

FILTER VALIDATION FAQs

What is Sterile Filtration Process Validation?

Sterile Filtration Process Validation is a documented, science- and risk-based program that demonstrates a sterile filtration process step consistently produces a sterile filtrate under defined operating conditions. Filter validation typically confirms that the selected sterilizing-grade filter and process parameters reliably achieve sterility assurance while maintaining product quality.

When is filter validation required?

Filter validation is generally required when:

- A product is sterilized by filtration (rather than terminal sterilization).
- A new product, filter, container closure, or manufacturing site is introduced.
- A process parameter changes (e.g., flow rate, pressure, temperature, hold time).
- Filter type, pore rating, material, or supplier changes.
- Bioburden levels, formulation, or upstream process changes may impact filtration.

What regulations and guidance apply to filter validation?

Filter validation expectations are typically aligned with:

- EU GMP Annex 1: Manufacture of Sterile Medicinal Products
- FDA cGMP (21 CFR Parts 210/211): Current Good Manufacturing Practice for manufacturing of drug products
- ISO 13408: Aseptic Processing of Health Care Products
- PDA Technical Report 26: Sterilizing Filtration of Liquids
- ASTM F 838: Standard Test Method for Determining Bacterial Retention of Membrane Filters Utilized for Liquid Filtration

Applicable references depend on product type (drug substance, drug product, biologic, ATMP), region, and internal quality standards.

What is the objective of a filter validation study?

Typical objectives include demonstrating:

- Sterilizing-grade filtration performance under worst-case conditions.
- Bacterial retention capability is appropriate for the process.
  - often linked to *Brevundimonas diminuta* (formerly *Pseudomonas diminuta)* challenge rationale
- Filter integrity testing strategy.
  - pre-use/post-use, limits, and correlation
- Process robustness across normal operating ranges and credible deviations.
- No unacceptable impact on product quality.
  e.g., adsorption, extractables/leachables risk, particulates

What products/processes does filter validation cover?

Filter validation may apply to:

- Sterile drug products (liquids, suspensions where feasible, some emulsions)
- Biologics (mabs, vaccines, recombinant proteins—case dependent)
- Buffers, media, intermediates, bulk solutions
- Final fill filtration and/or upstream sterile filtration steps

What is a "sterilizing-grade filter"?

A sterilizing-grade filter is a membrane filter validated to retain microorganisms, typically with a nominal pore size of 0.2 / 0.22 µm (or 0.1 µm for specific applications). "Sterilizing-grade" status is supported by manufacturer validation to the current revision of ASTM F838 - Standard Test Method for Determining Bacterial Retention of Membrane Filters Utilized for Liquid Filtration - and must be confirmed as suitable in the user's specific process (user sterile filtration process validation).

What is included in a filter validation service scope?

Parker will collaborate with you to determine the scope of your requirements, which typically include:

- Protocol generation
- Filter selection justification (material, size, configuration)
- Bacterial retention / microbial challenge study design and execution (as applicable)
- Integrity testing plan (pre/post-use, limits, wetting, method)
- Performance testing & compatibility (throughput, flow/pressure, fouling, integrity)
- E& L testing
- Final report with conclusions, acceptance criteria, and recommendations

How do you define "worst-case" conditions for sterile filtration?

Worst-case conditions are chosen to challenge the filtration step, commonly including but not limited to:

- Maximum bioburden and/or smallest expected microorganisms
- Maximum filtration time / hold time
- Maximum differential pressures
- Maximum viscosity / lowest temperature
- Longest pre-filtration hold (potential bioburden growth)

Is sterile filter process validation always required?

Not always. The need depends on:

- Product type and risk (e.g., final sterile drug product vs. Buffer)
- Existing platform knowledge and supplier data
- Regulatory expectations and internal policy
- Whether the filtration step is the final sterilizing step for product

However, microbial retention evidence is commonly expected for critical sterile filtration steps.

What organism is typically used for bacterial retention studies?

Historically, *Brevundimonas diminuta* (formerly *Pseudomonas diminuta)* is used because it is small and a rigorous challenge organism for 0.22 µm filters and is defined as the requirement in ASTM F838 - Standard Test Method for Determining Bacterial Retention of Membrane Filters Utilized for Liquid Filtration. Alternative organisms or approaches may be justified based on risk assessment and standard and/or if the drug formulation is biocidal to *Brevundimonas diminuta* (formerly *Pseudomonas diminuta)*.

What is filter integrity testing, and when is it performed?

Integrity testing verifies the filter is intact and performing as intended. Common tests:

- Bubble Point
- Diffusive Flow
- Pressure Hold

Typically performed:

- Pre-use (PUPSIT) where required/expected
- Post-use after filtration
- After sterilization or extended holds, as defined

Parker can advise on the most appropriate test method(s) for your application.

What is PUPSIT and when is it expected?

PUPSIT = Pre-Use Post-Sterilization Integrity Testing. It provides assurance that the sterilizing filter is intact after sterilization and before use. EU GMP Annex 1 strongly expects PUPSIT for sterilizing-grade filters, with limited, well-justified exceptions.

How are integrity test limits established?

Limits are typically derived from:

- Filter manufacturer specifications are correlated to full retention per ASTM F838 - Standard Test Method for Determining Bacterial Retention of Membrane Filters Utilized for Liquid Filtration.
- Correlation studies for product wet parameters to filter manufacturer specifications when water wet.

How is filter sizing (surface area) determined?

Sizing commonly considers:

- Required batch volume and target filtration time
- Expected differential pressure limits
- Viscosity and temperature
- Filter capacity/throughput data (vendor + user testing)
- Worst-case fouling and safety factors

A formal sizing study often includes scaled trials and extrapolation rules.

What are extractables and leachables:

- Extractables are compounds that can be released from polymeric/elastomeric materials when exposed to solvents. Testing performed to USP<665> is required.
  - Testing is typically performed under worst-case conditions using a Model Solvent Approach.
  - The objective is to identify and quantify compounds that could potentially become leachables in actual use.
- Leachables are compounds that migrate from polymeric/elastomeric filter materials into the process fluid under actual use conditions.
  - May impact drug product by introducing impurities that may affect patient safety (toxicity), product quality (stability/potency), and regulatory compliance.
  - Testing should be completed after storing the drug product in it's finished packaging.

What is extractables/leachables relevance in filter validation?

Filter validation may reference E/L to ensure the filtration step does not introduce contaminants. Depending on risk, data may include:

- Vendor extractables packages to USP<665>
- Leachables risk assessment tied to contact time/solvent conditions
- Targeted analytical verification of leachables if risk assessment indicates a requirement.

How are compatibility and chemical resistance confirmed?

Compatibility is assessed via:

- Vendor chemical compatibility guides
- Literature and platform knowledge
- Confirmatory lab studies at worst-case conditions (pH, solvent, surfactants, temperature, time)

What is the difference between filter validation and process validation?

- Filter validation (vendor): Demonstrates the filter design meets sterilizing-grade claims, to ASTM F838 - Standard Test Method for Determining Bacterial Retention of Membrane Filters Utilized for Liquid Filtration.
- User/process validation (sterilizing filtration process validation): Demonstrates the filter performs as required in your process, with your product, equipment, and operating conditions. Testing performed in-line with ISO13408 and PDA Technical Report 26.

What data and documentation deliverables are provided?

Typical deliverables:

- Approved protocol(s) with acceptance criteria
- Final report, including:
  - Conclusions and recommendations.
  - Raw data
  - Traceability to instruments/standards.
  - Deviations and investigations (if any)

How long does filter validation take?

Timelines vary with complexity, but typical ranges are:

- 2–6 weeks for planning, risk assessment, and protocol
- 3–4 weeks for execution (not including and E&L testing)
- 2–6 weeks for reporting and approval

What information is needed to start a filter validation project?

Parker will provide a filter validation request questionnaire, inputs include:

- Product/formulation details (pH, excipients, concentration, viscosity)
- Batch size, process description
- Bioburden history and limits
- Required filter details (type, pore size, area, configuration)
- Sterilization method (steam, gamma, autoclave) and hold times
- Integrity testing method and equipment
- Quality attributes to test

How is continued process verification handled after filter validation?

Ongoing monitoring may include:

- Routine bioburden and endotoxin trending upstream
- Routine filter integrity test results trending (pre/post-use)
- Differential pressure and filtration time trending
- Periodic review and requalification triggers (changes, deviations, trends)

When is revalidation or requalification needed?

Triggers often include:

- Filter material, supplier, or configuration change
- Equipment/housing change or sterilization cycle change
- Significant formulation or upstream process change
- New scale, new site, or new filling line
- Adverse trends (bioburden increases, frequent integrity failures)

What acceptance criteria are typically used?

Acceptance criteria are set per protocol and risk assessment, often including:

- Successful integrity tests (pre/post-use) within validated limits
- No microbial passage in challenge/retention study (per design)
- Filtration completes within time/pressure limits
- Product quality attributes meet specifications pre/post filtration

What industries can use this filter validation service?

Commonly:

- Pharmaceutical sterile drug products
- Biopharmaceuticals and vaccines
- Cell and gene therapy (case-by-case due to product sensitivity)
- Medical device fluids and sterile reagents (where applicable)

How much solution do I need to supply?

It's dependent on the testing required but typically 3-5 L but potentially more if sizing is required.

Are you able to handle our product?

Parker will determine this by conducting a full COSHH risk assessment that requires you supply an SDS for the product being tested.

Who completes the validation protocol?

Parker drafts the protocol based on the full completion of our questionnaire and further discussions with the validation scientist allocated to the program and sponsor. The completed protocol must be approved by the sponsor.

What product information can Parker provide for filter selection?

Data sheet, validation guide, product stewardship and extractables report.

What sterilizing grade products can Parker supply?

Sterilizing grade filters within Parkers filtration portfolio and include the following variants:

CLARIFLOW-B: Bacterial retentive grade

CLARIFLOW-P: Standard sterilizing grades

PROPOR SG: Standard sterilizing grades

PROPOR HC: High-capacity sterilizing grade

PROPOR MR: Mycoplasma retentive grade / high-capacity sterilizing grade

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