree.[1] LRV: log reduction value.

Regulatory guidance documents stipulate that the membranes used for the bacterial retention testing shall be representative of the process filter device including at least one membrane with a pre-integrity test value at or near the filter manufacturer's minimum integrity-test specification[1-4].

Interaction of the Filtration System with the Process Fluid

During processing the components of the filtration system should neither add (extractables and leachables) nor remove (adsorption) anything from the process fluid. A key component of aseptic filter system validation is to quantify the effects of both extractables, leachables and adsorption on the process fluid by empirical studies.

Extractables and Leachables Studies and Patient Safety Evaluation

Extractables are compounds that can be extracted from plastic or elastomeric materials in solvents of different physicochemical properties under aggressive conditions. Leachables are compounds that leach from the plastic or elastomeric materials into the drug product under normal use conditions, **Figure 3**.

Extractables are inherent to the processes of filtration system manufacturing and use. They may include materials of construction, wetting agents, residual solvents, antioxidants, unreacted monomers, lubricants, stabilizers, molding and lubricating agents and surfactants. Extraction variables such as temperature, contact time with solvents and sterilization methods all impact extractable levels: levels increase with extraction time, temperature, and more rigorous sterilization methods.

Although component manufacturers ensure that the materials of construction meet biosafety standards such as ISO 10993, USP <88> and <87>, these evaluations are conducted with solvents under conditions focused on extreme toxicity, which are beyond most pharma manufacturing process conditions. End-users must validate their critical filtration system operations to confirm they do not add extractables to the drug product to an extent that would alter the drug product safety or efficacy.

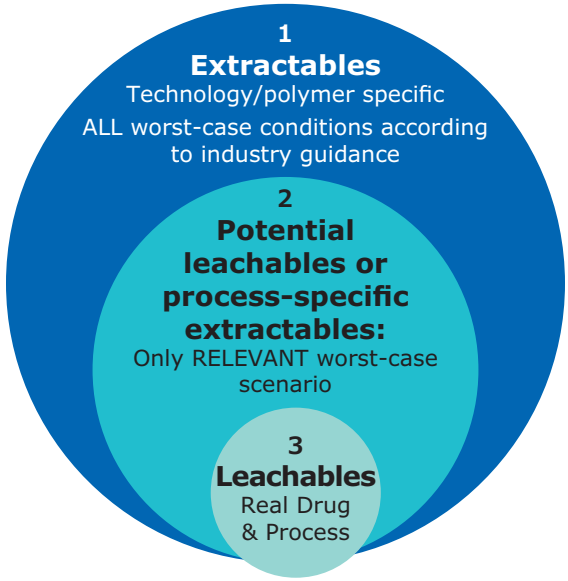


Figure 3. Relationship between extractables and leachables

Following the release by the Biophorum Operation Group protocol[7, 8] and with the elaboration of the USP <665> draft chapter on plastic components and systems used in pharmaceutical manufacturing, filter and single-use system manufacturers published comprehensive extractables and leachables information for their components, which meets regulatory guidelines[9].

For a drug product modelling, the most representative solvents combination includes solvents with a higher "leaching power" than that of the drug product. Those studies provide quantitative and qualitative information on the extractables level in the first filtrate volume. Extractables are analyzed using a wide range of analytical methods for identification and quantitation of volatile, semi and non-volatile organic compounds as well as elemental impurities[10].

The first step in an extractables evaluation is to identify all product-contact materials. Data are selected and compiled to reflect drug product and process specific conditions resulting in a list of compounds and amounts.

The second step is to perform a patient safety risk assessment for each compound comparing its extractables level to the threshold of toxicological concern, referencing information from ICH M7 guideline[11] or its Permitted Daily Exposure (PDE) level from ICH Q3C[12].

In addition, other considerations should include but not be limited to:

- Chemical compatibility between material and drug product
- Drug product modelling by representative model solvent
- Contact time
- Contact temperature
- Surface area-to-volume ratio
- Proximity of material to final product
- Extractable substance toxicity profile
- Dosage form
- Route of administration
- Target population: adults/children
- Posology

Based on outcome of the patient safety evaluation, application knowledge and risk assessment, it may be possible to introduce mitigation steps to reduce the levels of extractables. Such measures could include system pre-flushing or initial volume discarding, **Figures 4** and **5**.

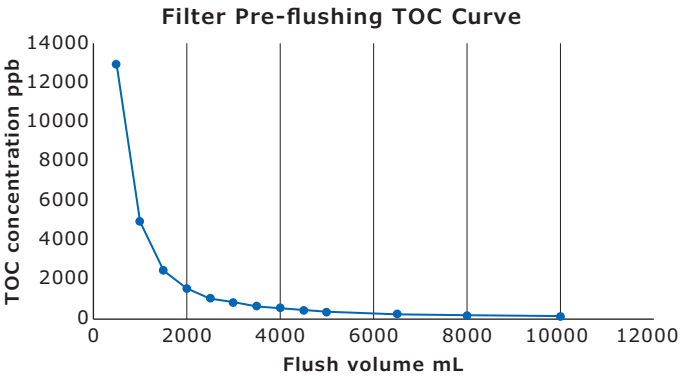


Figure 4: Benefits of pre-flushing on levels of Total Organic Carbon (TOC) in a 10" Durapore 0.22 µm filter.

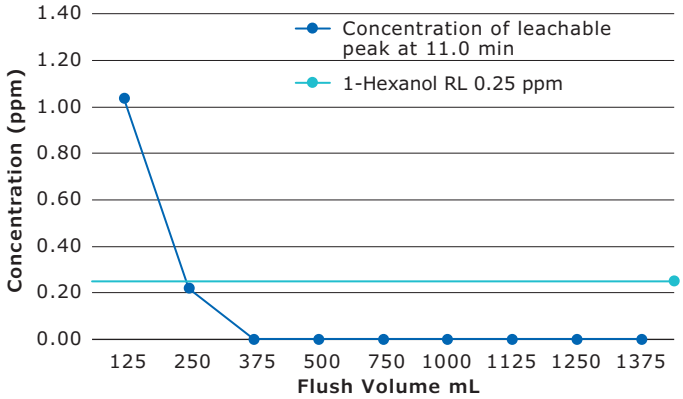


Figure 5: Examples of initial volume discarding for leachable peak at 11.0 min from 4" Durapore® 0.22 µm Gamma Irradiated filter.

Note: 1-Hexanol is used as a quantification standard which report limit is set at 0.25 ppm

If the patient safety evaluation based on extractables data identifies a potential risk for the patient, then a leachable study should be performed with the actual drug product under process-specific conditions. Leachables data is used to reassess patient safety to ensure that none of the compounds in the drug product are above the safety threshold. **Figure 6** summarizes the workflow for assessing extractables and leachables.

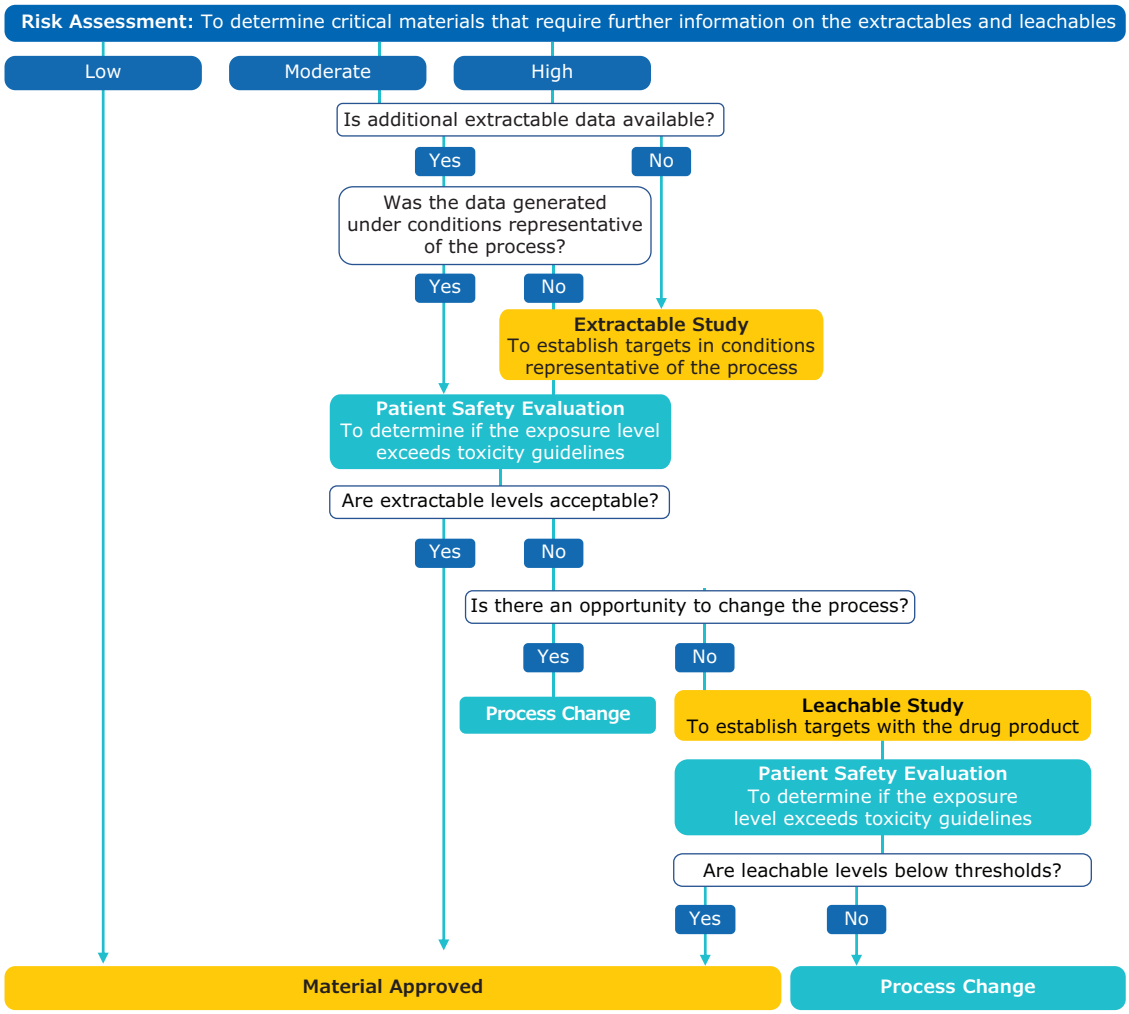


Figure 6: Approach for evaluating extractables & leachables and their impact on patient safety.

Binding Studies

The nominal transmission of the drug ingredients through a filtration system is carefully studied at the beginning of the filtration process and around process interruptions. Binding, or as they are sometimes known, transmission or adsorption studies, determine whether a given filter adsorbs components from a drug product. Binding can cause loss of active pharmaceutical ingredient (API) or excipient, induce biomolecule conformational changes and reduce activity or stability. If adsorptive interaction or conformational changes are observed, the drug manufacturer must determine if the interaction affects drug safety and efficacy. If it does, the filter should not be used for the manufacturing process. If it doesn't, it must be determined if it is possible to mitigate the effect of the filter on the drug product (e.g., pre flushing the filter membrane with a preservative to tie up the binding sites).

Product binding is assessed by product assays pre and post filtration. A drug ingredient binding dynamic may be affected by flow rate, API concentration, excipient concentrations, pH, ionic strength and temperature of the solution. For this reason, it is important to conduct binding studies on product filled under process conditions. In addition, binding studies should consider and assess the impact of interruptions in processing; these could increase exposure time of the drug product to potentially adsorptive medium.

Preliminary binding studies are most easily performed on 47 mm membrane discs by scaling down the process volume and flow rate based on the membrane area. Samples are collected from the process feed, filtrate fractions and from the pooled filtrate and analyzed for component concentration. These data enable calculation of the volume required for saturation of the filter binding capacity and the flush volume required for acceptable component concentrations in the drug product post filtration.

Binding studies are important especially for a final fill step but less critical for tank-to-tank filtration where adsorption of the API to the filter is often too low to be detected in product assays.

Chemical Compatibility

Chemical compatibility of the drug product and filtration system can be assessed by literature review or by testing a filter after exposure to the drug solution. Filter testing could assess filtration performance and include mass, flow time and bubble point using the standard fluid such as water (for hydrophilic filters). Filters could then be exposed to the drug product for the maximum process duration and maximum process temperature, then the filtration performance is re-assessed and compared to initial performance. Performance within the acceptance criteria confirms compatibility of the filter and drug product. Compatibility of the filter is also confirmed during the bacterial retention testing, since the filter membranes exposed to the drug product are expected to provide a sterile filtrate. Extractables test results can also inform chemical compatibility of the filter device since no extraneous compound other than the filter materials should be identified.

Product-Based Integrity-test Data

The integrity of sterilizing-grade filters is confirmed by either diffusion and/or bubble point testing with the membrane wetted with either standard fluid or product.

The diffusion and bubble point specifications for a sterilizing-grade filters are determined by the filter manufacturer following extensive testing using standard wetting fluids, such as water. However, in the production environment it is not always possible or practical to test the filter with water. In practice, a product-based integrity test is commonly used for inline filter integrity verification both pre-use (PUPSIT, Pre-Use Post Sterilization Integrity Testing) and post-use.

Because the drug product typically has a different surface tension and angle of contact with the membrane than the standard wetting fluid, bubble point values with process fluid are typically lower than those with standard wetting fluid. Similarly, because the process fluid contains solutes, the gas diffusion rate with process fluid is usually lower than the rate with water.

Consequently, when a sterilizing filter is wet with drug product, a product-specific filter integrity test (FIT) value should be established. Product specific integrity testing can circumvent problems with product-specific components binding to the membrane and potentially interfering with testing using a standard wetting fluid. As an example, polysorbate in product can bind to the membrane and be challenging to remove. Residual polysorbate could lower the bubble point and result in a false failure of integrity if a standard wetting fluid was used.

Product specific bubble point limit

The product specific bubble point limit is determined by a small-scale study: three filters from one membrane lot are wet with standard wetting fluid and bubble point tested. The filters are then dried and then wet with process fluid (from one lot of drug product) and bubble point tested again. Results from these studies are used to calculate the Bubble Point Ratio (BPR).

BPR= bubble point in process fluid (at process temp) / bubble point in standard wetting fluid (room temp)

This Bubble Point Ratio is used to calculate the product specific bubble point limit as outlined in **Table 3**.

Product specific diffusion limit

The product specific diffusion limit is determined after a preliminary bubble point evaluation with the product on one membrane disc: it is then possible to set the product-specific diffusion test pressure with the following formula: BPR x standard fluid diffusion pressure.

Three filter devices (4" in size) are wetted and diffusion tested with standard fluid under standard conditions of pressure and temperature. Filters are then dried, wet with product, and tested at the process temperature for diffusion at the test pressure determined during the preliminary step. Results from these studies are used to calculate the Diffusion Ratio (DR) between the process fluid at process temperature and the standard wetting fluid at room temperature. This Diffusion Ratio is used to calculate the product specific diffusion limit. **Table 3** provides an example of both standard and product specific bubble point and diffusion values for a sterilizing grade Durapore® 0.22 µm membrane filter.

Table 3: Example of laboratory scale product-specific limit determination

	Standard fluid bubble point value at 22 ± 4°C *mbar*	Product bubble point value at 22 ± 4°C *mbar*	Bubble Point Ratio (BPR)	Standard fluid diffusion value at 2760 *mbar* at 22 ± 4°C *mL/min*	Product diffusion value at 2100 *mbar* at 22 ± 4°C *mL/min*	Diffusion Ratio (DR)
Filter 1	3790	2971	0.78391	2.75	1.11	0.40364
Filter 2	3735	2885	0.77242	3.09	1.15	0.37217
Filter 3	3759	2907	0.77334	2.84	1.12	0.39437
Average ratio	$BPR_{average}$= 0.77656			$DR_{average}$= 0.39006		
% CV	0.82			4.15		
Product specific FIT limit	Minimum $BP_{Product}$ = $BP_{Standard\ fluid}$ x BPR = 3450 mbar[1] x 0.77656 = 2680 mbar			Maximum Diffusion $rate_{product}$ = $D_{Standard\ fluid}$ x DR = 5.0 mL/min[1] x 0.39006 = 2.0 mL/min at 2100 mbar		

[1]Bubble point (BP) and diffusion rate values (D) from the Certificate of Quality for an Optiseal® cartridge filter (Cat no. LAGL04TP6).
Note: Results may differ depending on local rounding rules

The study at lab scale can be repeated for two additional lots of process fluids and filters especially in the case of known raw material, product, or process variability.

In-process monitoring

Following this initial determination of product specific integrity limits, it is recommended to confirm at production scale by monitoring and trending. This is achieved by verifying that product-wet integrity test data fall within the expected in-process diffusion and bubble point windows, show low dispersion and that the level of retest is low and acceptable.

Figure 7 shows two examples of in-process monitoring for product specific bubble point:

- Case 1: Production scale data match the small-scale results.

- Case 2: The right scenario illustrates some production scale data which fall outside the proposed window limits from small scale studies. If this situation should arise, the product specific FIT limit must be re-evaluated as detailed in our Application Note 'Establishing Product specific bubble point values for sterilizing-grade filters' AN1505EN00[13].

In-process verification of integrity test limits is part of the performance qualification (PQ) of integrity testing procedures and is an elaboration of the installation qualification/operational qualification (IQ/OQ) of the automatic integrity test equipment.

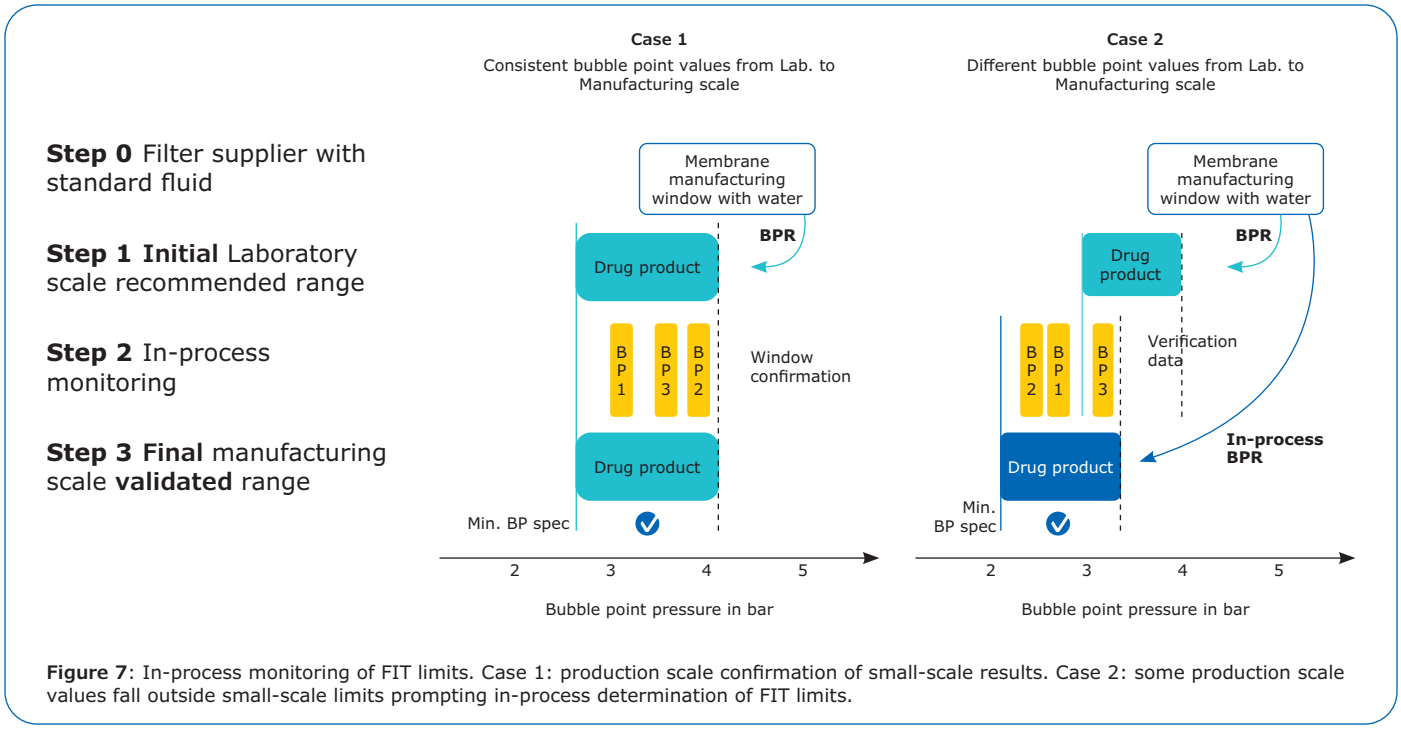


Figure 7: In-process monitoring of FIT limits. Case 1: production scale confirmation of small-scale results. Case 2: some production scale values fall outside small-scale limits prompting in-process determination of FIT limits.

Validation of the sterilization of the filtration system

Filtration systems in the pharmaceutical industry are sterilized either by moist heat – autoclave or steam in place - within the end-user facility. Alternatively, sterilization with ionizing irradiation may be performed by the supplier and sterilization contractor. Validation of the sterilization process confirms that the sterilization is effective at the minimum exposure conditions and that the maximum conditions do not adversely affect the filter.

Steam sterilization

Steam sterilization is critical for the sterility assurance of the final product and regulatory authorities require thorough validation programs. Since filtration systems are resistant to steam treatment, overkill sterilization processes, that produce a 12-log reduction of heat resistant micro-organisms, are used. An overkill sterilization process is defined by the FDA as "a process which is sufficient to provide at least a 12-log reduction of microorganisms having a minimum D value of 1 minute"[1]. The D value is the time necessary to achieve a 1 log reduction in number of a reference micro-organism, usually *Geobacillus stearothermophilus*.

The filtration system sterilization process should be qualified with classic design qualification (DQ)/IQ/OQ of the heat transfer equipment, that is either the system to be sterilized in place or the autoclave. The activity is formally supported by standards and guideline including ISO 17665[14], EN285[15], ISO13408-5[16], PDA Technical Reports 48[17] and 61[18].

The filter is one of the most difficult parts of the system to sterilize, as the membrane matrix and other plastic components make the quick and uniform steam penetration difficult. Validation of filter sterilization cycles begins with a thorough thermal mapping, and identification of cold spots.

Filters are installed, controlled for their integrity, and submitted for sterilization. The sterilization system should contain thermocouples to confirm temperature uniformity throughout, and triclamp fittings facilitate the insertion of the thermocouples into the system, **Figure 8**. The thermocouples are connected to a data logger, calibrated against an internationally recognized standard.

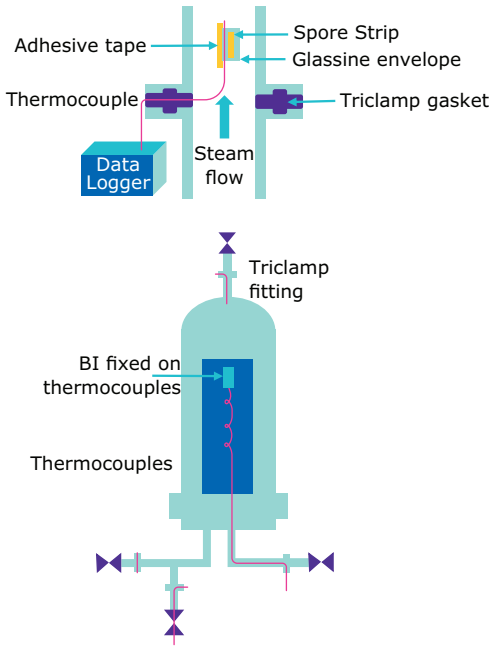


Figure 8: Position of thermocouples and biological indicators in a filtration system

Validation of the sterilization procedure involves triplicate studies to confirm that the sterilization procedure is adequate, and that heat distribution in the unit is achieved in a reproducible way.

The thermal mapping study carried out earlier identifies the most difficult areas to sterilize; typically, the drains, vent legs, plastic tubing, and filters. Once defined, these slowest heating points must be adequately challenged to demonstrate uniform heat distribution and steam penetration in all parts of the equipment.

Because some critical areas may reach a correct temperature but not proper lethality, due to the presence of air pockets, validation of the sterilization process requires both biological indicators and thermocouples. This combination confirms that both the required temperature and moisture levels are reached to assure lethality throughout the system.

Bacillus stearothermophilus spores are the standard indicators used for the validation of steam sterilization processes because they are resistant to moist heat. The most commonly used configurations, spore strips, consist of a paper inoculated with the microorganism. They are installed adjacent to thermocouples and must be securely fixed with adhesive tape resisting to high temperature, **Figure 8**.

Biological indicators are supplied with certificates that guarantee resistance (D-value) at a given temperature. Generally, populations of 10^6 spores with a D-value of 2 minutes at 121 °C are used to validate the sterilization process; this would require an exposure of at least 12 minutes at 121 °C to kill all indicators. The calculated sterilization time is then doubled to reach the 12-log reduction required for overkill sterilization; this is the origin of the typical filter sterilization time of 30 minutes at 121 °C.

Upon completion of the sterilization cycle, the indicators as well as positive controls are incubated in the appropriate medium (typically tryptone soya broth) for seven days at 55 °C. For acceptable sterilization, all exposed biological indicators must be sterile (zero growth), and positive controls must show normal growth.

After the sterilization validation study, the Standard Operating Procedure (SOP) must be confirmed and properly documented, and the personnel in charge of filter steaming must receive appropriate training. Finally, the validation team confirm that operators understand the SOP and carry it out properly.

Ionizing irradiation

Today, sterilization of single use equipment for bioprocessing predominantly uses gamma irradiation. Other technologies such as X-ray irradiation may be used and qualified with the same approach. The validation and operations of the gamma sterilization process is governed by the ISO 11137 standard[19].

The validation of the gamma sterilization process for single-use filtration system includes:

1. Average bioburden determination of system components
2. Low dose conformation of sterilization (10^{-1} Sterility Assurance Level (SAL))
3. Dose mapping (PQ of irradiation process)
4. Quarterly low dose audits including bioburden determination
5. Monitoring routine irradiation dose

Typically, most of this work performed by contract laboratories. Although the end-user does not need to validate the irradiation sterilization process, it is expected they obtain a summary of the sterilization process from the single-use system supplier together with quarterly reports of dose verification and certificates of processing. Obtaining and maintaining this documentation in conjunction with auditing the supplier is sufficient verification for the process.

Aseptic process simulation (APS)

The final confirmation that the aseptic filtration and filling process is robust, comes from the aseptic process simulation or media fill. In this evaluation, bacterial growth media is filtered and filled into sterile containers following execution of all processing steps including global filtration system installation, sterilization, priming, flush and FIT, by the trained operators. Three successful consecutive media fill runs are necessary to establish that the filling line can reliably operate with its sterilization, container sterilization/introduction, filtration process, aseptic filling, stoppering and interventions.

Validation Documentation

All testing required for the validation of the sterilizing filtration must be documented and all test results recorded. End users must be able to provide relevant document packages on their validation program for the drug product filing for inspection. All documentation should be easily understandable by reviewers and must be kept up to date. The validation documentation package ensures that all the required testing has been conducted under controlled conditions and the information gained during the exercise will help the end user solidify the process working limits.

Validation Master Plan (VMP)

The VMP is the starting point of the validation procedure and should include the purpose and scope of the exercise, the description of the test methodologies and their rationale.

Validation Protocol

The validation protocol describes the pre-established acceptance criteria and must be approved by the validation team. It should include a description of products and process conditions, summarize the rationale for the selection of worst-case testing conditions and provide details for materials and methods.

Validation Report

Testing is performed as described in the validation protocol. The recorded results must comply with the pre-determined acceptance criteria. The validation report should contain the product and filter batch identification, test results and conclusions.

Validation Summary Report

The summary report is the final documentation which consolidates information from the various validation documents. It summarizes the conclusion from the validation studies.

Conclusion

Beyond the filtration system qualification and validation described in this document, operator training and process controls are critical elements in assuring sterility in aseptic processing. This robust framework provides documented evidence and confidence that medicinal products manufactured in an aseptic process are safe for administration to patients.

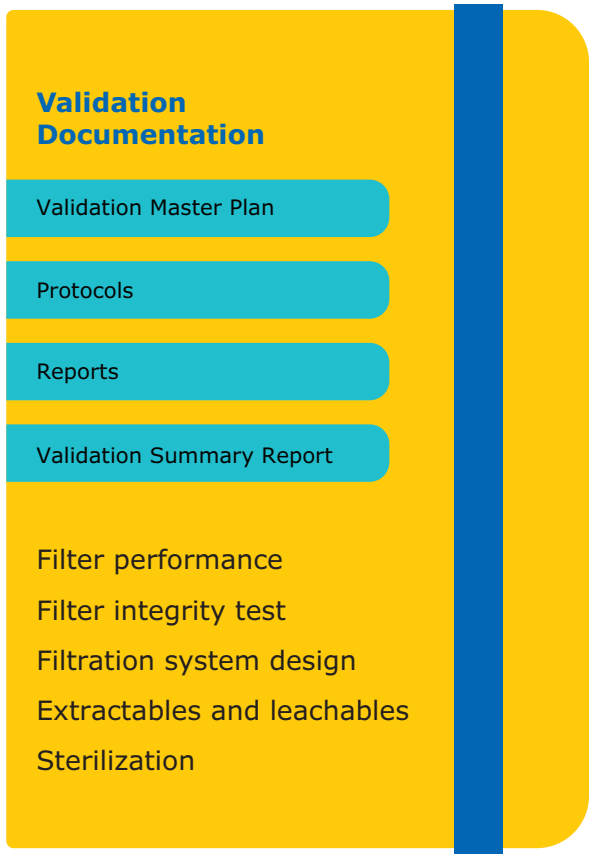


Figure 9: Validation documentation for sterilizing filtration in aseptic processing

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