Quality by Design in Critical Filtration Operations

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Objectives

- Define quality by design (QbD) and Quality Risk Management (QRM)
- Define the levels of filtration in simple and complex operations
- Show QbD approach in critical filtration
- Show a design space approach for sterile liquid and gas filtration
- Use a qualification approach to critical filtration
- Identify key vendor and user responsibilities
- Examine operations in the sterile core for aseptic filling
- Compare single, serial and redundant approaches to sterile filtration

US Regulators Vision of the Future

“The Desired State: A Mutual Goal of Industry, Society, and the Regulators

A maximally efficient, agile, flexible pharmaceutical manufacturing sector that reliably produces high-quality drug products without extensive regulatory oversight.”

Janet Woodcock; Oct 2005

How do we Achieve the Desired State?

Three Key Concepts

- ✓ Quality by design and the design space concept — ICH Q8
- ✓ Quality Risk Management — ICH Q9
- ✓ Robust Quality Systems — ICH Q10

Key Regulatory Concerns

Efficacy / Strength	Does the qualified filtration process result in product / residues that interfere with final product strength or efficacy?
Identity & Purity	Does the qualified filtration process result in product / residues that interfere with final product purity?
Safety	Does the qualified filtration process result in product / residues that are toxic to the patient?

Important consideration –
How may this filtration activity affect the pharmaceutical company's quality or product / risk assessment process

Simplify the Filtration Process with Filter Categories

Recommended that filters are reviewed site-wide and divided into 3 categories

Critical

- The filter directly affects product quality
  - Examples: vent filter on a sterile hold vessel, sterile liquid filter, viral filter

Moderately critical

- The filter indirectly affects product quality
  - Examples: vent filter in a grade C area, bioburden reduction filter

Service

- The filter does not affect product quality
  - Examples: distribution gas filter, water prefilter

Uses definitions from PDA Technical Reports 26 (liquid filters) & 40 (gas filters), and ISPE Baseline Guide to Commissioning and Qualification

What is Quality by Design (QbD)

Quality by design (QbD)

Quality by Design is a systematic approach to development that begins with predefined objectives and emphasizes product and process understanding and process control, based on sound science and quality risk management.

ICH Topic Q8 Annex. Pharmaceutical Development.

Steps in QbD

- Define your product (**& impurity**) profile and what the product should do
- Define your CQAs for the product and critical in process steps
- Define process element (CPPs and control points)
- Determine operating ranges to consistently yield acceptable product & process.
- Define your design space and operate in a controlled way within it

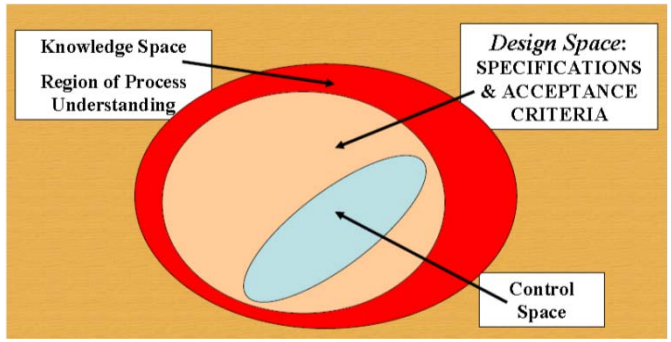
Today's Focus – Critical Filter Design Space

Design Space

- Defined as: "the multidimensional combination and interaction of input variables (e.g., material attributes) and process parameters that have been demonstrated to provide assurance of quality." ICH Q8(R2), http://www.fda.gov/downloads/Drugs/Guidances/ucm073507.pdf
- Demonstrated range of all process parameters where process meets the CQAs
- Consists of Knowledge space, design space and control space

Challenges

- Characterize CPPs to assess their impact on CQAs
- Build application model: Empirical (DOEs) or physical laws
- Accommodate scaling and variability



"Implementation of Quality by Design". J.F. Haury, Amgen 2006
http://www.fda.gov/downloads/AboutFDA/CentersOffices/CDER/ucm118776.pdf

Overall picture of quality by design

Product & process design and development

Define desired product performance upfront; identify product CQAs

→ Design formulation and process to meet product CQAs

↕

Understand impact of material attributes and process parameters on product CQAs

↔ Identify and control sources of variability in material and process

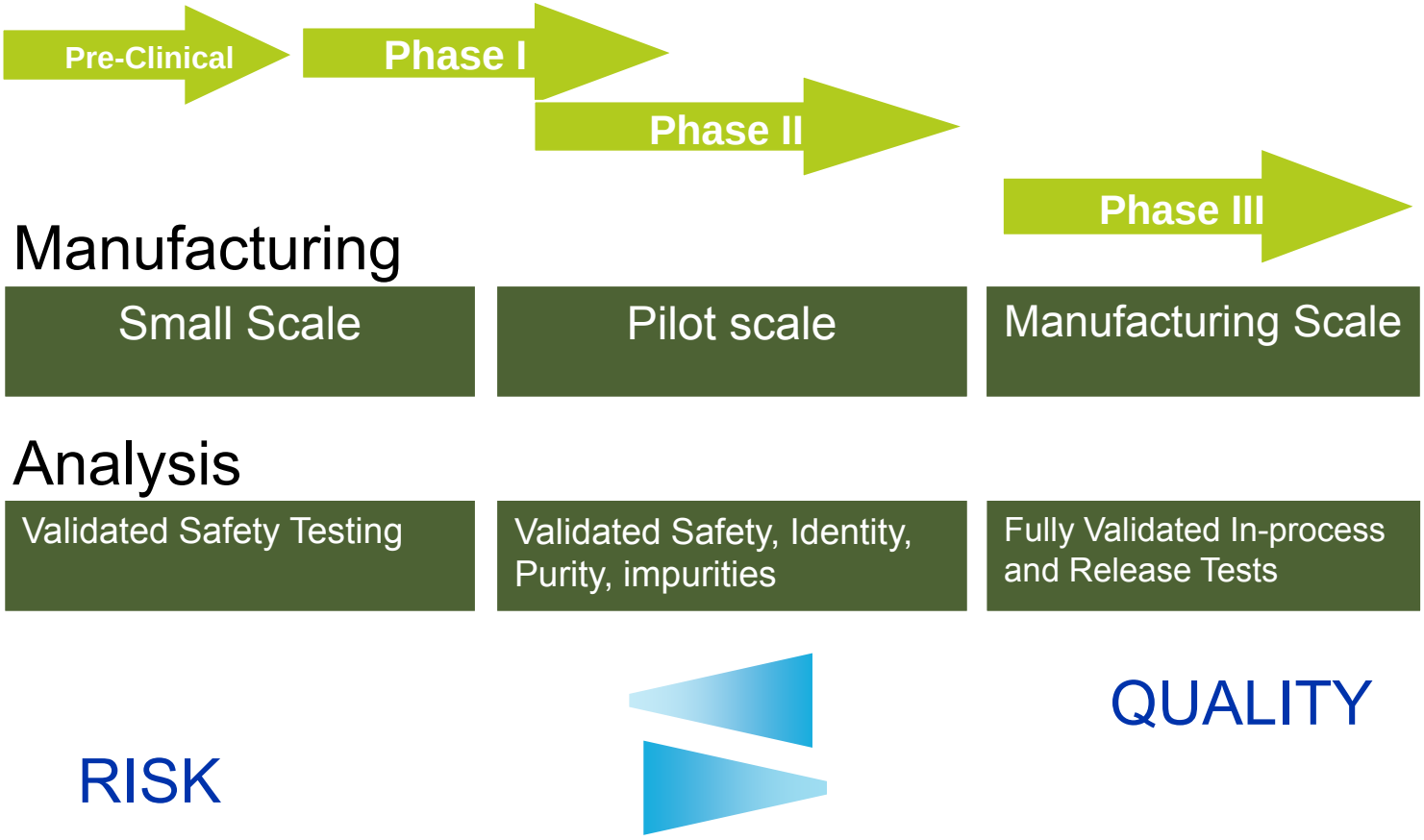
↔ Continually monitor and update process to assure consistent quality

Risk assessment and risk control

Implementing Quality by Design - Helen N. Winkle, FDA, Sept 2007

When Should QbD Considerations Occur?

As early as possible!!

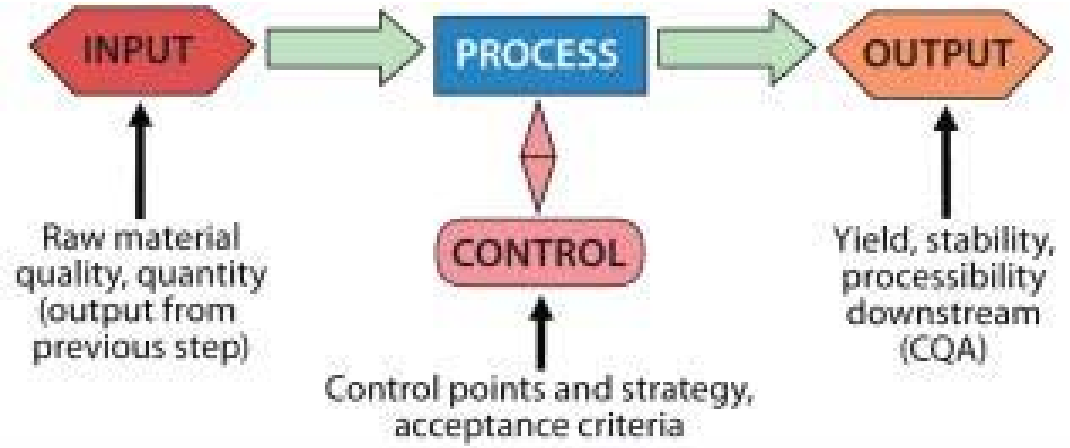


Why is QbD Important for Critical Filtration & Aseptic Processing?

- It defines the process and product parameters in which the filter will need to work to produce sterile filtrate
- It is the first part of a critical filter duty statement (a.k.a. “Fit for Use” or “Fit for Purpose” or “Filter URS”)
- It is proof that the pharmaceutical company meets cGMP requirements (“documented scientific evidence”)
- It provides documented scientific evidence of risk assurance
- It is an expected part of the pharmaceutical company’s approach to critical processes that affect the key regulatory concerns

Why can Critical Final Filtration QbD be Easy?

Link raw material attributes & process parameters to CQAs



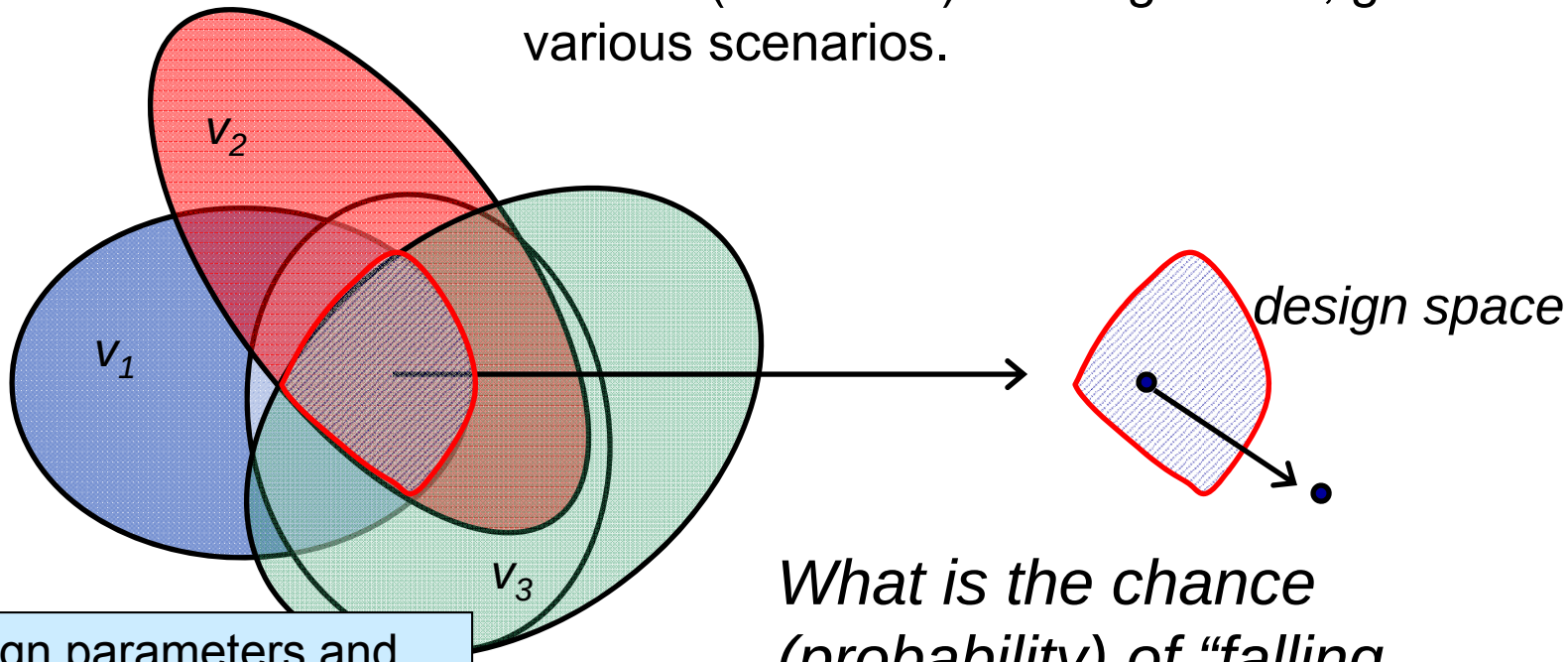
In many cases of final sterilizing liquid & gas filtration

Input material quality attributes = Output material attributes

Source: How QbD and the FDA Process Validation Guidance Affect Product Development and Operations, Part 1, Peter H. Calcott, (November 2011), Bioprocess International (http://www.bioprocessintl.com/analytical/downstream-validation/how-qbd-and-the-fda-process-validation-guidance-affect-product-development-and-operations-part-1-323457/

QRM and the Production Design Space

Risk analysts estimate probabilities of being outside (or inside!) of design limits, given various scenarios.



Design parameters and their intersection in a "design space" concept

What is the chance (probability) of "falling outside" of the design space per unit time?

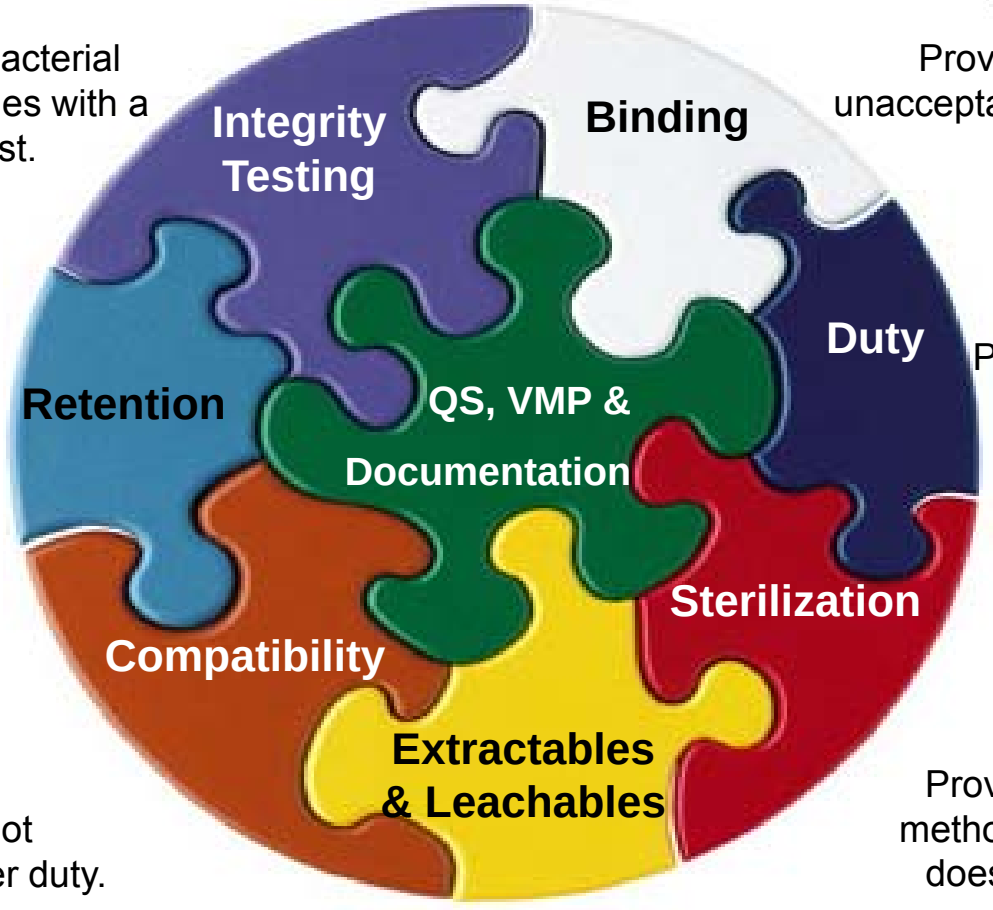
Critical Filtration Operations in Biopharmaceuticals

8 Elements of Sterile Filtration Qualification

Represent “worst case” process conditions, process fluid, filter performance and microbiological challenge

Prove the filter’s bacterial retention capabilities with a non-destructive test.

Prove the filter does not unacceptably remove stream components.



Prove the filter removes bacteria from the stream compliant with ASTM 838-05 and regulations

Prove the filter meets all performance & duty requirements within product & process conditions.

Prove the stream does not adversely impact the filter duty.

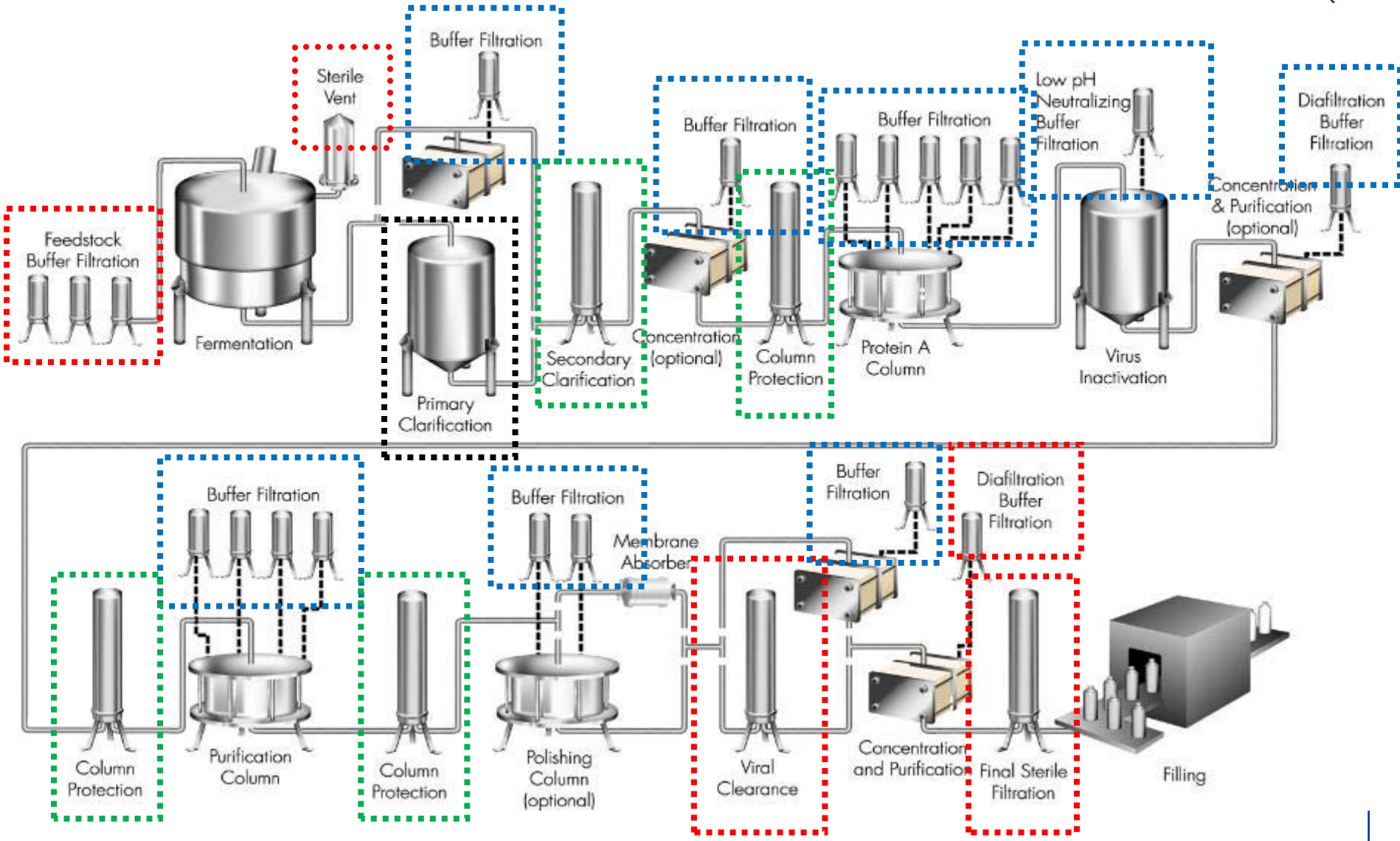
Prove the sterilization method is effective and does not compromise the filter.

Identify, quantify, and assess impact of compounds that migrate from filter to process stream.

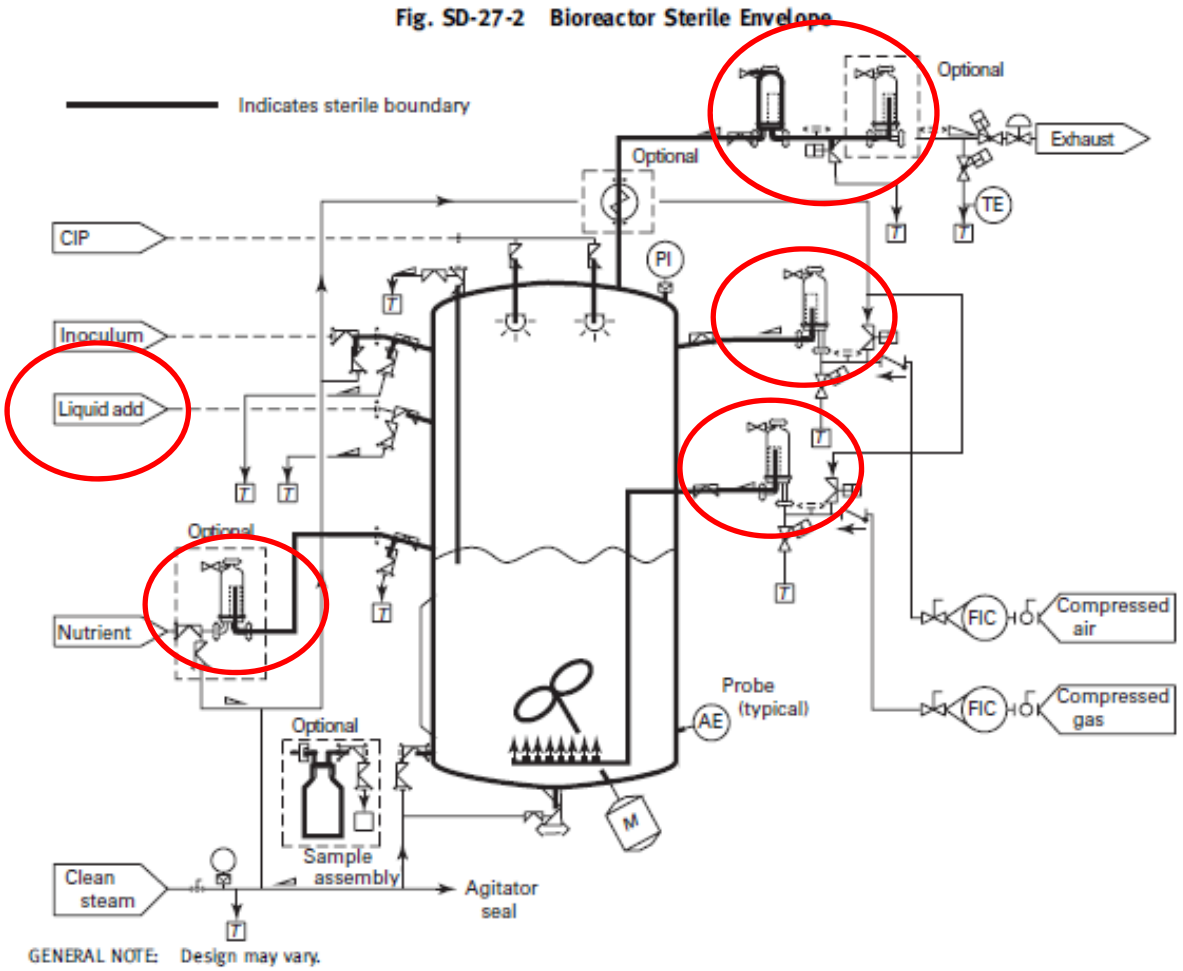
Prove the filter does not adversely affect the process stream

Filters in a Generic Biological Process

Filter groups come from their location, and classification in the process, not the regulations, guidelines or filter label. Key output is process/product risk



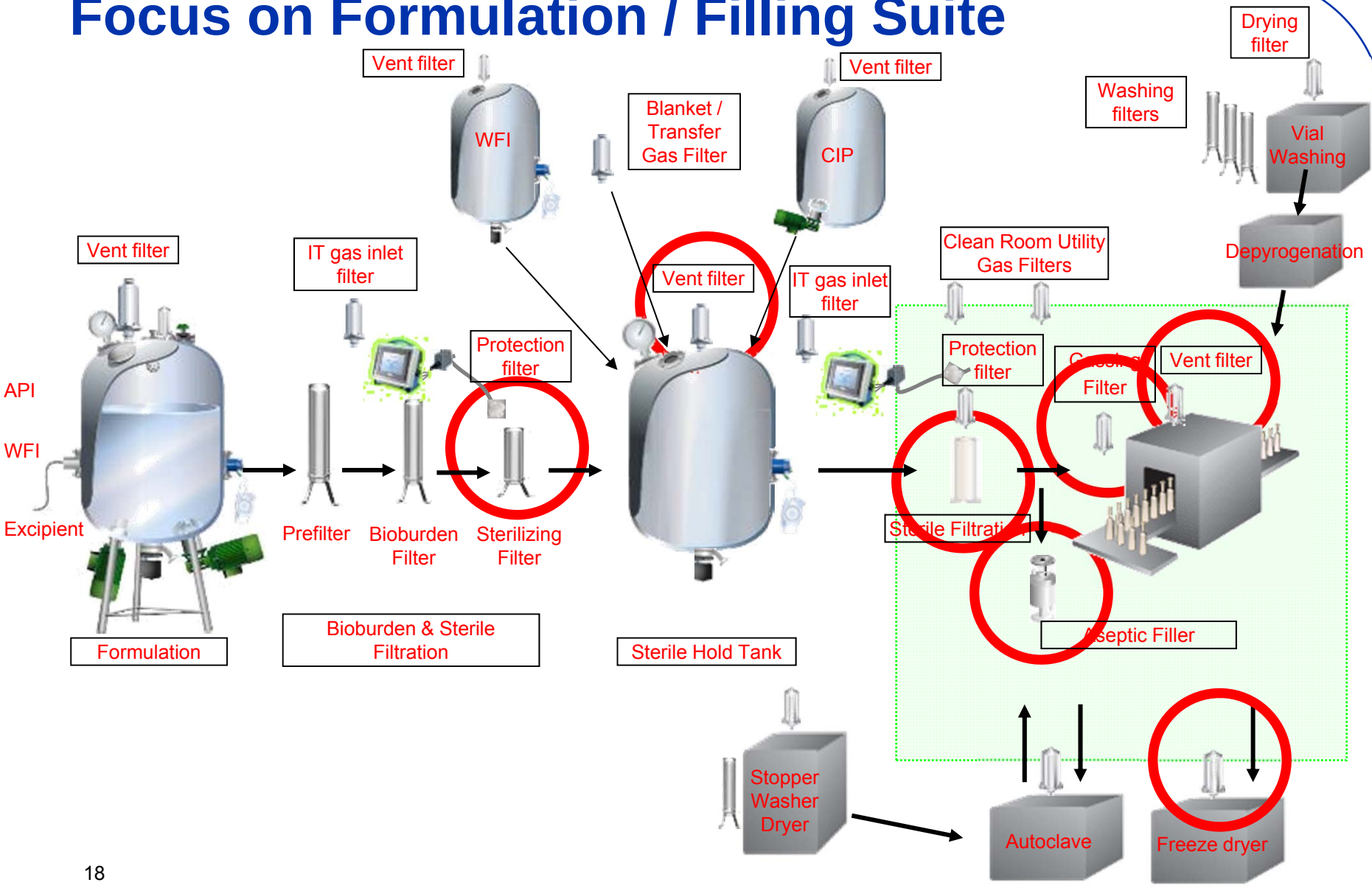
Critical Filters Around the Bioreactor / Fermenter



- Service filters not shown
- Clarifying, prefilters not shown
- Critical gas filters
  - Overlay, sparge, exhaust
- Critical liquid filters
  - Media, additives
- For redundant or serial filters, furthest away defines sterile boundary

From ASME BPE-2009 Bioprocessing Equipment

Focus on Formulation / Filling Suite



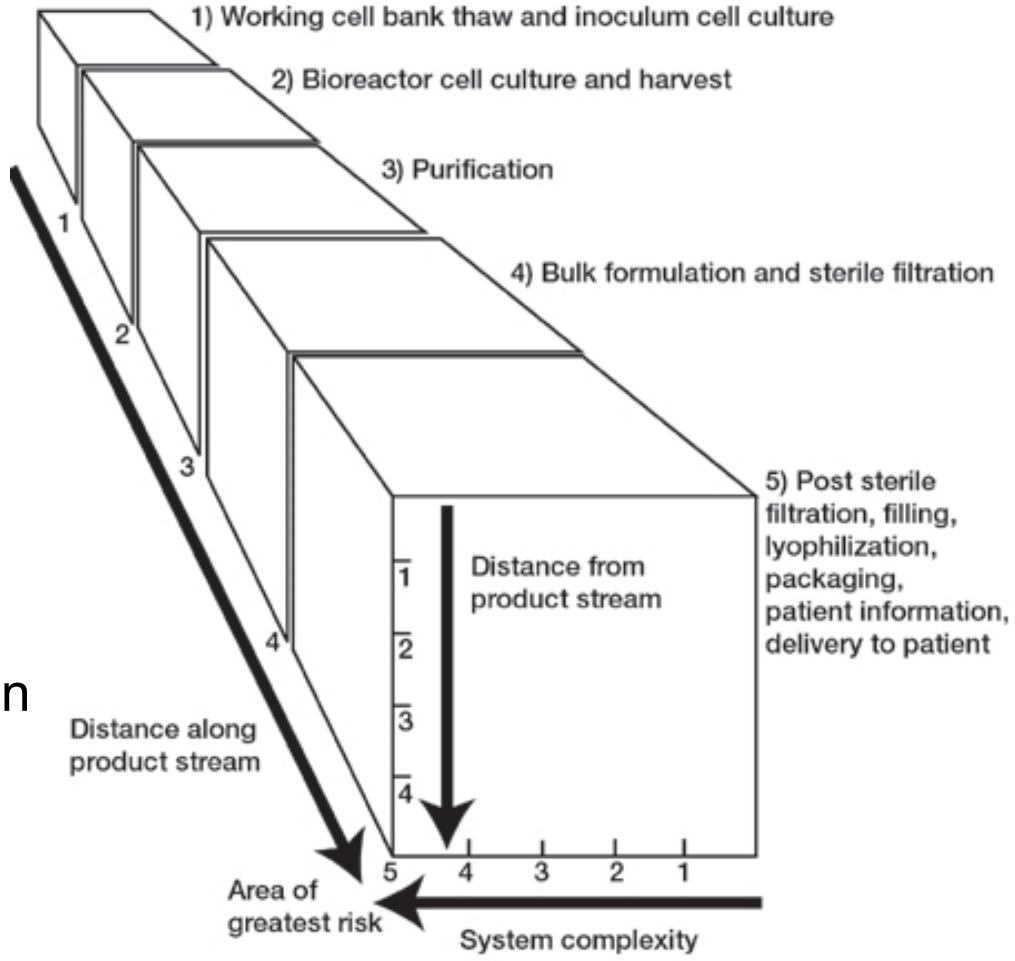
3D System Risk Assessment Tool

Considers

- a system‘s distance from the process stream
- its location along the process stream
- the system‘s complexity

Highest score is highest risk

This tool is mainly used to assign risk level to an overall complex system



From IVT Autumn 2008, pp70-76, J Oliver Baxter Bioscience

Examples of Sterilizing Filtration Risk

Risk = process location x operation complexity x product contact

Bioreactor liquid media filter

Risk = 1 x 2 x 2	4

Bioreactor Gas Filter

Risk = 1 x 3 x 2	6

Sterile hold tank gas filter

Risk = 4 x 2 x **5**	40

Final POU liquid filter

Risk = 5 x 4 x 5	100

NB: Severity, use time, process condition, defect detection, economics not considered

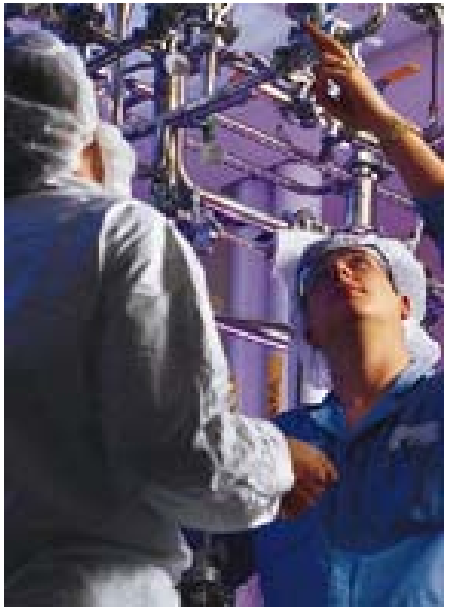
Sterilizing Filter QbD Responsibility is Shared

Vendor Responsibilities

- Filter Design Qualification
- Filter Fabrication Process Qualification
- Filter Product Quality

User Responsibilities

- Vendor Auditing
- Filter Selection
- Filter/Product Validation Studies
- Process Validation
  - System Design
  - Validation
  - Sterilization
  - Cleaning
  - Operator Training



Responsibilities of the Filter Manufacturer

Know and control the membrane and device manufacturing processes

Ensure a robust well defined membrane is used

Determine critical control points, critical quality attributes

Validate filter claims and manufacturing process

Validate filter sterilization process (for presterilized filters)

Establish and document and support product release specifications

Meet and document regulatory and compendial requirements in validation or quality documentation

- Non-Fiber releasing
- Endotoxin
- In vivo/In vitro Toxicity
- Sterilizing-grade performance
- Extractables

Filter User Responsibilities

Define the operation space (requirements)

Establish filter/product compatibility

Audit vendor and contract laboratory

Validate test methods

Train & qualify operators

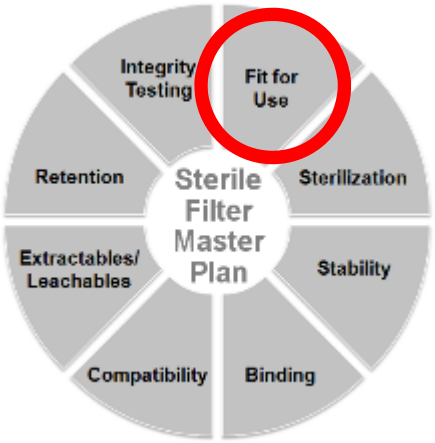
Validate filter sterilization

Validate equipment cleaning

Validate filtration process

Operate within manufacturer's specifications
or within user documented and user defined conditions where quality attributes have no additional risk

Define Duty (fit for use) as part of QbD



Sterilizing Filter Operating Space

Feedstock

Volume

Contact Time

Flowrate

Pretreatment / Prefiltration

Inlet Pressure

Differential Pressure

Yield

Ease of Use / Handling

Sterilization Method

Integrity Test Method

Characteristics Required to be Maintained for Linear Scaling

Constants determined after a filter is selected

Feedstock

Pretreatment / Prefiltration

Contact Time

Pressures

Yield

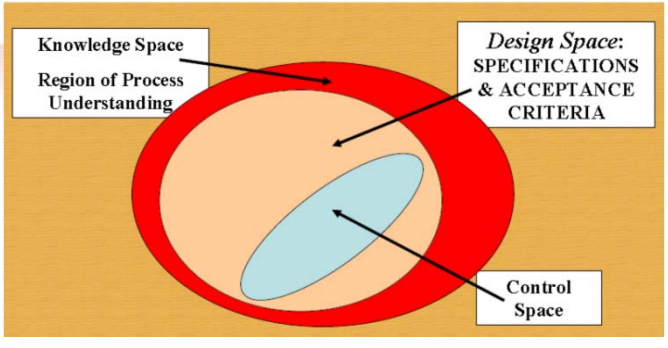
Load (= Volume / Filter Area)

Flux (= Flowrate / Filter Area)

Filter Retention Testing – Showing how User & Vendor can Combine Strengths to Help Ensure QbD

Vendor

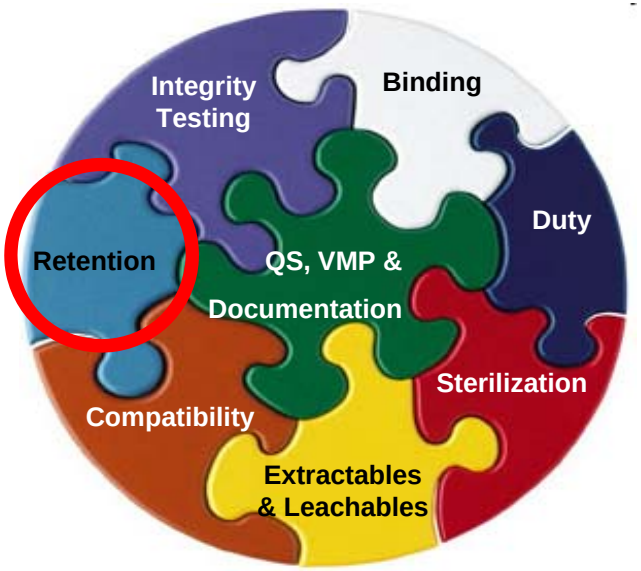
User



User

Retention: What are the requirements

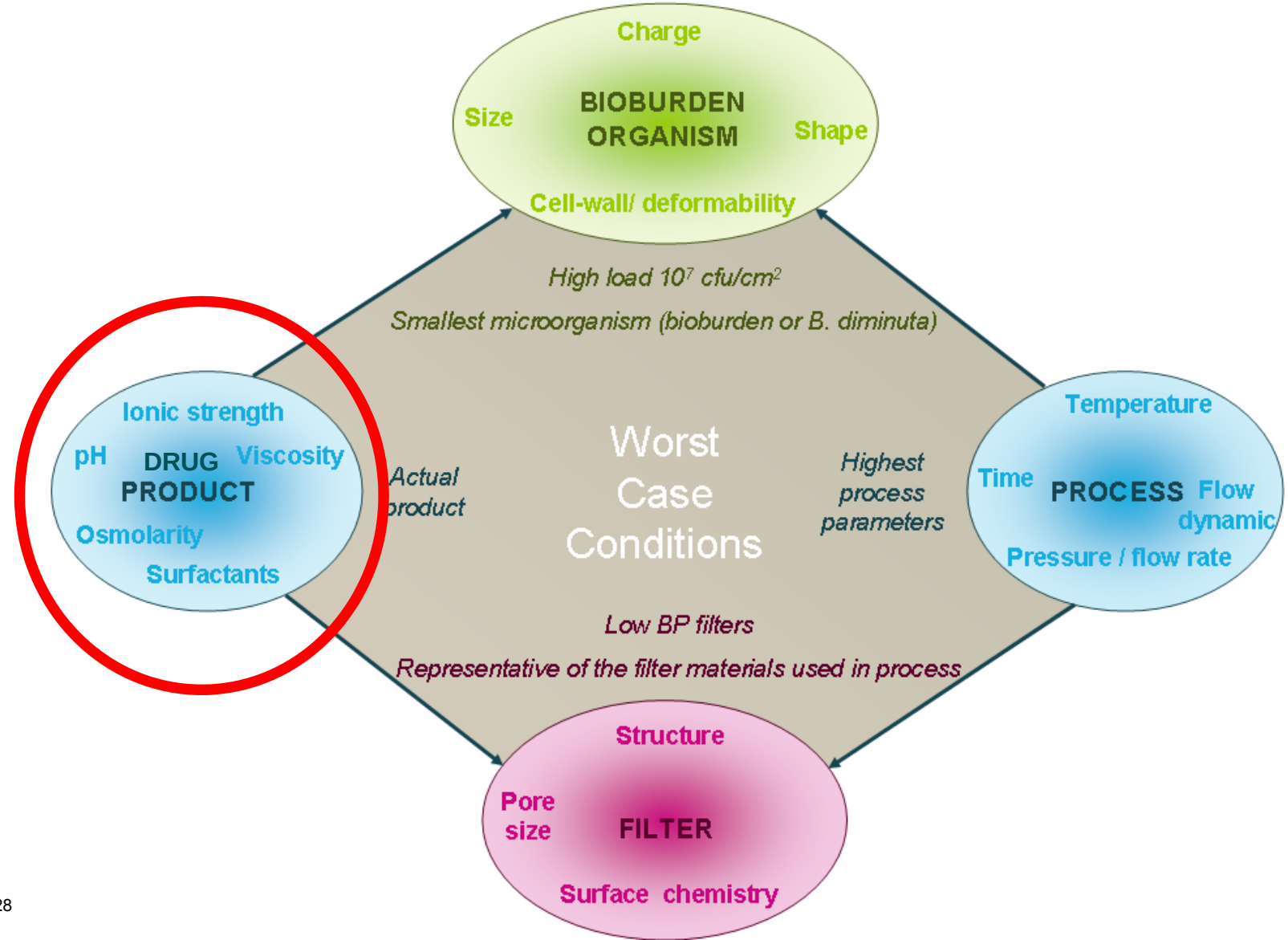
"All Sterilization Processes Should be Validated."
WHO Annex 6: Good Manufacturing Practices for Sterile Pharmaceutical Products section 5.4 page 273



"Whatever type of filter or combination of filters is used, validation should include microbiological challenges to simulate "worst case" production conditions. The selections of the microorganisms to perform the challenge test (e.g. P. diminuta) has to be justified. The nature of the product may affect the filter and so the validation should be performed in the presence of the product……"
PIC/S Guide for Inspectorates: Recommendation on the Validation of Aseptic Processes

A summary should be provided containing information and data concerning the validation of the retention of microbes and compatibility of the filter used for the specific product.
US FDA Guidance on Sterilization Validation

Defining the worst case conditions

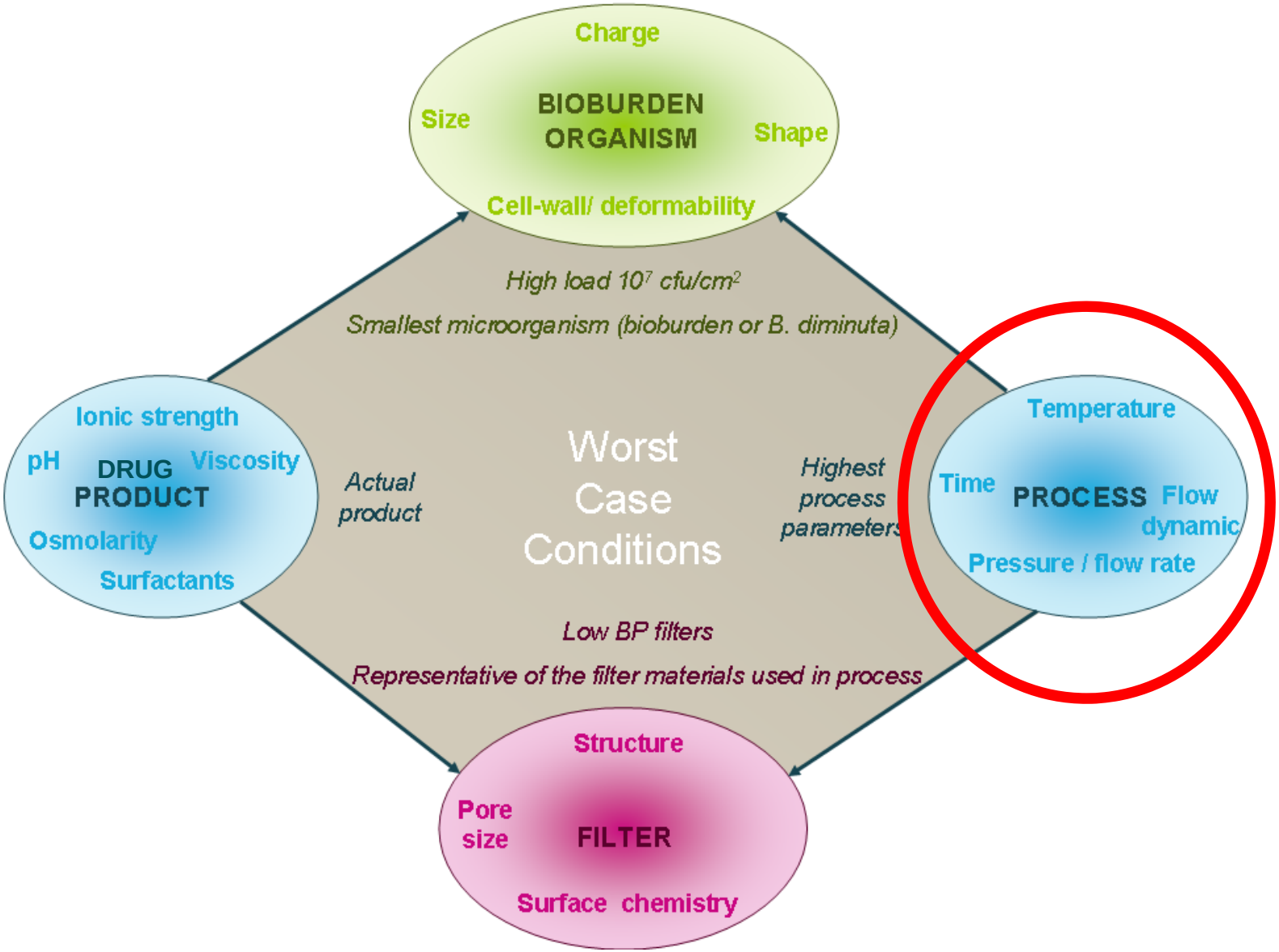


Product chemistry – Worst case conditions

	Main effect	Worst-case value
Osmolarity	Size of organism	Highest
Surface tension	Retention mechanism	Lowest
pH	Organism proliferation	5 - 9
	Filter compatibility	Highest
	Retention mechanism	Lowest & highest
Ionic strength	Retention mechanism	Lowest & highest
Viscosity	Retention mechanism	Highest

This becomes part of the design space consideration

Defining the worst case conditions



Process Parameters – Worst case conditions

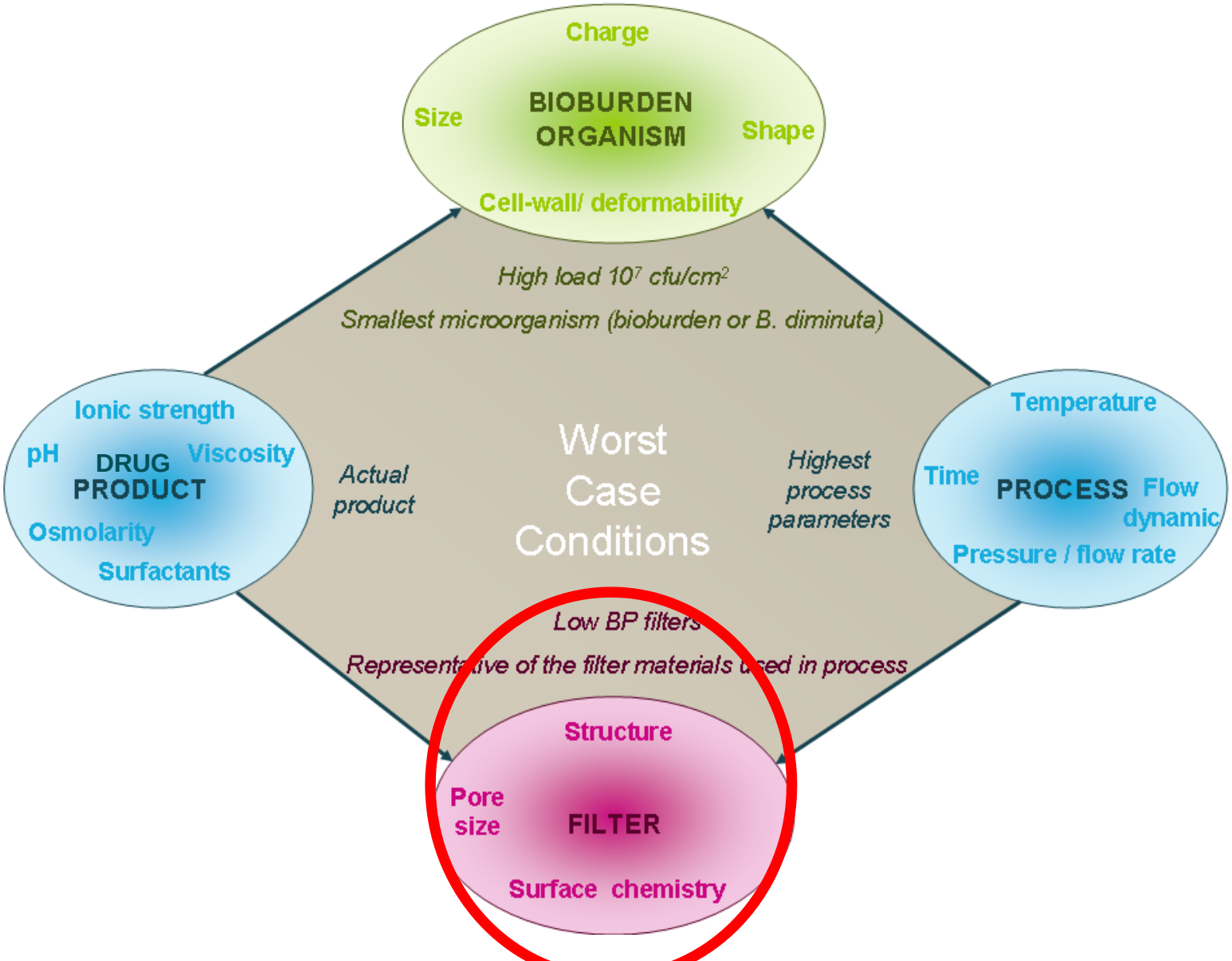
	Main effect	Worst-case
Pressure or Flow rate	Retention mechanism	Highest
Filtration time	Grow-through Bio-burden proliferation	Highest
Hydraulic shock	Blow-through	Highest
Temperature	Membrane compatibility Bio-burden proliferation	

→ In-line integrity testing

→Include any static holding time as well as non routine interventions & events

This becomes part of the design space consideration

Defining the worst case conditions



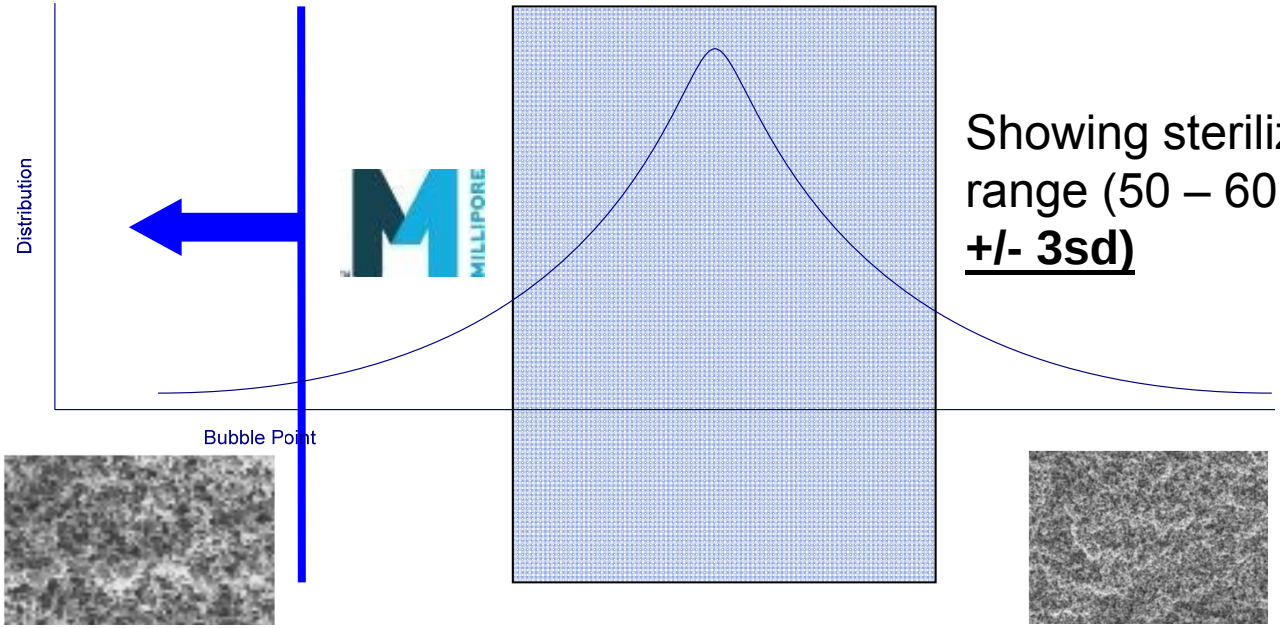
Filters - Worst Case Filters

Use of "Low" Bubble Point Filters

In general, FDA has stated that membranes within 10% of the minimum specification are adequate

"One test filter at or near (~10%) minimum B.P. (pre-challenge)." (Sweeney 2007 GPhA Fall Tech. Conference)

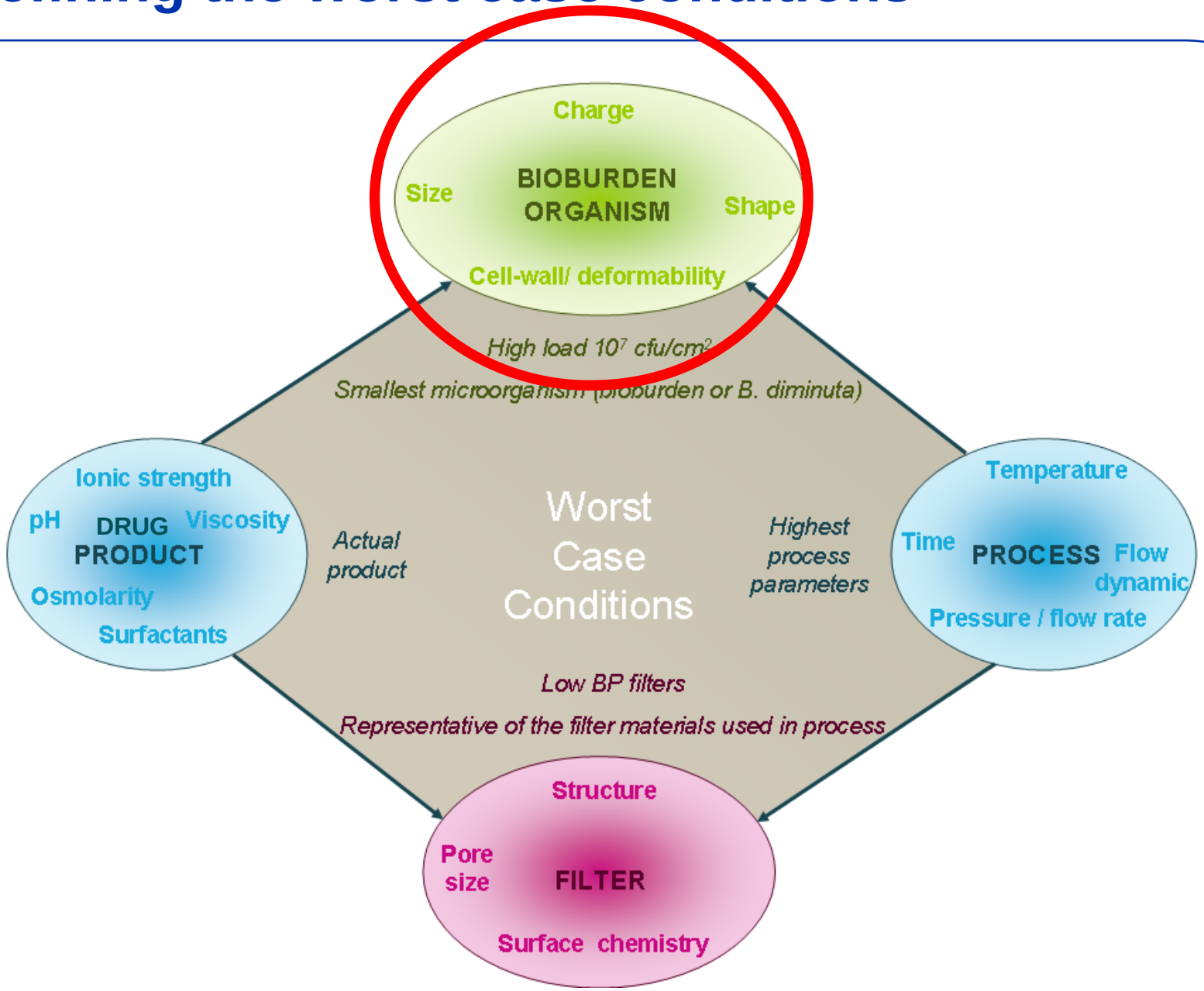
Worst-Case Selection Threshold



Showing sterilizing grade bubble point range (50 – 60.5 psi) and mean **(55.5 +/- 3sd)**

ISSUE – meeting FDA "recommendation" in this case is only mean bubble point. Retention test should show lowest expected bubble point otherwise sterilizing filter design space is compromised

Defining the worst case conditions



Challenge microorganism – worst case

B. diminuta & FDA Guideline

- *"B. diminuta* is the reference micro-organism ..."
- "... but one has to assure that actual bio-burden does not contain micro-organisms of a size and/or concentration that would reduce the targeted high level of filtrate sterility assurance"

More and more observations & comments from FDA & EMEA auditors

Know your bioburden - Review environmental monitoring program results to identify small water-borne organisms in the facility

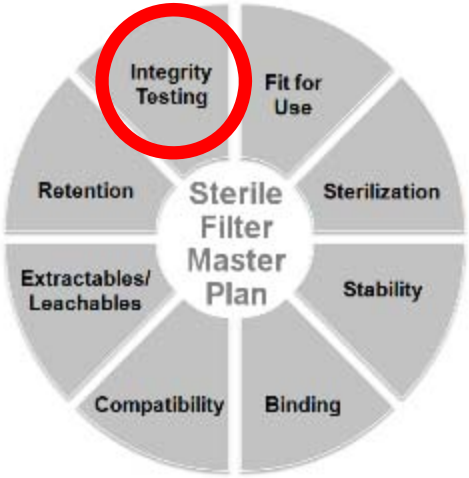
Size organism in drug product and compare with B. diminuta

Use previously determined boundary conditions and process details to outline retention test conditions

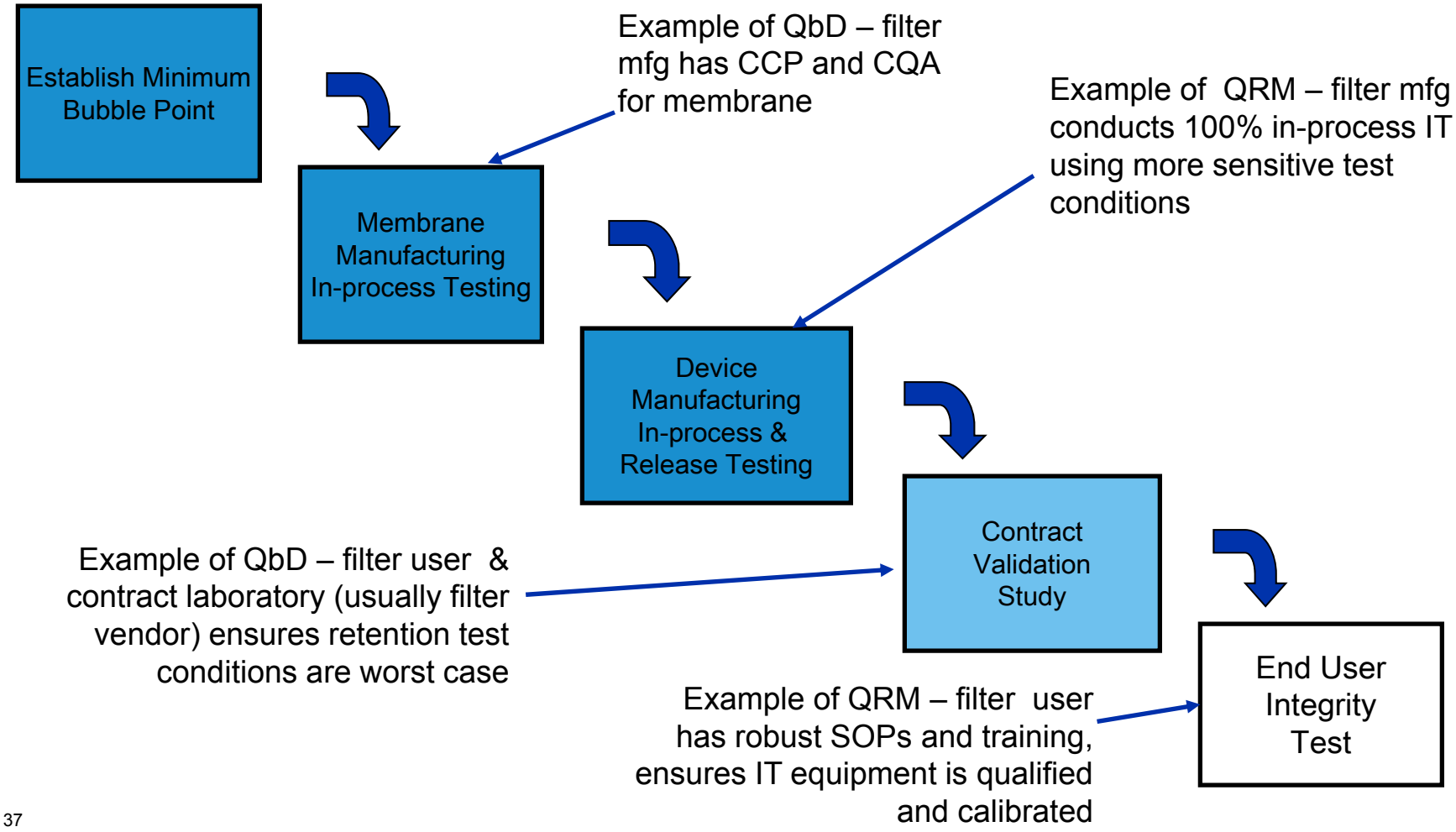
Specified by filter user, included in test protocol by contract lab

This becomes part of the design space consideration

Filter Integrity as an Example of User – Vendor Cooperation



Multilevel Approach to Sterilizing Filter Integrity Testing



QbD Aspects of Integrity Testing

Filter vendor must show a correlation between bacterial challenge (aka “destructive testing”) and filter integrity testing (aka “non-destructive testing”)

Filter retention tests must include examples of filters whose integrity test values represent the “worst case” (e.g. low bubble point)

Equipment used in end-user integrity testing must be qualified over the range of conditions expected (e.g. bubble point, flowrate)

End-user integrity testing procedures must be qualified

Integrity test values should be tracked

End-user integrity test specifications must be directly linked to quality document (e.g. certificate of quality, product-based test study)

Integrity test specifications must be checked on a regular basis

Hydrophilic Filter Qualification – TR26

Table 4.1-1 Qualification and Validation Recommendations

Criteria	Filter User	Filter Manufacturer	
	Device	Membrane Disc	Device
Bacteria retention in water or saline lactose broth (SLB) with integrity test correlation in water or solvent	-	Q, L	Q, L
Bacteria retention in product	V*	-	-
Chemical compatibility, effects on filter integrity	V	Q	Q
Extractables	V	Q	Q
Leachables	E	-	-
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	-	Q	Q
Bacterial endotoxin	V	-	Q, L
Particulate matter	E	-	Q
Non-fiber release	E	-	Q
Total Organic Carbon (TOC) and conductivity	E	-	Q

N.B. Does not include filter modules process operating parameters (e.g. Size, connections, capacity, temperature, pressure, etc.)

L = Lot release criteria
Q = Qualification
V = Process-specific validation
V* = Can be performed in disc or device format
E = Evaluate the need for testing

Checking Key Qualification Elements for Moderately Critical / Critical Liquid Filtration

- Chemical compatibility ✓
- Duty ✓
- Binding / Adsorption ✓
- Integrity testing ✓
- Sterilisation ✓
- Extractables / Leachables ✓
- Product stability (if required) 
- Microbiological Retention ✓

Hydrophobic Filter Qualification – TR40

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)

Note differences between hydrophilic and hydrophobic qualification recommendations

Q = Qualification Testing

V = Validation Testing—Process-Specific

E = Evaluate Applicability to Process

R = Recommendation for Validation

L = Filter Lot-Specific Release Criteria

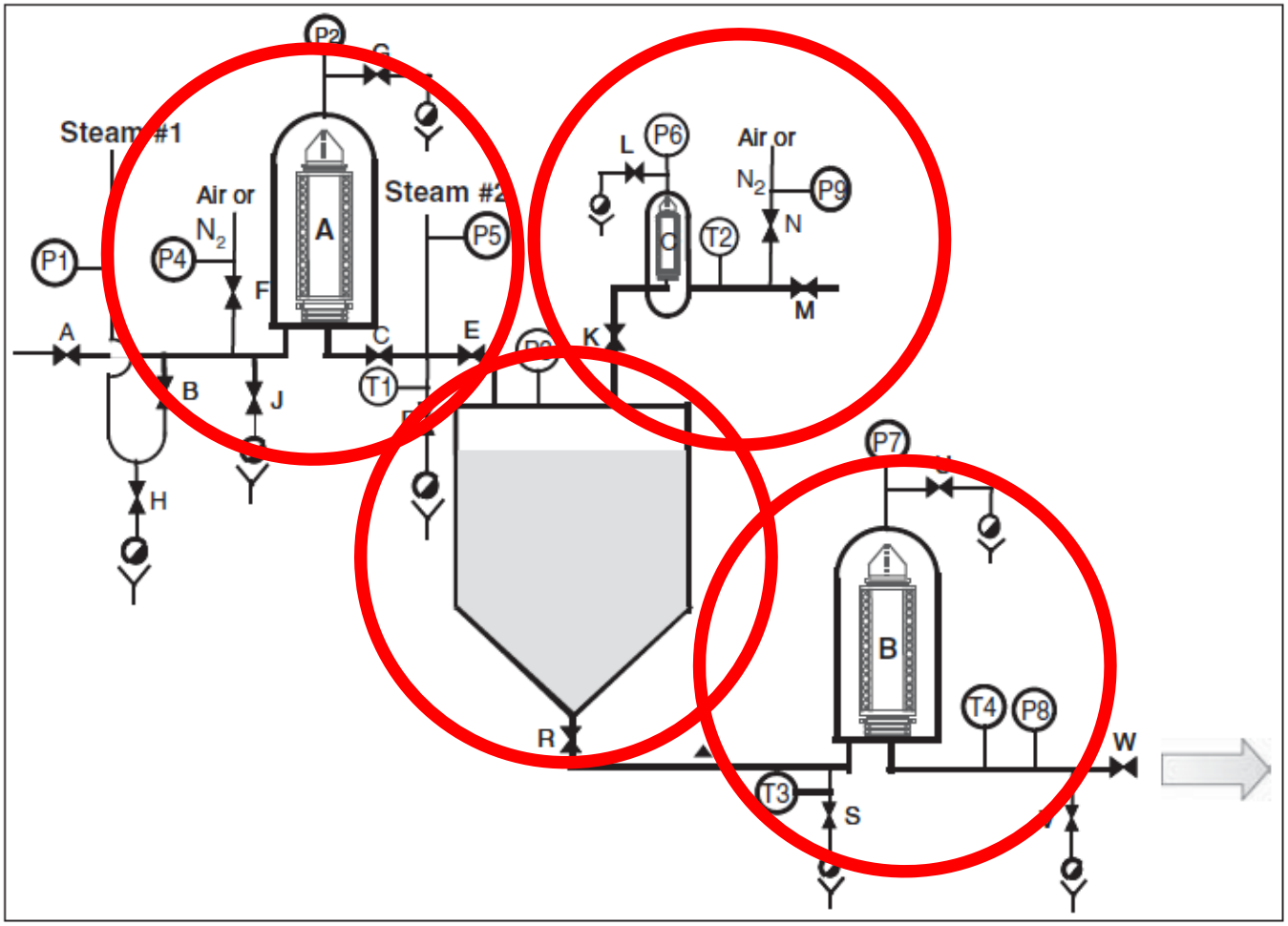
Checking Key Qualification Elements for Moderately Critical / Critical Gas Filtration

Chemical compatibility*	✓	materials of construction
Duty*	✓	compare with flow vs. dP in VG
Binding / Adsorption	⊗	no product contact
Integrity testing	✓	need to do IT test of filter
Sterilisation	✓	need to ensure filter is sterilized
Extractables / Leachables	⊗	no product contact
Product stability	⊗	no product contact
Microbiological Retention*	✓	**Ensure** actual operating conditions are less that conditions in VG during aerosol or liquid retention testing

*** = documentation check**

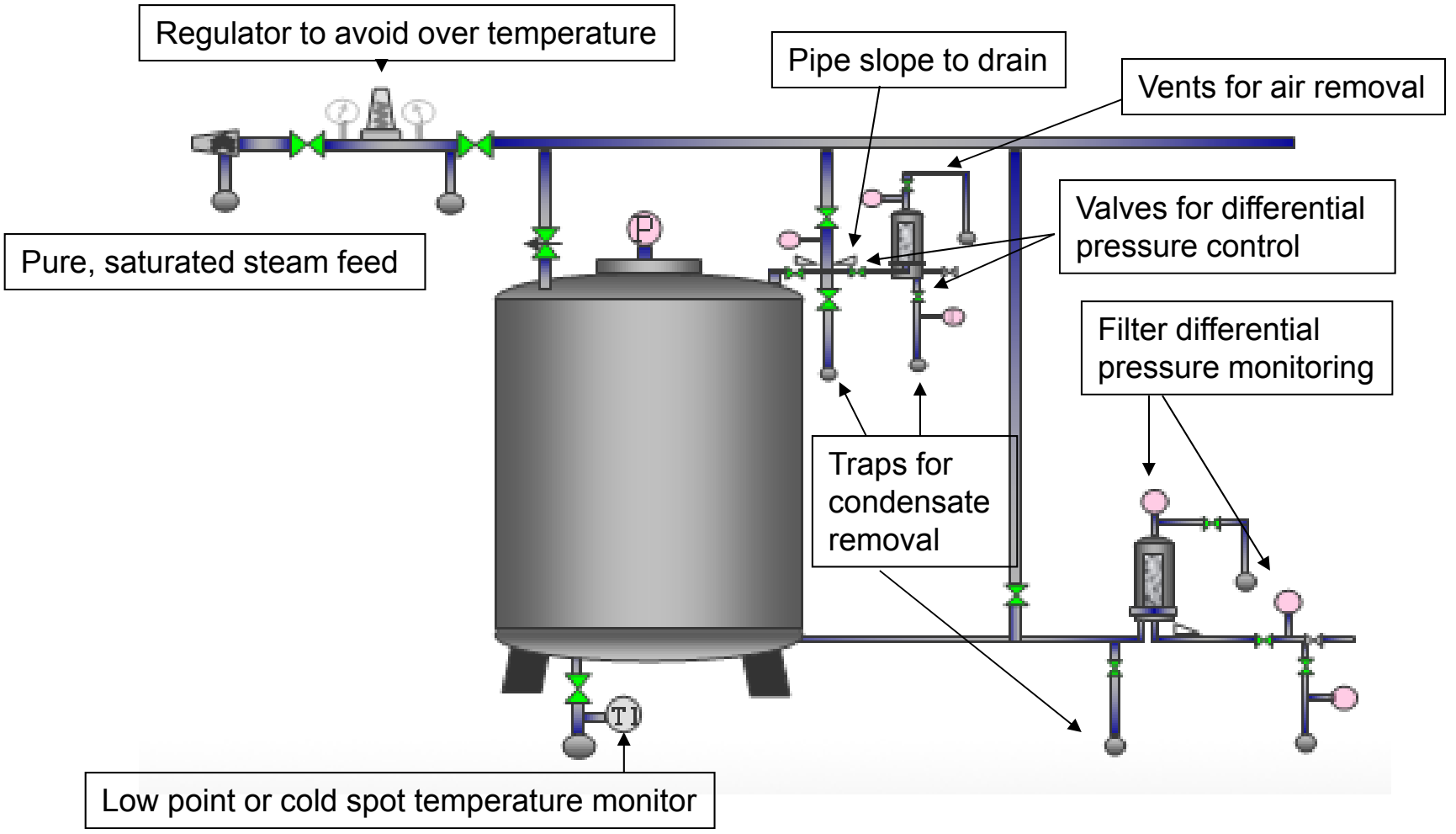
Sterilizing Filter System Design

Example - Sterilization System Design for Sterile Hold Tank and POU Filter



From Simon Cole "Steam Sterilization of Filters"

Some Steam Sterilization Design Considerations

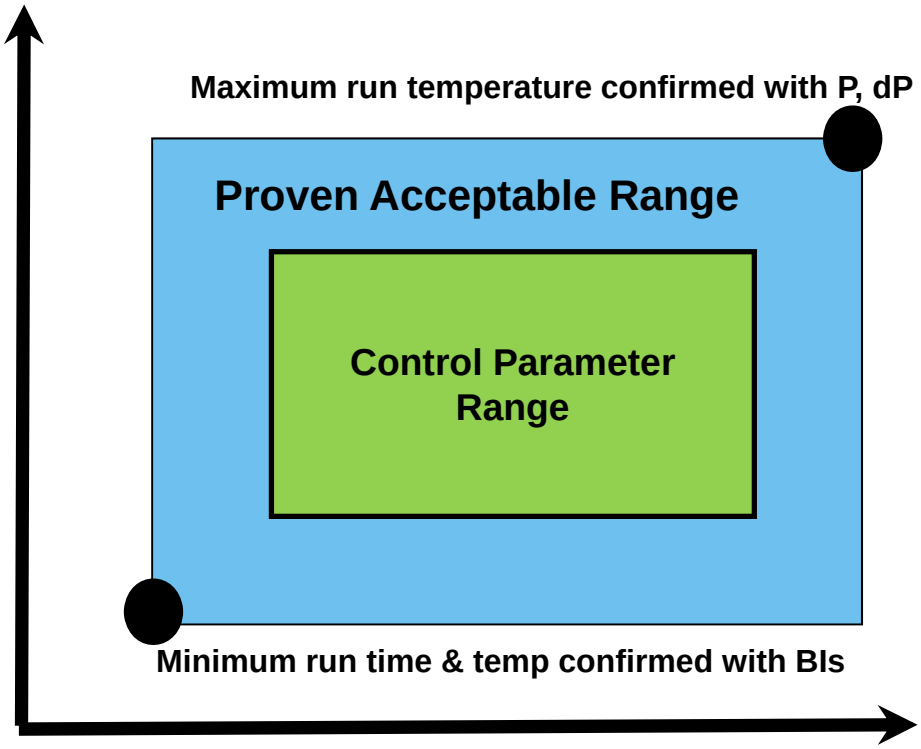


Mapping Design Space for Filter Sterilization

Temperature

Maximum established by cartridge passing integrity test after SIP cycle

Minimum established by sterilization validation to achieve required “kill”



During whole cycle, important to;

- **Establish both minimum and maximum F_o ,**
- **Monitor temperature**
- **Monitor filter differential pressure**

Maximum established by cartridge passing integrity test after SIP cycle

Minimum established by sterilization validation to achieve required “kill”

Practical Approaches

Summarizing the Sterilizing Filter Design Space

Process Attributes

Yield, time, pressure, temperature, flowrate, volume, sterilization method and conditions, pretreatment, integrity test

Product Attributes

pH, ionic strength, osmolarity, formulation, product concentrations (active, excipient, etc.), acceptable impurity levels

Microbiological Attributes

Species / Identity, concentration

Product Testing Priority - Risk-based Approach

Consider the product formulation and preparation method

Allows priorities to be set when progressing through qualification

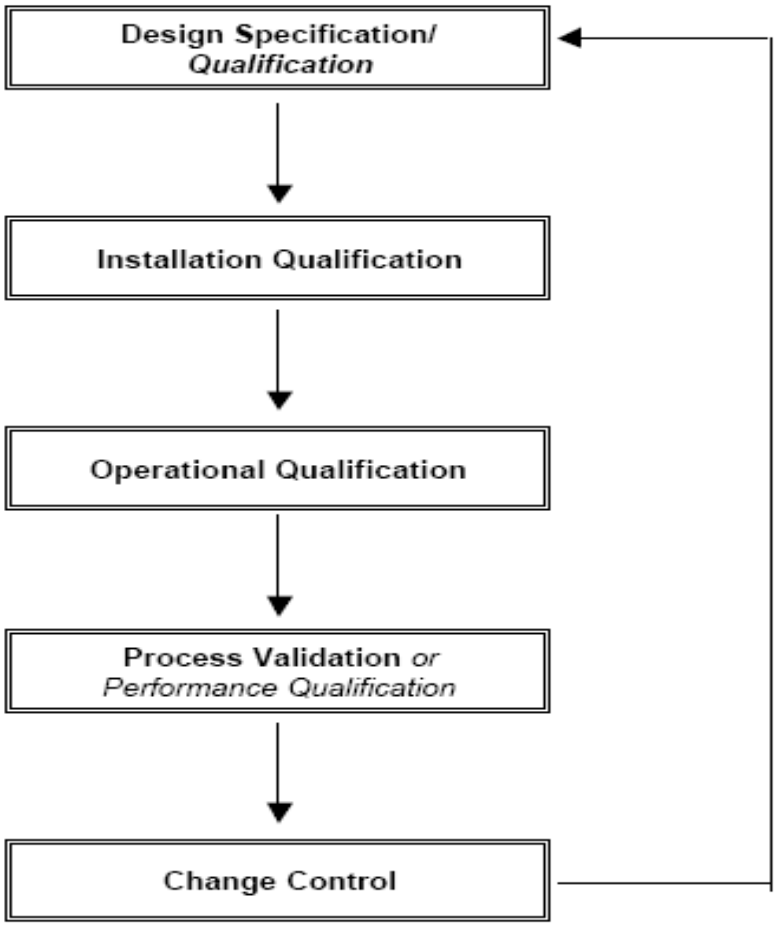
Examples of formulation and production risk differences;

- 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

Include in master plan with project charting approach

Validation Process, Key Vendor and Contract Laboratory Documentation for Sterilizing Filtration



Data Sheet
Validation Guide

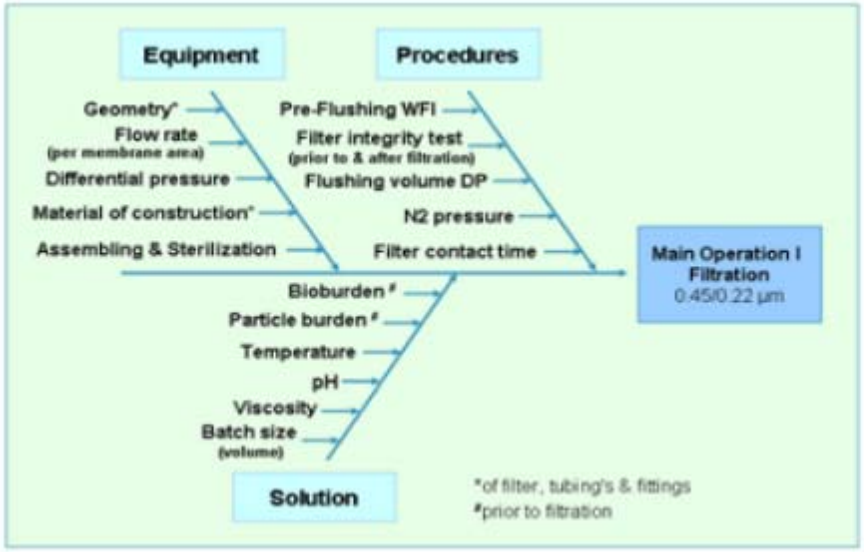
Adsorption study
Product Specific Integrity Testing
Sterilization qualification
Bacterial Retention Testing
Extractables / Leachables Testing
Toxicity assessment

Example - QbD Applied to Sterile Filtration

A-Mab study

1. Definition of target process

2. Process parameters



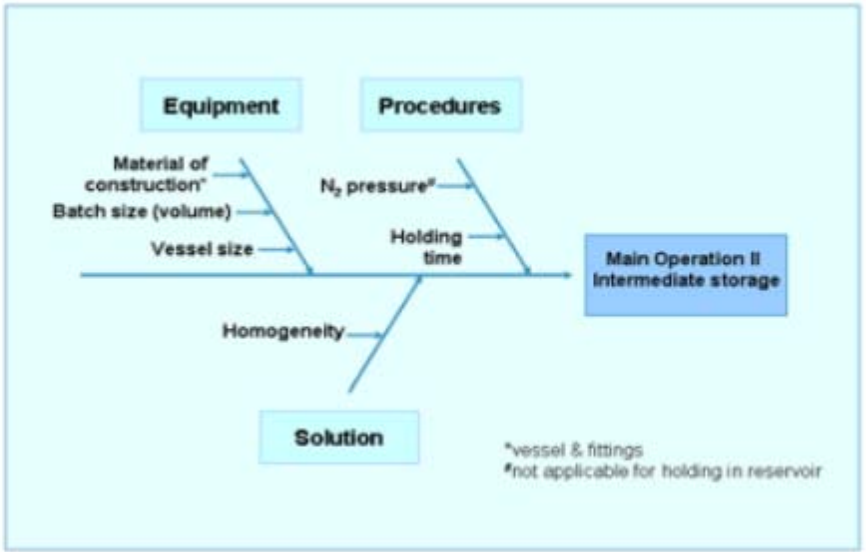


Table 5.13 Initial Risk Assessment for Filtration Unit Operations

Quality Attribute	Aggr.	Visible particles	Sub-visible particles	Bacterial Endotoxin	Sterility	Rationale / Comment	Score
Rank	10	7	10	10	10	NA	NA
Drug Substance Container							
(0.45 µm/ 0.22 µm and 0.22 µm/ 0.22 µm)							

Cycle II – Intermediate storage							
Material of construction[1]	7	7	7	1	1	Adsorption of formula components and leachables can induce aggregation and fragmentation	209
Homogeneity of the solution[1]	1	7	7	1	1	Solution homogeneity affects filter performance	149

7. Process control

Conclusion

QbD approach begins at product development and continues through product life-cycle

Vendor documentation supports end-user QbD

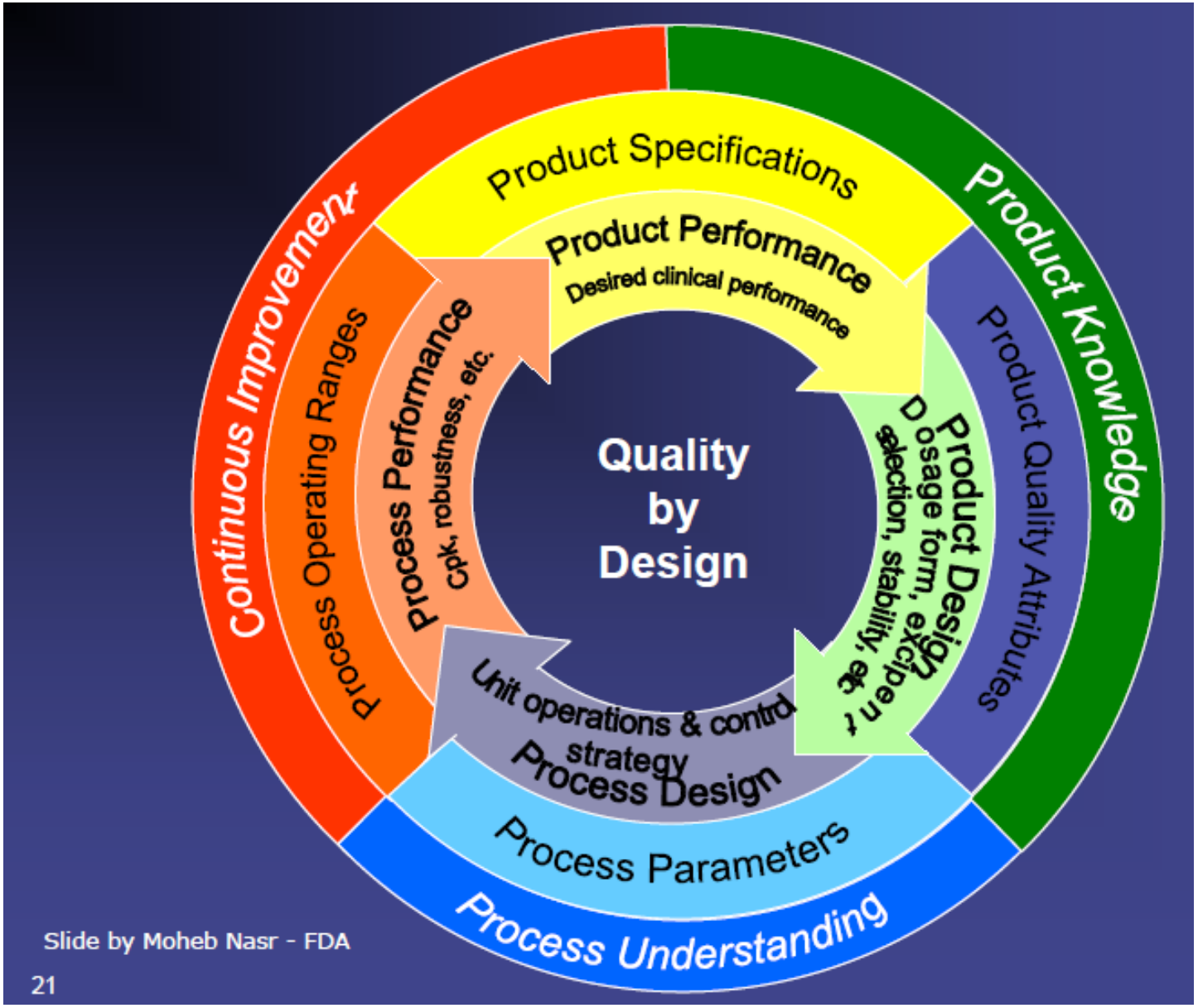
User documentation identifies risk and maps the design space

Adjusting or transferring or accepting processes should include checks for QbD

QbD is another way of looking at process information that should already be available

Quality by design and quality risk management support and strengthen cGMP approaches

If you don't start with a sterilizing grade filter, there isn't anything that you can do to add sterility assurance


Quality by Design
Product Specifications
Product Performance
Desired clinical performance
Product Knowledge
Product Quality Attributes
Product Design
Dosage form, excipient selection, stability, etc.
Process Design
Unit operations & control strategy
Process Parameters
Process Understanding
Process Performance
Cpk, robustness, etc.
Process Operating Ranges
Continuous Improvement
Slide by Moheb Nasr - FDA
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Thank You for your Attention!
May we be of Further Assistance?

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