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Validation of Sterilising and Virally Retentive Filters

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- Definitions
- Examples of Process Filter Functions
- Regulatory View on Filter Validation
- Overview of Validation Recommendations
  - TR26 – Sterilising Liquid Filters
  - TR40 – Sterilising Gas Filters
  - TR41 – Virus Filtration
- Simplifying Filter Validation
  - Chemical
  - Biological
  - Physical
- Conclusion

What this is NOT

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- A replacement for comprehending regulatory guidelines and regulations
- A replacement for US FDA 483's and warning letters
- A summary of the >120 pages of PDA technical reports
- A presentation appropriate to one filter supplier
- All-encompassing

Statements in this talk reflect the professional opinion of the speaker and should not be construed as Millipore policy.

Useful Definitions

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- **Validation** - Action of proving, in accordance with the principles of Good Manufacturing Practice, that any procedure, process, equipment, material, activity or system actually leads to the expected results. (PICS)
- **Extractables** - any chemical component that is removed from a material by application of an artificial or exaggerated force (e.g. solvent, temperature, time). (PDA TR26)
- **Leachables** - a chemical component that migrates from a contact surface into a drug product or process fluid during storage or normal use conditions. (PDA TR26)
- **Critical applications -** where process fluids "are in direct contact with sterile final product or critical surfaces of the associated equipment." (PDA TR40)
- **Moderately critical applications -** are those where the filtered gas will not be in direct contact with exposed sterile product or surfaces." (PDA TR40)
- **Sterilising Filter** – "a sterile filter of nominal pore size of 0.22 micron (or less), or with at least equivalent micro-organism retaining properties" (PICS) "A sterilizing grade filter should be validated to reproducibly remove viable microorganisms from the process stream, producing a sterile effluent" (FDA)

Filters in a Typical Sterile and Aseptic Filling Process

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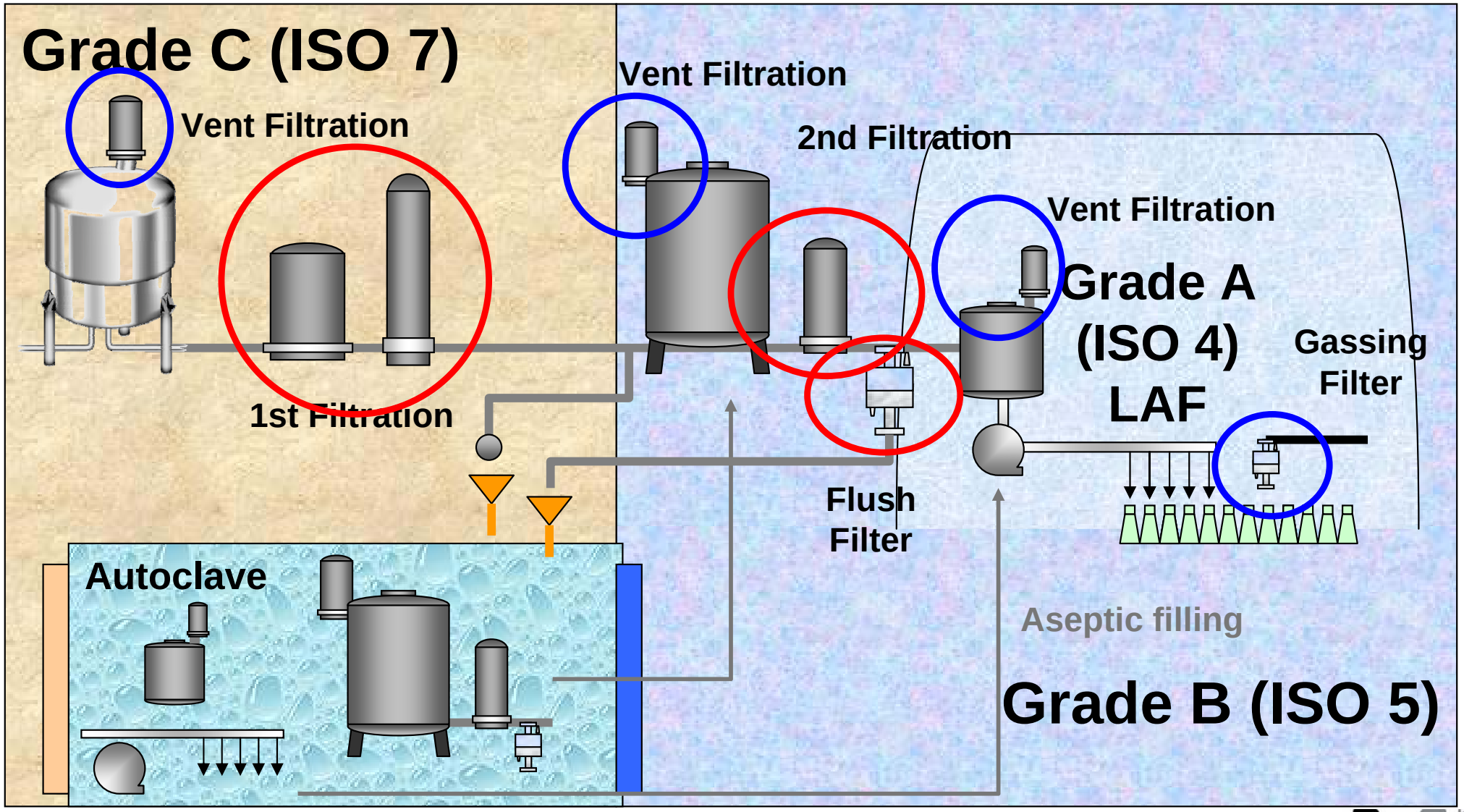

Filters in a Complex Biological Process

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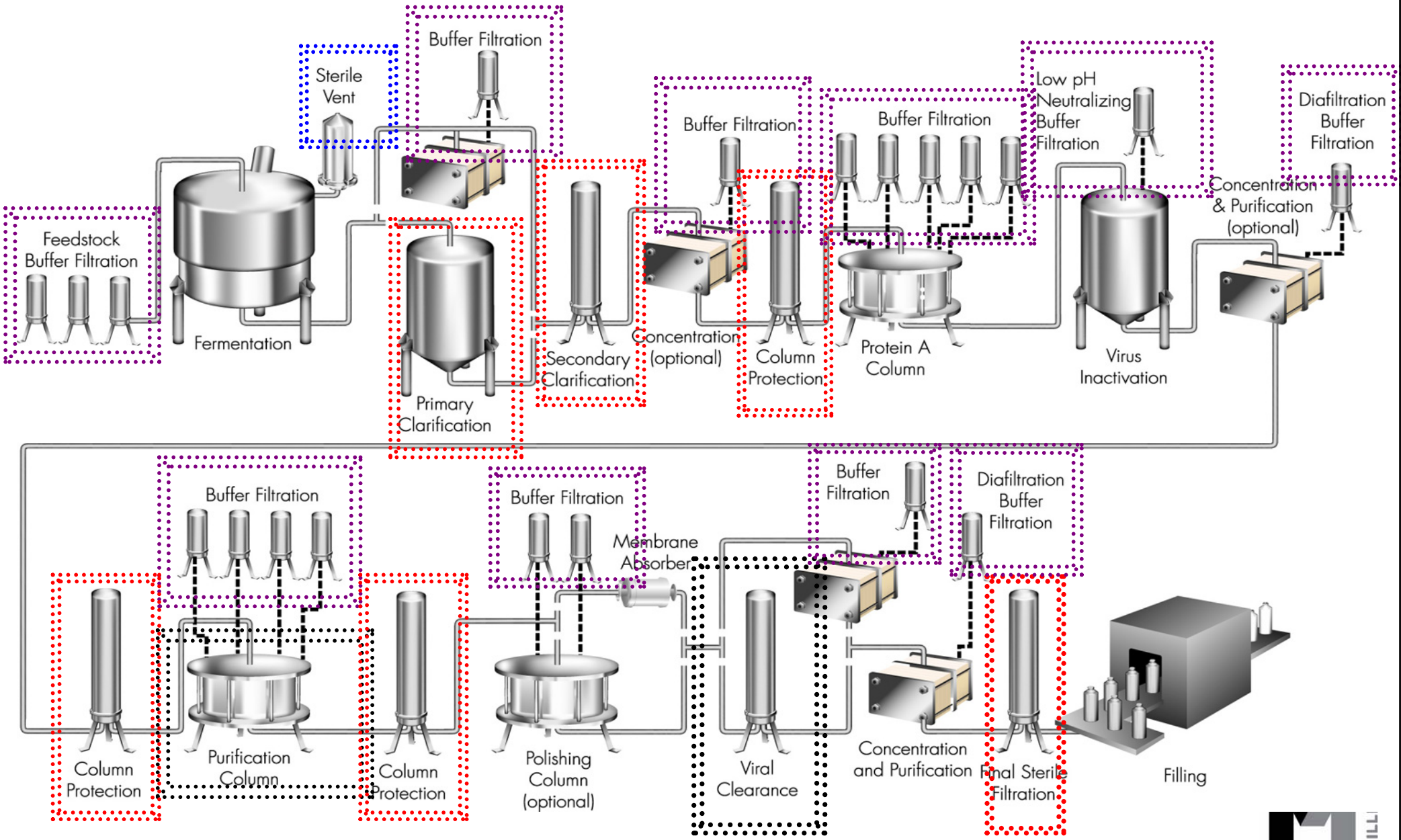

Filter and Production Process Validation Strategy

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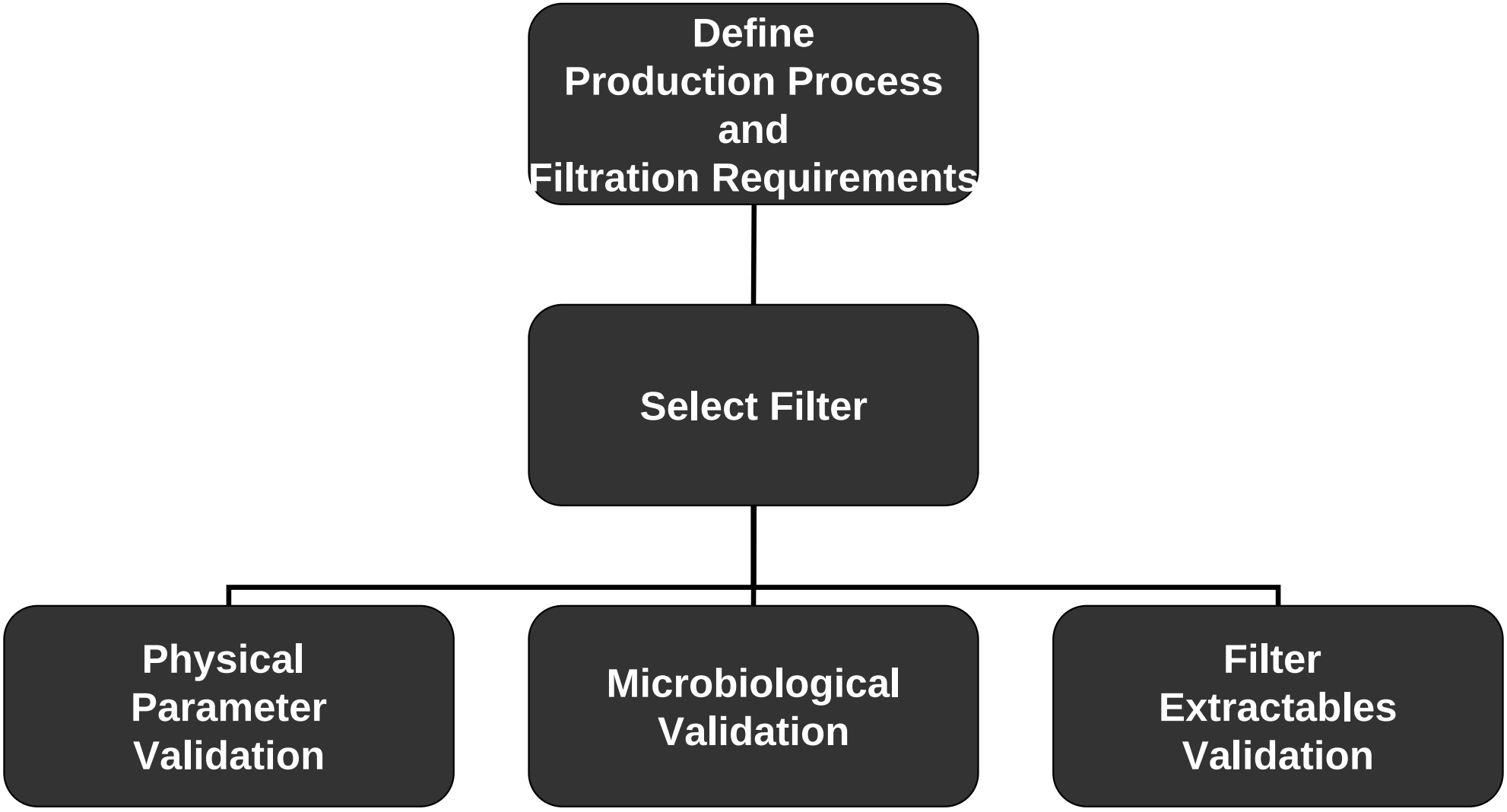

From TR26

An FDA View of Filter Validation

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- Filter Validation Study Report: Methods and Results
  - Challenge organism (include ATCC#)
  - Viability of challenge organism in product and/or suspending fluid over challenge period
  - Justification for recirculation, surrogate fluid, or “worst case” fluid.
  - Use of at least three test filters (separate lots) and one 0.45 μm (parallel) control filter.
- Comparison of production versus validation parameters
- Bubble point (B.P.) specs and wetting agent(s).
  - One test filter at or near (~10%) minimum B.P. (pre-challenge).
  - Alternative: Use minimum B.P. value in retention study to establish in-process B.P.
  - Calculation of product-specific integrity test acceptance criteria (if applicable)

    - Neal J. Sweeney, Ph.D. FDA/CDER/OGD Microbiology Team
      2007 GPhA Fall Technical Conference, October 11, 2007

FDA Approach to Microbiological In-Process Controls

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- Provide pre-filtration bioburden acceptance criteria
  - Alert/action levels
  - Testing frequency
- Validate maximum bulk hold times
- Incorporate in media fills or perform “stand alone” hold time validations
- Pre- and post-filtration integrity testing of sterilizing filter
  - Acceptance criteria
  - Wetting agent

    - Neal J. Sweeney, Ph.D. FDA/CDER/OGD Microbiology Team
      2007 GPhA Fall Technical Conference, October 11, 2007

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Sterilising Liquid Filter Validation

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Filters in a Typical Sterile and Aseptic Filling Process

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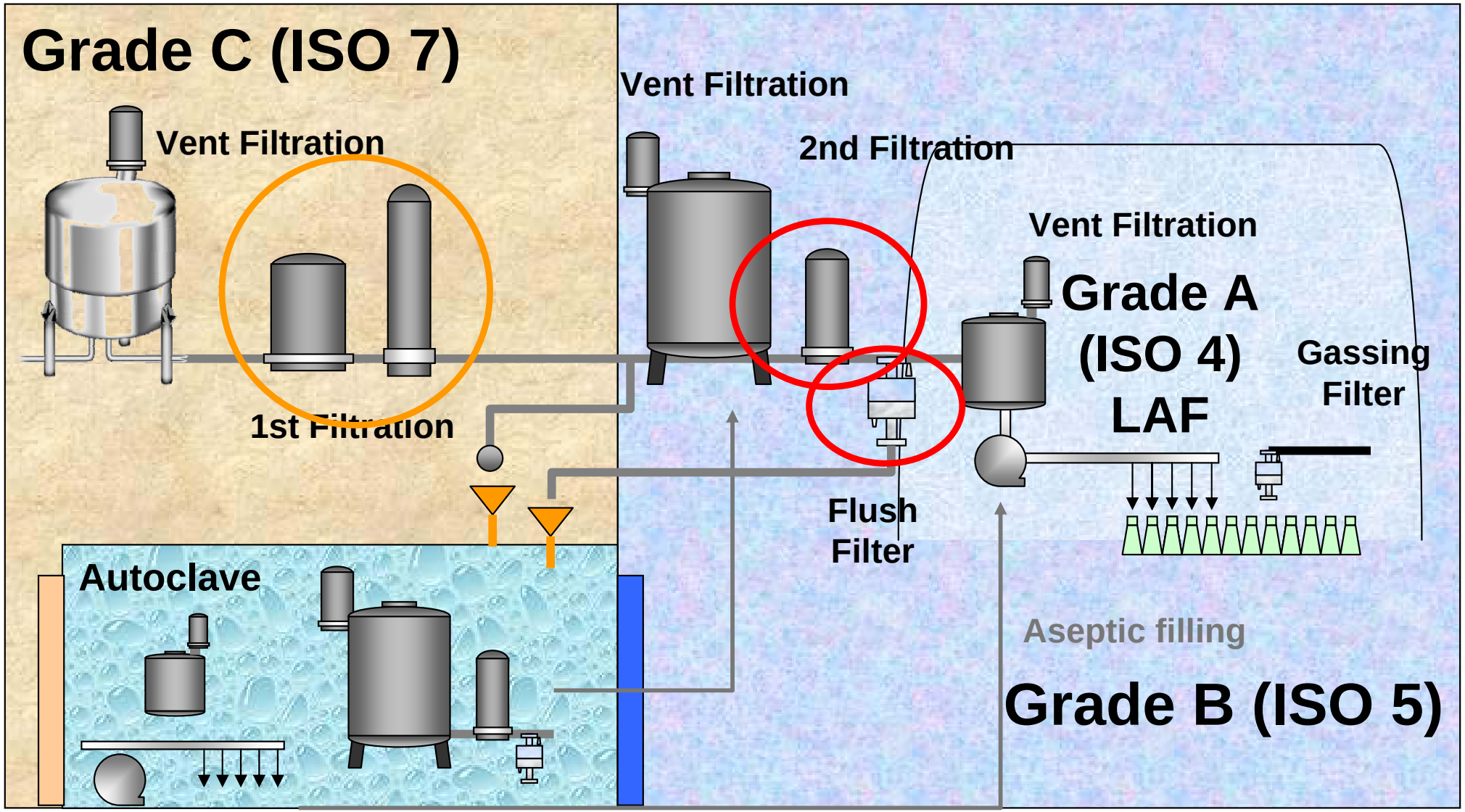


What Filters need to be Qualified in a Simple Filling Process

- Sterilising liquid filter
- Bioburden reduction filter
- Sterilising gas filters
- But not all filters need to be qualified in the same way or in the same depth

Sterilising Filter Validation

- Provides documented evidence that the filter meets process objectives
  - Demonstrates the filter retains microorganisms to produce a sterile filtrate
  - Ensures the filter does not alter the product in an objectionable way
  - Ensures the product does not adversely affect the filter
  - Ensures the physical process parameters do not adversely affect the filter or the product

TR26 Sterilising Filter Validation Recommendations

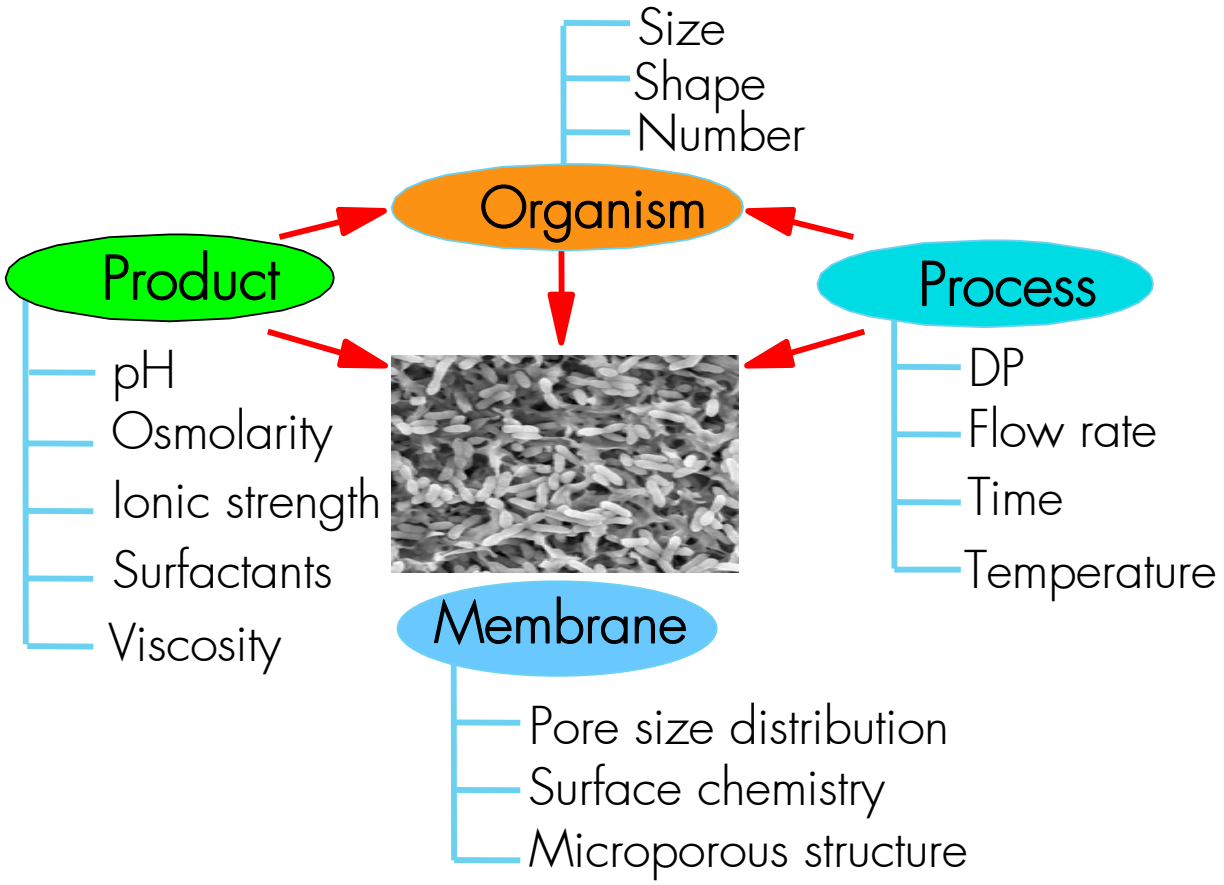
Table 4.1 – 1 Qualification and Validation Recommendations

Criteria	Filter User	Filter Manufacturer	
	Device	Membrane Disc	Device
Bacteria retention in water or SLB with integrity test correlation in water or solvent	-	Q, L	Q
Bacteria retention in product	V*	-	-
Chemical compatibility, effects on filter integrity	V	Q	Q
Extractables	V	Q	Q
Leachables	V	-	-
Sterilization method, effects on filter integrity	V	Q	Q
Integrity test (water or solvent)	V	Q, L	Q, L
Integrity test method selection (product)	V	-	-
Toxicity testing - USP Class VI	-	Q	Q
USP bacterial endotoxin	V	-	Q, L
USP particulate matter	E	-	Q
USP non fiber release	E	-	Q
TOC and conductivity- USP Purified Water	E	-	Q

L = Filter manufacturer's lot release criteria
Q = Filter manufacturer's qualification
V = Process specific validation testing
V* = Can be performed in disc or device format
E = Evaluate the need for testing

Note the high suggested level of process specific validation

Bacterial Challenge Testing Considerations



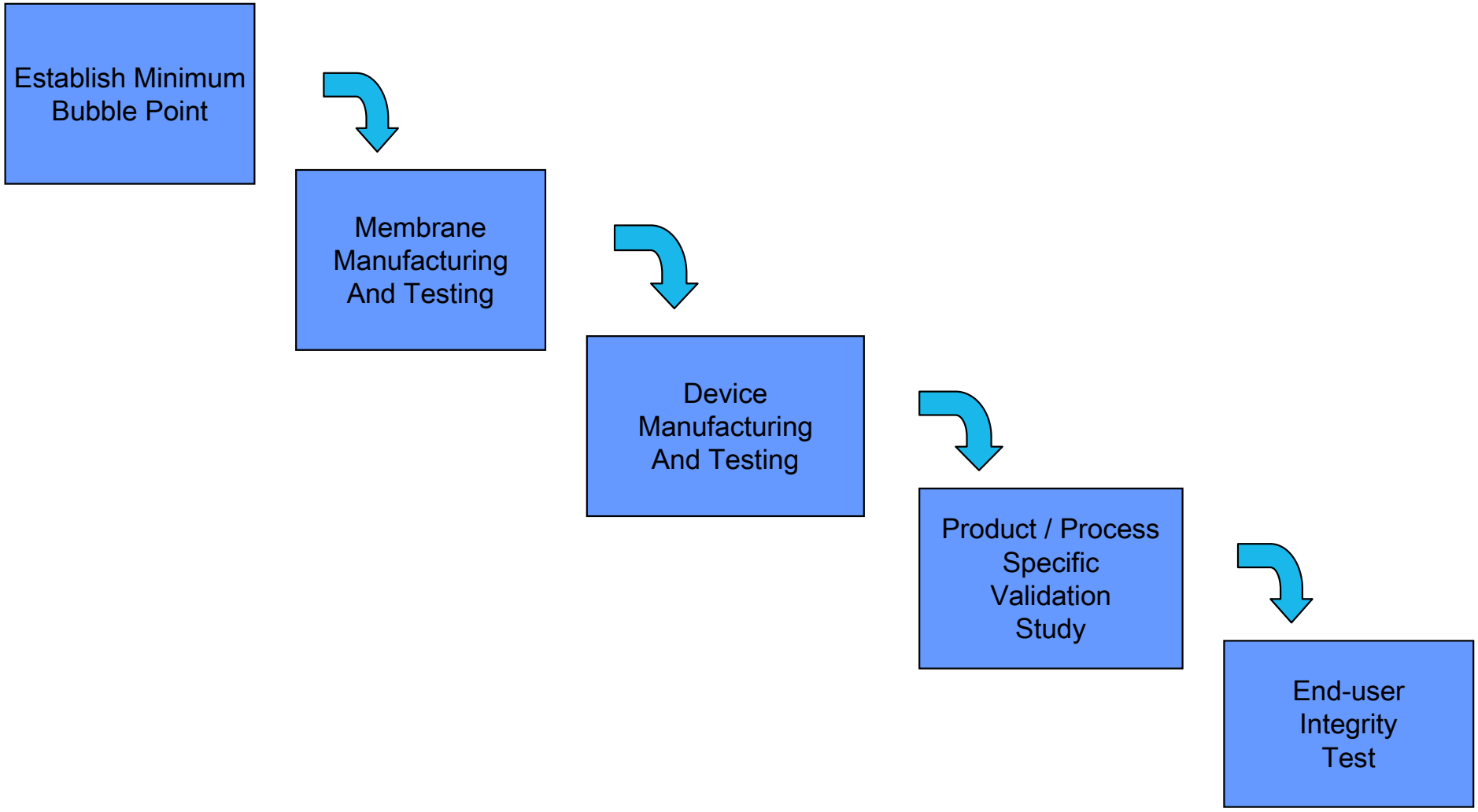
Retention is a four-way interaction
Process parameter knowledge & control is vital

- Challenge test micro-organism
  - B.diminuta (ATCC 19146) OR
  - Natural bioburden
    - Need to speciate and size
    - Ties in with EM program
- Scale-down process
- Direct innoculation
  - When feasible
- Ensure retention testing conducted on products identified as being microbially sensitive
  - Establish a formal “risk based” approach to retention testing in cases of multiple product facilities
- A standard method for qualifying microbially retentive membrane filters is described by ASTM
- “Some filter manufacturers have described alternative acceptable test methods” (TR26)

Additional Points to Consider during Sterilising Filter Validation

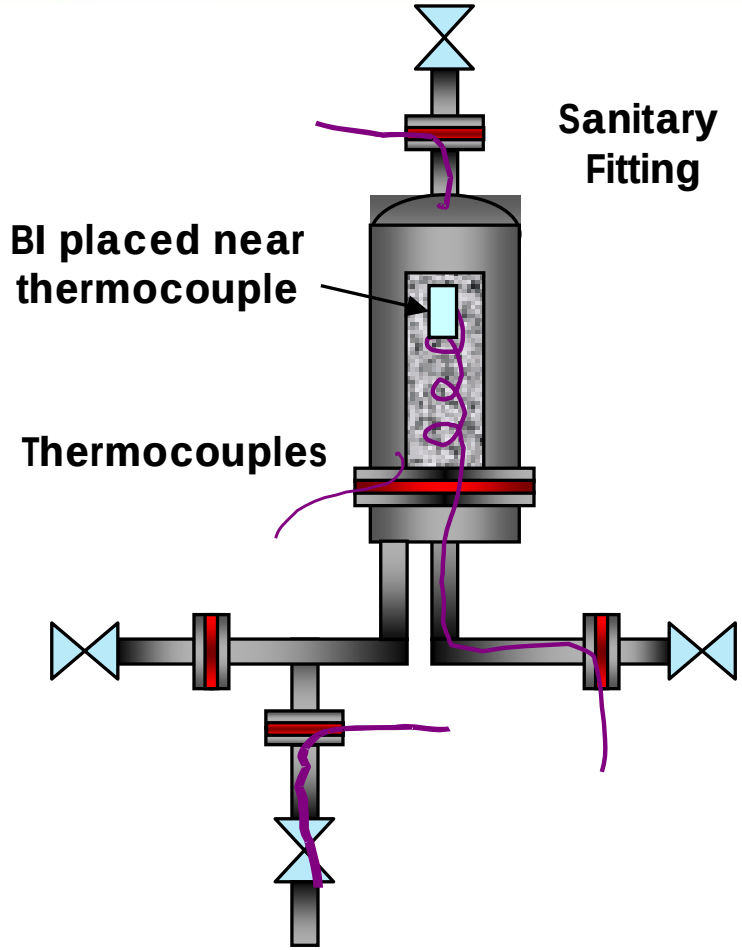
- Volume / Area ratio is critical
- Non-destructive integrity test should correlate with bacterial retention
- Testing should use membrane samples exhibiting integrity test values close to minimum bubble point or maximum diffusional flowrate
- Filter support documentation may include a validation guide, FDA Drug Master File (DMF) number, product literature, specification sheets, technical bulletins, and application notes.

Integrity Testing – More than just the pre and post-use tests



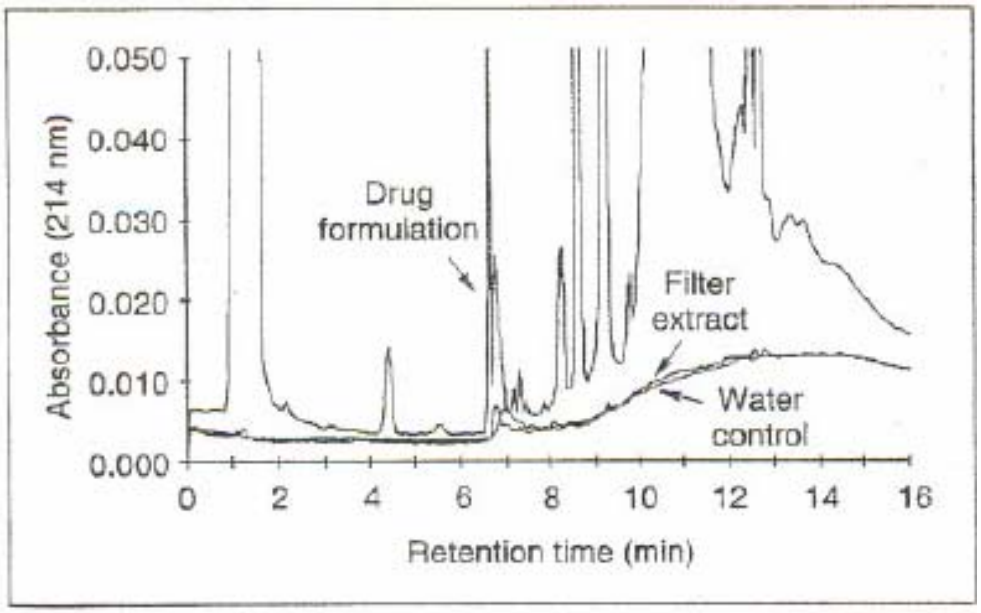
Can be included in vendor audit to ensure consistency and control

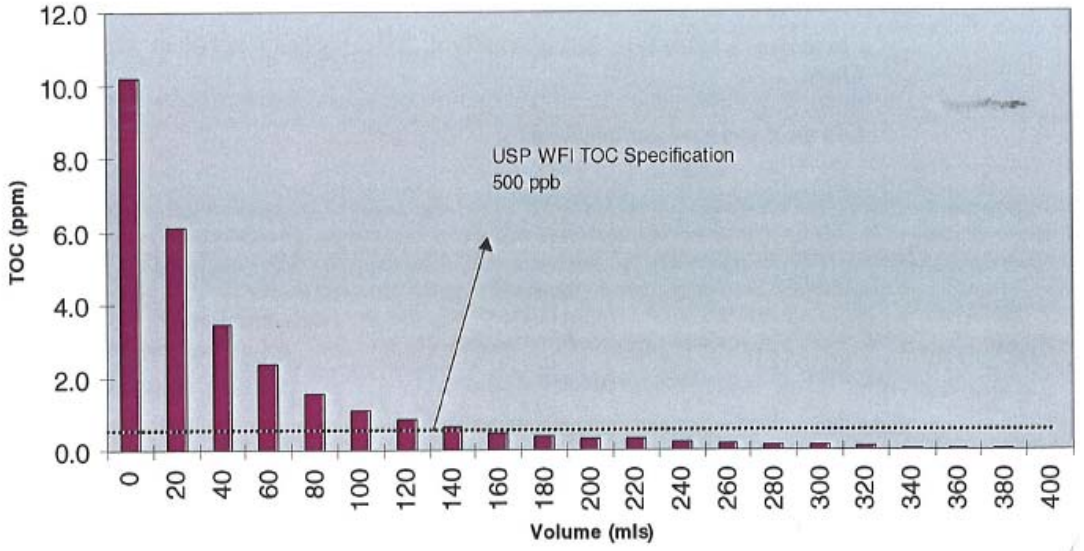
Example of Physical Testing - Sterilising Studies



- Sterilising cycle qualification should include pre-SIP integrity testing, standard SIP cycle, cooling cycle and post-SIP integrity testing
- SIP qualification should include maximum **and** minimum Fo

Example of Chemical Testing - Extractables





- Knowledge of Extractables level is important in relation to:
  - Filter flush volume determination
  - Small volume applications-where dilution of extractables is minimal
  - Direct filling-where extractables levels are highest in first vials filled
- Extractables may be qualified by the filter manufacturer using model solvents and specific laboratory conditions
- Flushing the filters prior to use can further reduce these levels as demonstrated by TOC flush curves – measures leachables

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Sterilising Gas Filter Validation

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Filters in a Typical Sterile and Aseptic Filling Process

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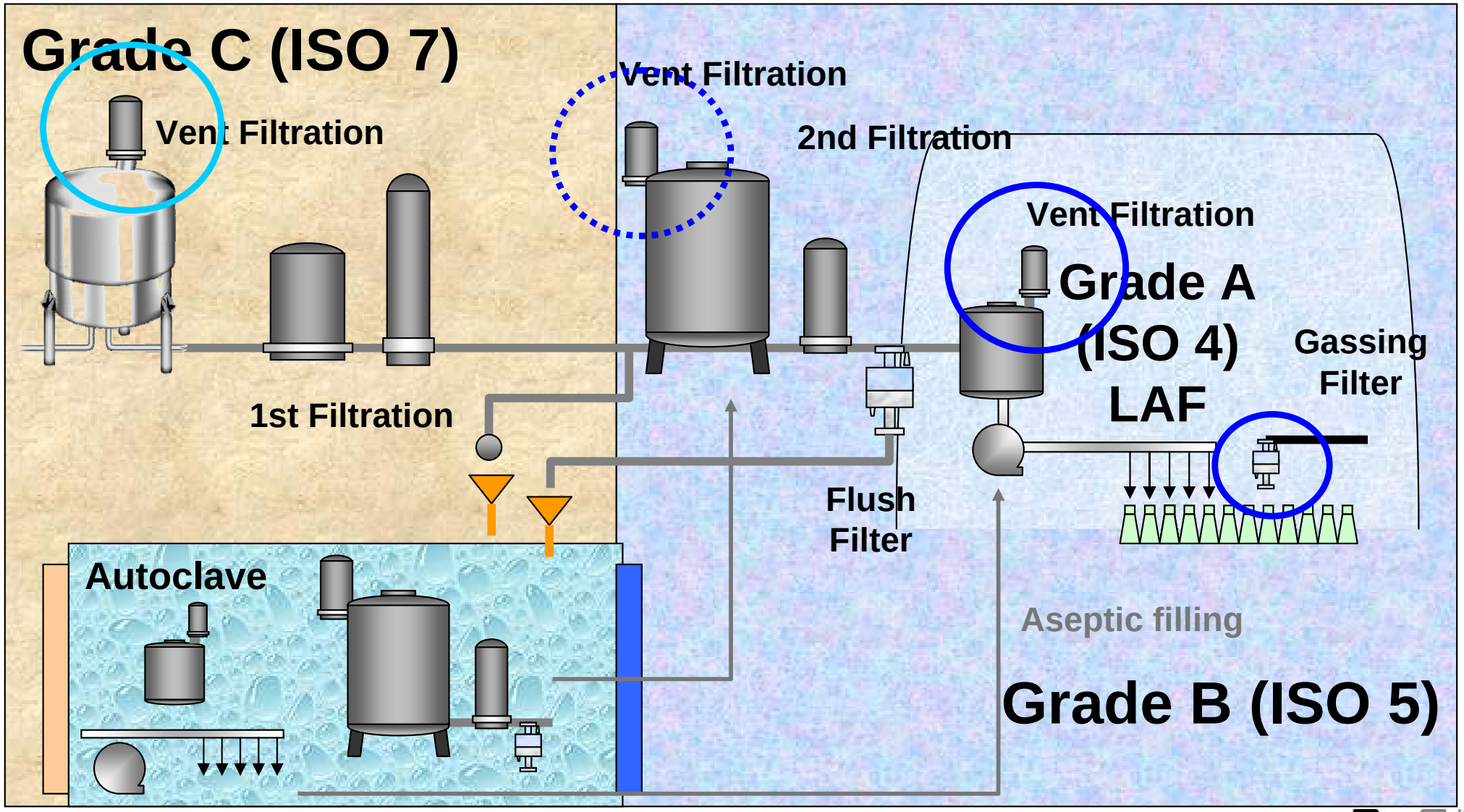


Sterilising Gas Filters Work Differently

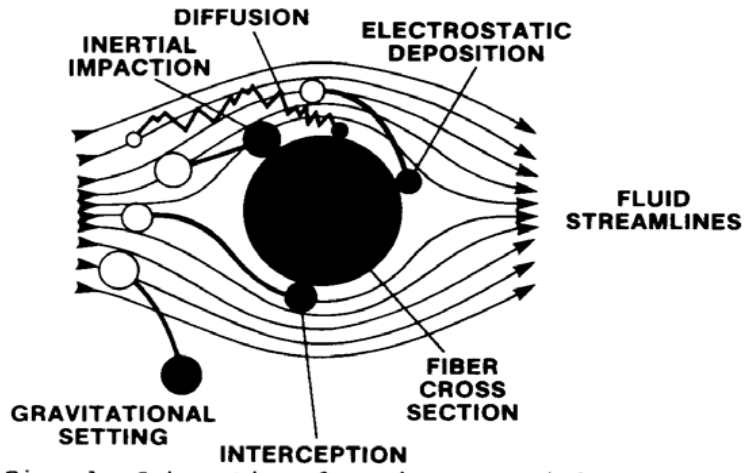
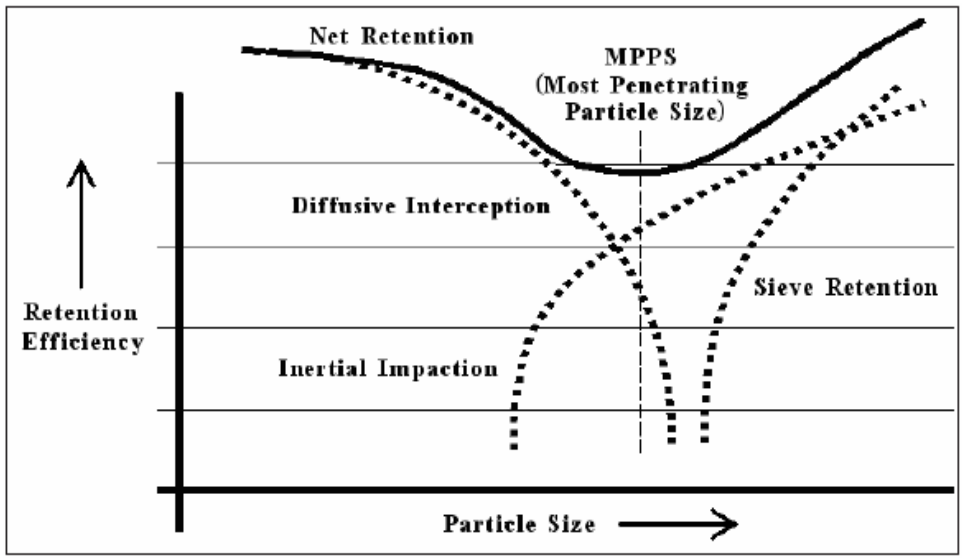


Fig. 1--Schematic of various particle capture mechanisms.



- Most applications involve air or nitrogen, and the filtration efficiency for smaller particles is greatly enhanced in gas filtration
- Particulate (incl. microbiological) retention mechanisms include
  - Size exclusion
  - Inertial impaction
  - Diffusional interception
  - Electrostatic attraction
- Dry gases ensure excellent particulate retention – bacterial and virus
- Wet filters provide worst-case challenges

TR40 Gas Filter Validation Recommendations

Tests Commonly Performed by Filter Users and the Filter Manufacturers—General Industry Practices

Criteria	Filter User	Filter Manufacturer	
	Filter Device	Membrane Disc	Device
Bacteria Retention/ Integrity Test Relationship Data	(E)	(Q)	(Q)
Integrity Test		(Q/R/L)	(Q/R/L)
Integrity Test Methodology and Selection	(E)	(R)	(R)
Microbial/Viral Retention (Liquid/Aerosol)	(E)	(Q/L)	(Q/L)
Compatibility/ Service Life	E/V	(Q/R)	(Q/R)
Toxicity Testing		(Q)	(Q)
Effects of Sterilization Methods on Filter Integrity	(E/V)	(Q)	(Q)

Q = Qualification Testing

V = Validation Testing—Process-Specific

E = Evaluate Applicability to Process

R = Recommendation for Validation

L = Filter Lot-Specific Release Criteria

?

Why isn't this validated as part of process specific testing

Note the low suggested level of process specific validation

Highlights for Gas Filter Validation

- There is no specific standard that defines the retention requirements for a membrane filter used to sterilize gases
- Liquid bacterial challenge testing represents a worst-case condition for sterilizing gas filters because the retention efficiency in liquids is much lower than in gases
- Focus is on evaluation of vendor testing and suitability of documentation compared with filter duty
- Aerosol testing using bacterial and or viruses is difficult and complicated – hence vendor testing is logical

Highlights for Gas Filter Validation

- Vendor documentation is more critical in gas filter validation than with any other filter in the process
  - Process and product specific retention testing is generally not required
  - Filter manufacturer's qualification data should be evaluated carefully to justify the applicability to a given specific process
  - Compatibility and service life testing is often difficult to do
  - Any integrity test is meaningful only when it can be correlated to specific microbial retention characteristics.
  - Compatibility of the filter under actual use conditions should be demonstrated which may be done by integrity testing the filter before and after exposure to the expected process conditions

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Virus Filter Validation

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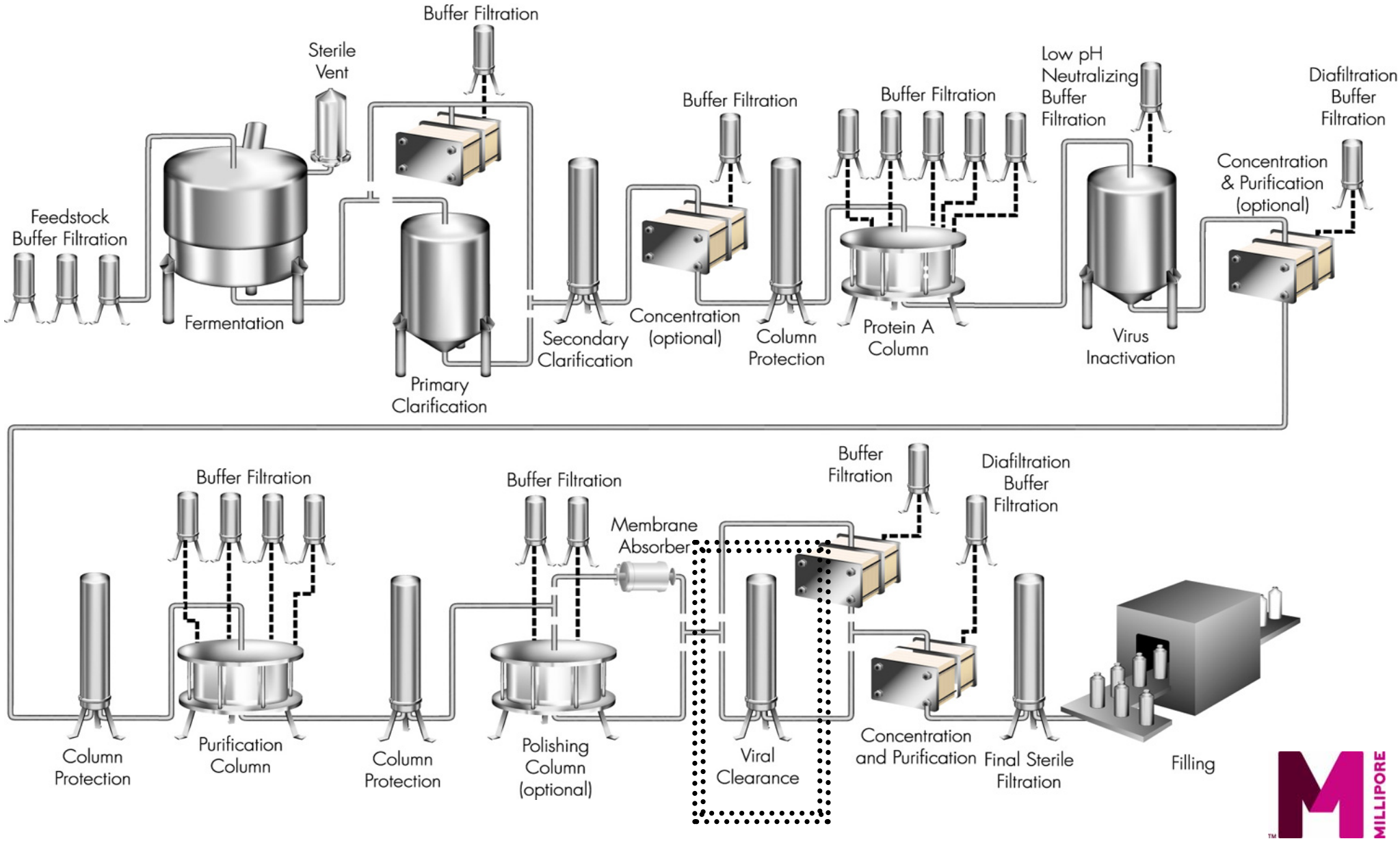
Filters in a Complex Biological Process



TR41 Liquid Filter Validation Recommendations

Criteria		Filter User	Filter Manufacturer	
		Process Filter Assembly	Membrane Disc	Process Element
Viral/Phage Retention/Integrity Test Relationship Data			(Q)	(Q)
Integrity Test	Water/Solvent	(V)	(Q/R/L)	(Q/R/L)
Integrity Test Methodology and Selection		(V)	(R)	(R)
Viral/PhageVirus Retention	Model Solution		(Q/L)	(Q/L)
	Product	V (membrane disc)		
Viral/Phage Retention/Viral/Phage Integrity Test Methodology		(V)	(Q)	(Q)
Effects of Chemical Compatibility on Filter Integrity		(V)	(Q)	(Q)
Toxicity Testing			(Q)	(Q)
Extractables/Leachables		(V)	(Q/R/L)	(Q/R/L)
Effects of Sterilization Methods on Filter Integrity		(V)	(Q)	(Q)

Tests Commonly Performed by Filter Users and Filter Manufacturers—General Industry Practices

Q = Qualification testing

V = Validation Testing—Process Specific

R = Recommendation for Validation

L = Filter Lot-Specific Release Criteria

Note the very high suggested level of process specific validation

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Viral Filter Microbiological Testing

- Select test virus(es)
  - Bacteriophage can be used as a model
- Evaluate viral stock preparation method
  - Avoid aggregation
  - Maximise viral titre
  - Confirm filterability
- Viral spike volumes
  - Feedstream + viral stock =
- Test conditions –
  - Protein concentration, operating temperature, differential pressure, flowrate, process volume / filter area ratio, rinse volume / filter area ratio, flux decay
- Filter configuration
- Integrity testing
- Assay method qualification
- Toxicity determination

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Suggested Viral Panel – ICH Q5A

Virus	Genome	Envelope	Family Genus (*11, 30*)	Size (nm)	Shape	Resistance to Physico-chemical Treatment
Porcine parvovirus (PPV)	DNA	No	Parvoviridae Parvovirus	18–24	Icosahedral	Very High
Mice Minute virus (MMV)	DNA	No	Parvoviridae Parvovirus	18–24	Icosahedral	Very High
Mammalian orthoreovirus (MRV-3)	RNA	No	Reoviridae Orthoreovirus	60–80	Spherical	High
Suid herpesvirus 1 (SuHV-1)	DNA	Yes	Herpesviridae	120–200	Spherical	Medium
Xenotropic murine leukemia virus (X-MLV)	RNA	Yes	Retroviridae Gammaretrovirus	80–110	Spherical	Low
Bovine Viral Diarrhea Virus (BVDV)	RNA	Yes	Flaviviridae Pestivirus	50–70	Pleo-Spherical	Low

Table I. Characteristics of possible model viruses.

- Contrast this with microbiological requirements for sterilising liquid and sterilising gas filters
- Large viruses have standard challenge protocols using coliphage PR772 and based on 6 log reduction of a 64-82nm virus and >95% passage of IVIG
- Small virus protocol under development - using bacteriophage PhiX-174 (~28nm as a model)
- Phase 1 clinical trials should show retrovirus retention

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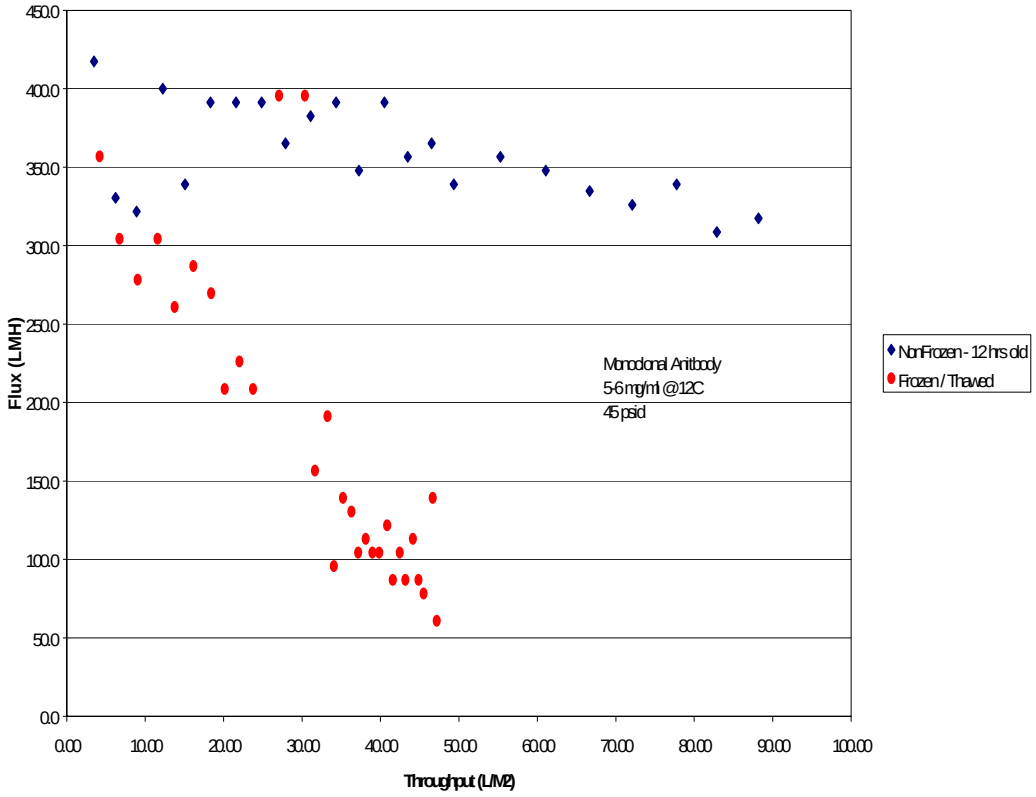
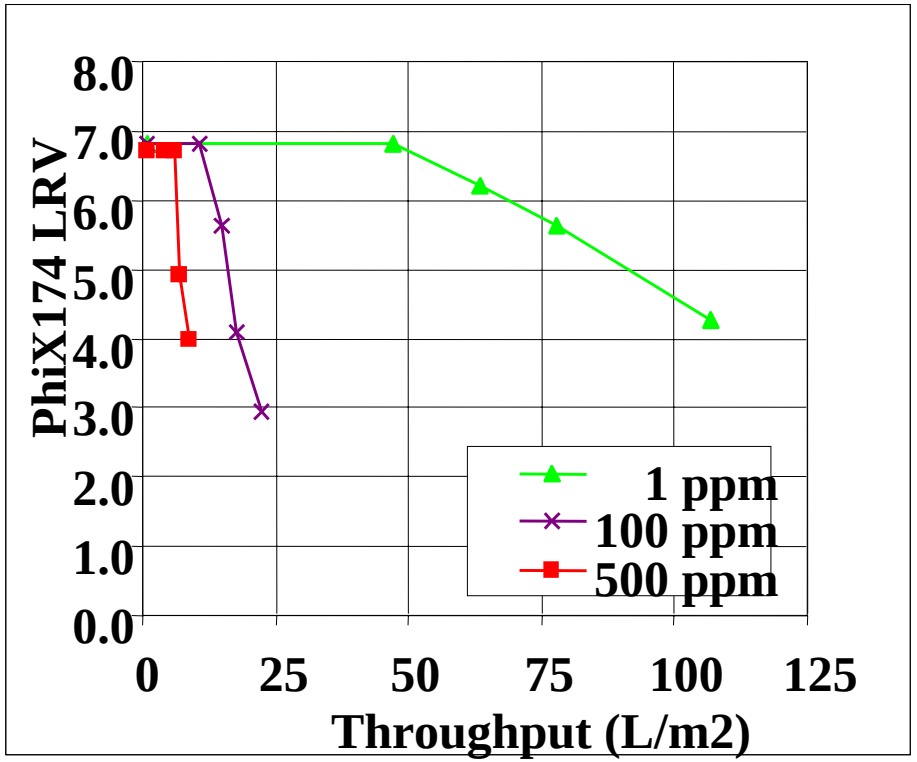
Major Spiking Study Issues in Viral Testing





- Viral spiking qualifies filter use and volume/area ratio
- Feed preparation can block filter prematurely
- Viral filter retention changes according to loading and flux decay
- ICH Guidelines advise maximum spike volume of 10% compared with challenge volume

Reduce Risk with Integrity Testing Strategy

- Level 1 - Membrane retention using model particle (e.g. phiX-174) and membrane integrity test to ensure manufacturing is tightly controlled.
- Level 2 – Test 100% of devices using classical integrity test (e.g. diffusion, bubble point).
- Level 3 – Lot release testing using model particle (e.g. PhiX-174), classical integrity test (e.g. diffusion, bubble point) on a lot release basis that will meet claims as per Validation Guide and certificate of quality.
- Level 4 – End-user integrity test to confirm absence of gross handling or installation defects
    - TR40 includes useful end user integrity testing guidelines and suitability evaluation recommendations

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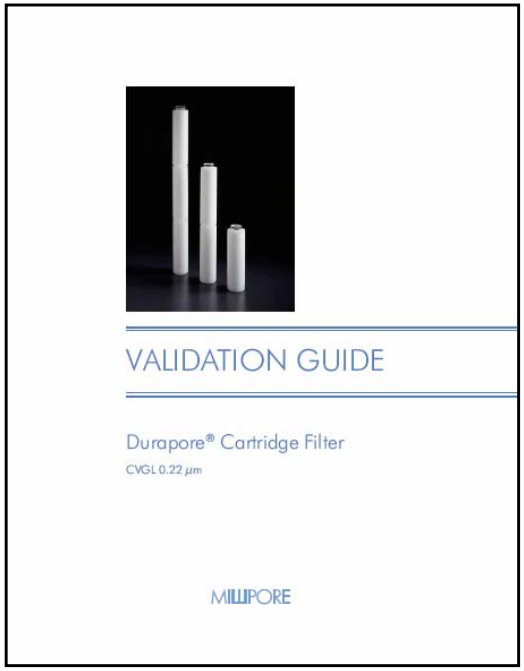
How to Simplify and Strengthen Filter Qualification Exercises



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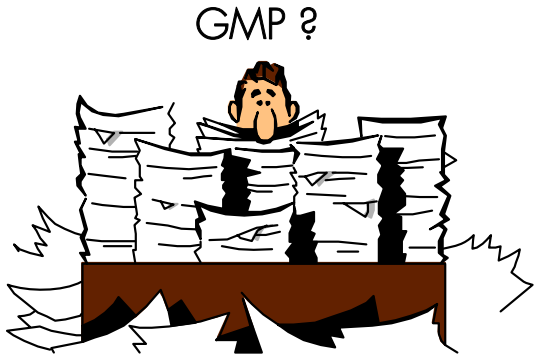
What do Regulators Require?

- Documentation covering
  - Suitability for duty
  - Process definitions
  - Bacterial retention
  - Integrity testing
  - Sterilisation process
  - Adsorption / Extractables
  - Risk analysis based approach to processing and product impact
  - Quality by design



Filtration Master Plan

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- A subset of and consistent with site validation master plan
  - Should present an overview of the entire filter validation operation, its organisational structure, its content and planning.
  - Should include the list / inventory of the filter and filter-related to be validated and the planning schedule.
  - Summarises the firm's overall philosophy, intentions and approach to be used for establishing performance adequacy for filters used on-site that are that are critical for yielding a quality product
  - Should be a summary document and should therefore be brief, concise and clear.
  - Multidisciplinary involvement – including external team members
  - Uses authorised standardised working and operating procedures

Need to Use a Risk-based Approach

Higher Risk	Factor	Lower Risk
Higher levels, Diminutive organisms	Bioburden	Lower levels Large organisms
Higher	Differential pressure	Lower
Higher	Flow rate	Lower
Growth promoting	Product	Bactericidal or preserved
Ambient and higher	Temperatures	Refrigerated
Longer	Time	Shorter

From TR26

- Consider the product formulation and process conditions
- Allows priorities to be set when progressing through a major qualification exercise
- Examples
  - Sterile filtered & Aseptically filled
    - Without preservative
    - With preservative
  - Terminally sterilised
    - Without preservative
    - With preservative
- Start with high risk categories but be sure to include all products that require filter qualification
- Recognise product grouping – same active in different packaging / strength

Step-wise Approach to Filter Qualification

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- Chemical compatibility
- Duty
- Binding / Adsorption
- Integrity testing
- Sterilisation
- Extractables
- Microbiological Retention

Listed in suggested order of testing – but should be identified in planned validation timeline

Use of Process Parameters

- **Product attributes**
  - Ingredients
    - Concentration
    - pH, viscosity, density, solubility, ionic strength
  - Known incompatibilities
- **Process attributes**
  - Filter train
  - Batch volume, Flowrate
  - Contact time
  - Pressure
  - Temperature, Sterilisation method
  - Bioburden
- **Grouping**
  - “Families of products with the same ingredients, varying only in concentration, may be validated by challenging the concentration extremes and accepting the intermediate concentrations by bracketing. If a single product is determined to be a worst case representative, then rationale and data should accompany the model.” TR26


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Additional Considerations in Critical Filter Validation

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- Some additional filter user responsibilities:
  - Audit its filter vendor(s)
  - Write operating procedures
  - Train and qualify operators, validation staff and engineers
  - Validate usage cycles
  - Operate within manufacturer's specifications or defined specifications
  - Validate each filtration process on a case-by-case basis
  - Investigate filter related deviations and react appropriately
  - Implement change controls
  - Conduct risk analysis
  - Regularly review processes
  - Construct suitable comparability protocols

Conclusion

- The filter validation process starts with a review of all filters used in the production or development process
- Focus should be on filters in critical applications
- Filter validation goes well beyond retention testing and comprises physical, chemical and biological testing
- Risk assessment is important
- PDA technical reports provide industry standard background documents
- PDA documentation is aligned with regulatory requirements
- Filtration Master Plan provides practical approach to filter validation
- Vendor and contract laboratory relationships can greatly assist filter validation