# validation needs for sterilization by aseptic filtration

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**Ramesh Raju**
Associate Director - Provantage Validation Services

MERCK

# Overview

- Key Regulatory and Industry guidelines
- 8 elements of filter validation
- Risk assessment for filter extended use / re-use
- Revalidation requirements
- Defining the “worst case” in the validation plan

# Filter Validation Discussed in Regulatory and Industry Guidelines

*WHO Annex 6: Good Manufacturing Practices for Sterile Pharmaceutical Products section 5.4 page 273*

"All Sterilization Processes Should be Validated."

FDA Aseptic Processing Guidelines (2004)
Correlate filter performance with filter integrity testing
Include microbiological challenges to simulate 'worst case' production conditions

FDA Sterilization Process Validation (1994)
data concerning the validation of the retention of microbes and compatibility of the filter
Any effects of the filter on the product formulation should be described (e.g., adsorption of preservatives or active drug substance, or extractables).

PIC/S Guidance Documents
Aseptic Processing, cGMP Guidance, VMP, Sterility Testing, etc.

ISO/DIS 13408-2 Aseptic Processing
Filter Pre-selection shall take into account chemical and physical characteristics of the filter, as established by the filter manufacturer. Bacterial retention performance of filters shall be validated in a fluid-specific manner or for fluid groups under worst case conditions in production.

PDA Technical Report 26 (2008)
"Filter manufacturers typically publish results of tests performed according to applicable compendial methods to qualify the filter as suitable for pharmaceutical applications. This qualification documentation supports, but does not replace, performance qualification as a part of process validation conducted by the filter user."

# 8 Elements of a Sterile Filtration Validation

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

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

Prove the filter removes bacteria from the stream per ASTM 838-05.

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.

[4] Prove the stream does not adversely impact the filter.

Prove the filter does not remove stream components.

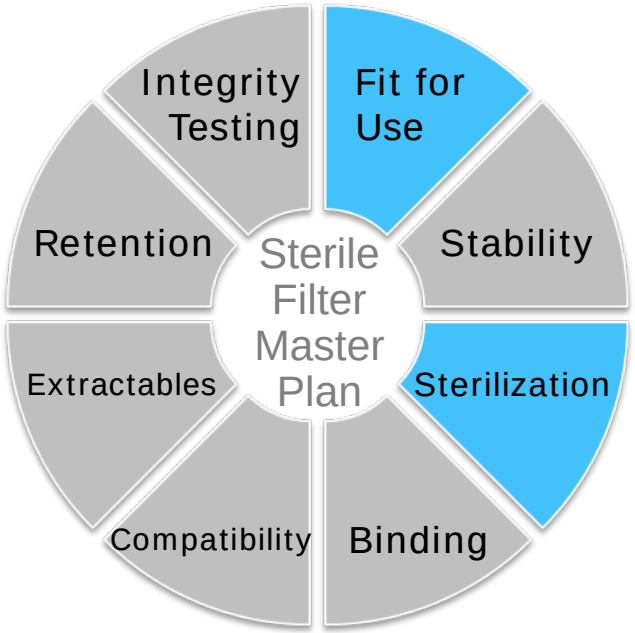
# PDA TR 26

## 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 |

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

# What are the regulatory requirements?




"Before any sterilisation process is adopted its **suitability for the product** and its **efficacy in achieving the desired sterilising conditions** ...should be demonstrated by physical measurements and by biological indicators where appropriate."

"The validity of the **process should be verified** at scheduled intervals, **at least annually, and whenever significant** modifications have been made to the equipment."

"**Records should be kept** of the results."

*EC guide to GMP for sterile medicinal products*
*Revision of annex 1 (2009)*

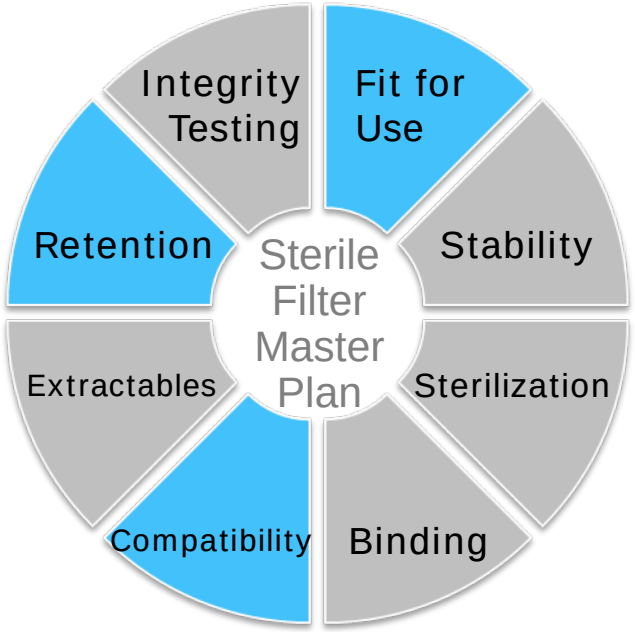
# What are the regulatory requirements?

"All Sterilization Processes Should be Validated."

*WHO Annex 6: Good Manufacturing Practices for Sterile Pharmaceutical Products section 5.4 page 273*

"A sterilizing grade filter should be validated to **reproducibly remove viable microorganisms from the process stream**, producing a sterile effluent"

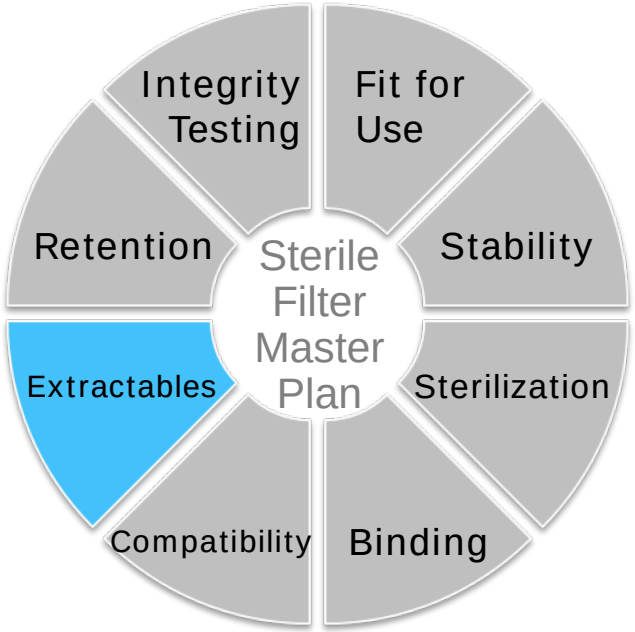
*2004 FDA Guidance for Industry Sterile Drug Products Produced by Aseptic Processing*




"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"

*FDA Guidance for Industry for the Submission Documentation for Sterilization Process Validation in Applications for Human and Veterinary Drug Products, November 1994*

# What are the regulatory requirements?



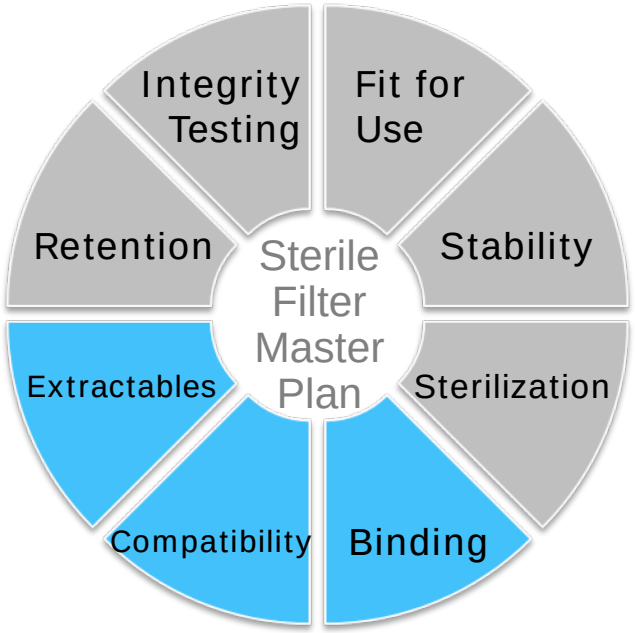

"Production equipment shall not present any hazard to the products. The parts of the production equipment that come into **contact with the product must not be reactive, additive or absorptive** to such an extent that it will affect the quality of the product and thus present any hazard."

*European Commission, EUDRALEX Volume 4, "Good Manufacturing Practices, Medicinal Products for Human and Veterinary Use", Chapter 3, "Premise and Equipment", 2003*

# What are the regulatory requirements?

"Equipment shall be constructed so that surfaces that contact components, in-process materials, or drug products shall **not be reactive, additive, or absorptive so as to alter the safety, identity, strength, quality, or purity of the drug product** beyond the official or other established requirements."

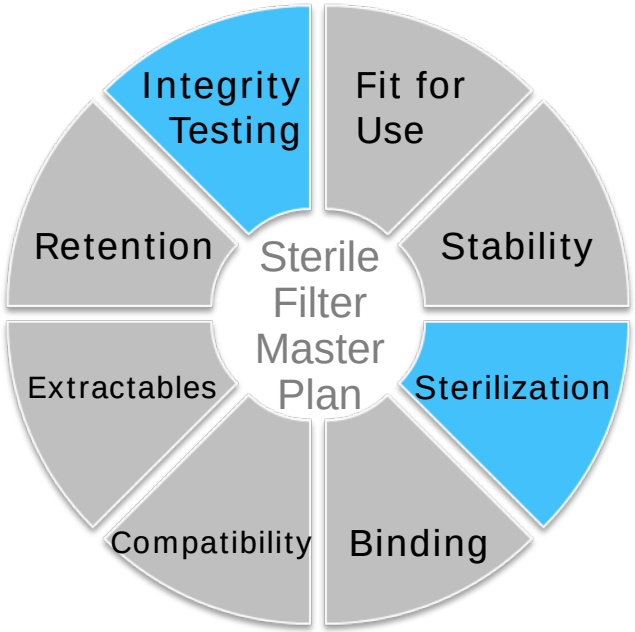
*FDA, Code of Federal Regulations, Part 211, "Current Good Manufacturing Practice for Finished Pharmaceuticals", Part 211.65, "Equipment Construction", 2005*




"When considering **chemical compatibility**, it is important to include **all filter components** under investigation"

*PDA Technical report N°26, 1998*

# What are the regulatory requirements?



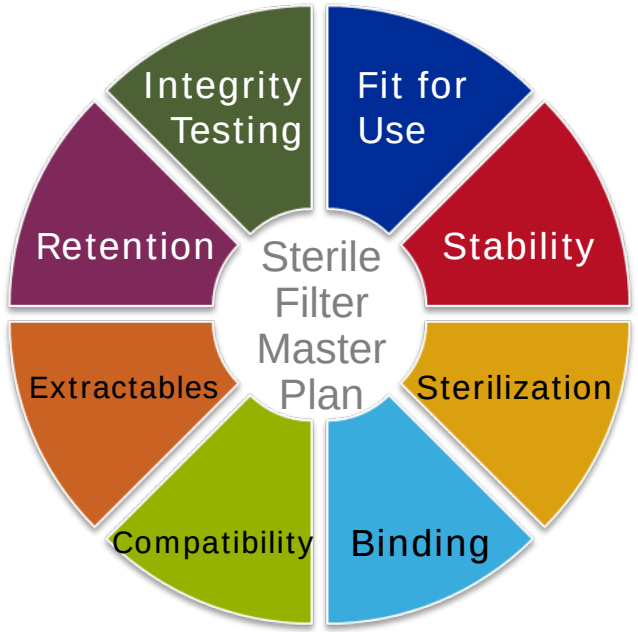

"The **integrity of the sterilised filter** should be **verified before use and should be confirmed immediately after use** by an appropriate method such as a bubble point, diffusive flow or pressure hold test."

*European Commission, EUDRALEX Volume 4, Annex 1*

*Manufacture of Sterile Medicinal Products*

# Regulatory Requirement to Simulate Process Conditions

"It is vital that laboratory experiments simulate actual product conditions …"
*FDA Guideline on Sterile Drug Products Produced by Aseptic Processing (2004)*




"pH and viscosity of the material to be filtered, flow rates, pressures, temperature, compatibility of the material with the filter itself, and the effect of hydraulic shock are factors of production which can affect filter performance and which should be simulated during validation of filtration processes"
*FDA Guideline on Sterile Drug Products Produced by Aseptic Processing (2004)*

# Regulations Related to Extended Use and Re-Use

## EU GMP Annex 1 Manufacture of sterile medicinal products 2008

- "The same filter should not be used for more than one working day unless such use has been validated.

## US FDA Sterile Drug Products Produced by Aseptic Processing 2004

- "Sterilizing filters should be routinely discarded after processing of a single lot. However, in those instan repeated use can be justified, the sterile filter validation should incorporate the maximum number of lots to be processed."

## PDA Technical report 26 Revised 2008

- "Filter reuse is typically not practical or recommended for pharmaceutical purposes. However, if a sterilizi filter is reused, justification should be provided, and reuse parameters should be validated."
- "Sterilizing filters should be routinely discarded after the processing of a single lot. However, in instances where repeated use can be justified, the sterile filter validation, including integrity testing, bacterial challenge and cleaning should incorporate the maximum number of lots to be processed."

# PDA TR 26

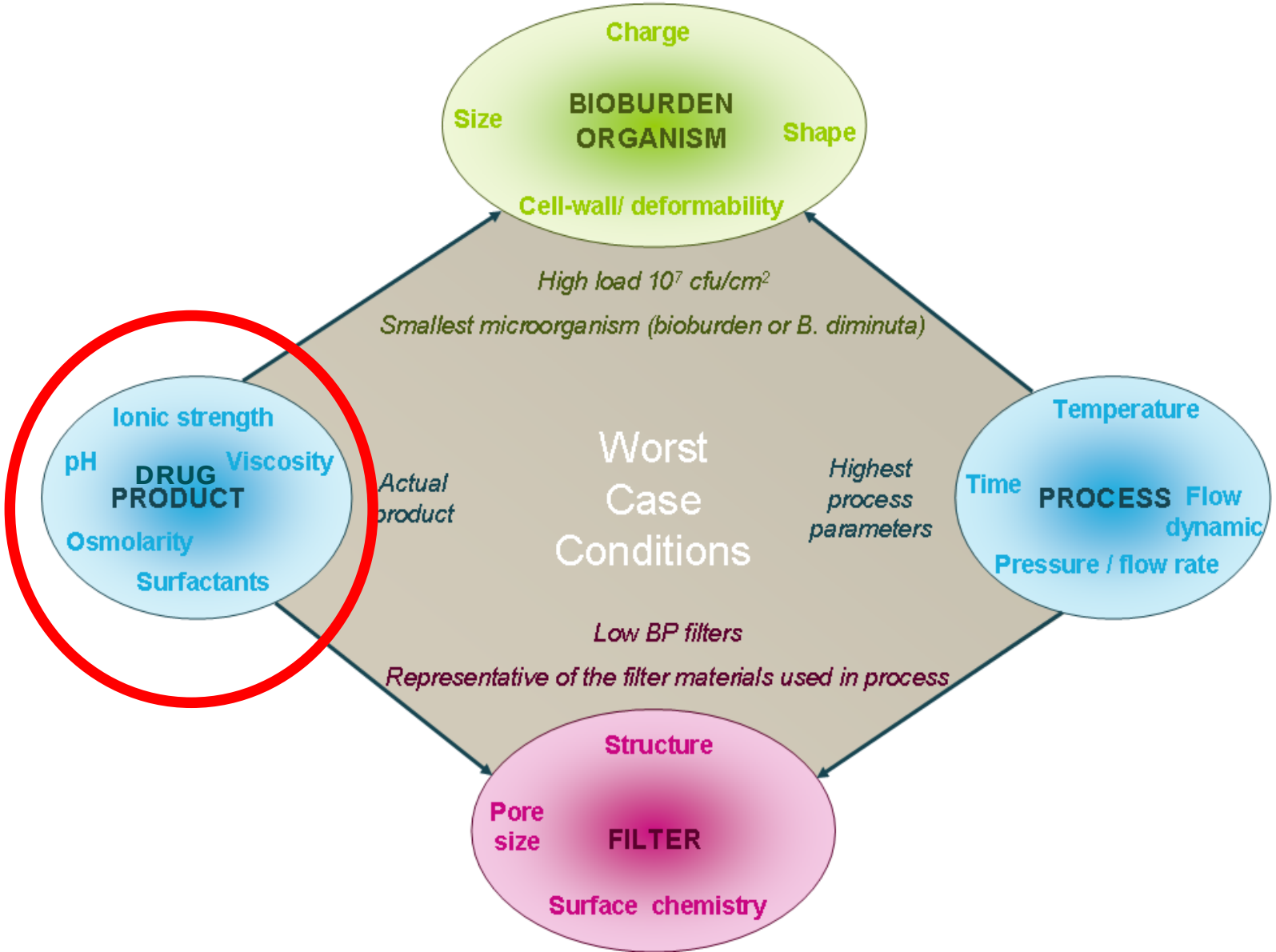
## 4.1.1 Revalidation

Once a filter is validated for use in a given process, further validation is required only when changes to limits are made. Some changes that may require revalidation include, but are not limited to:

- An increase in volume to be filtered through a given filter area
- Product formulation changes, including product concentration, pH or conductivity
- Sterilization procedure changes
- The temperature of the filtrate

A risk assessment should be performed to evaluate the potential impact of these changes. The quality unit should approve all changes that potentially impact the CGMP compliance of the system.

# Defining the “worst case” in the validation plan



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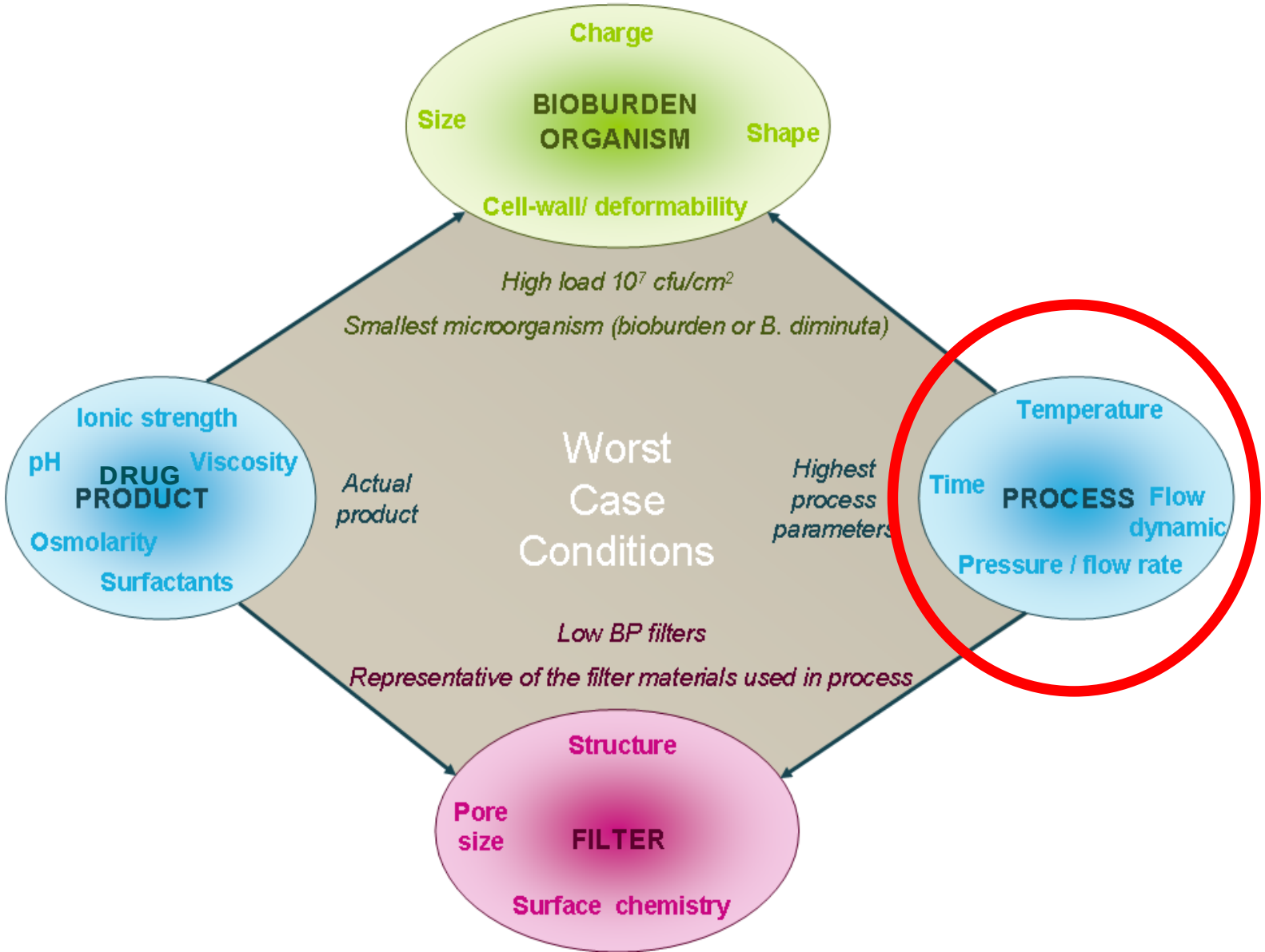

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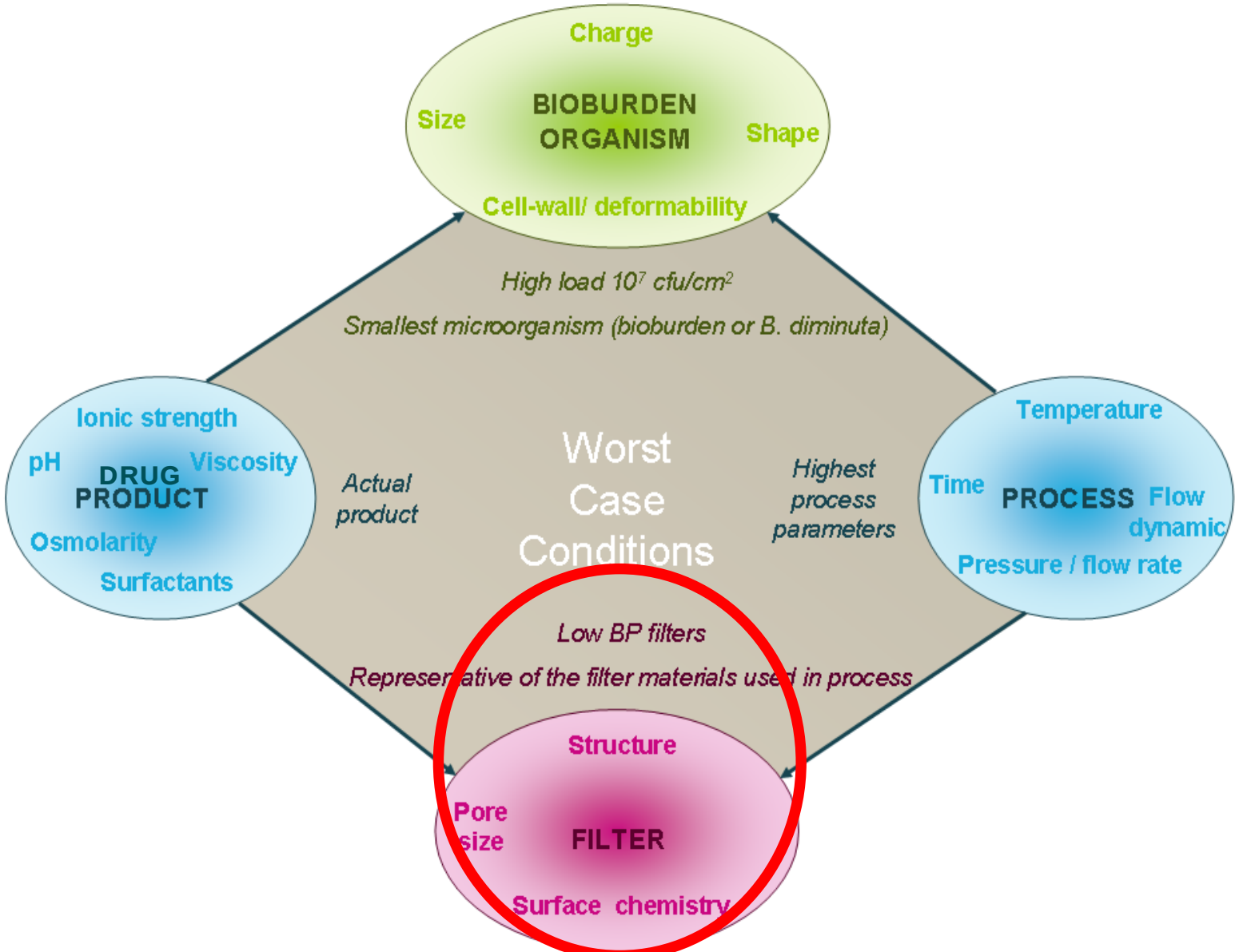

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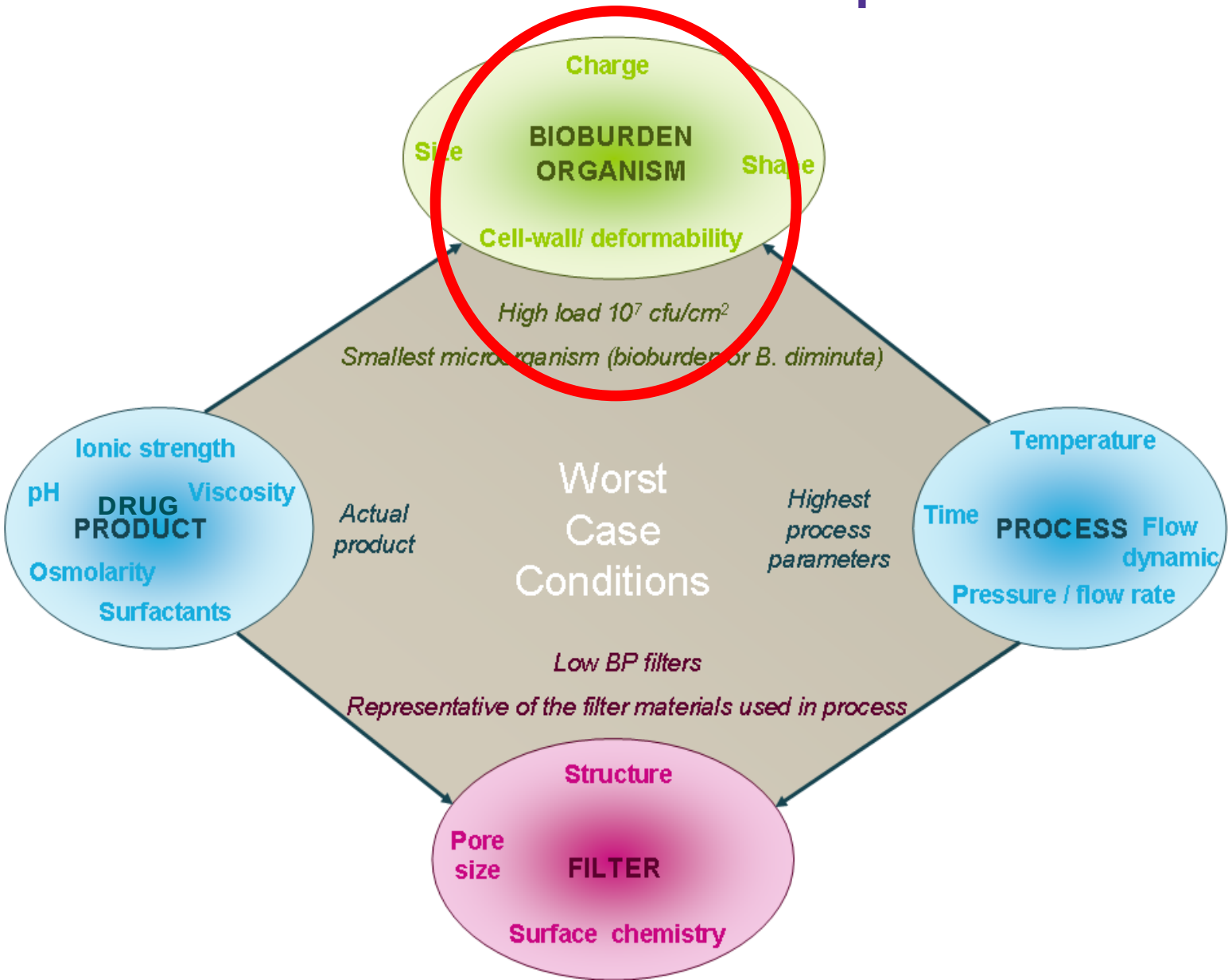


# Chemical compatibility

## 4.5.2 Chemical Compatibility

The chemical compatibility of the filter device has to be evaluated to avoid potential filter damage or alteration and to avoid fluid contamination by either leachables or particulates. Chemical compatibility testing should encompass the entire device and depends on the fluid, filtration temperature and contact time. Since there may be numerous chemical interactions between the filter device components and the process fluid or solvents, the typical chemical compatibility table provided by the filter manufacturer is commonly used as a starting point for further testing. Additional studies should be performed by the filter user. Common chemical compatibility tests include integrity, tensile strength, NVR, extractables, particulates, flow rate, optical or scanning electron microscopy (SEM), burst pressure and membrane / O-ring thickness. *(24)* Use of a combination of tests is recommended, since a single test might not be able to detect subtle incompatibilities.

**Compatibility – filters / filter assembly / bags, connectors ……**

**Compatibility – Testing or Certification**

# Product-wetted integrity tests

Differences between product wetted integrity test values and reference fluid wetted integrity test values are due to differences in test gas solubility, the diffusion constant and the surface tension of the wetting fluid.

The scaled-down study is only the first part of the validation; the second part consists of obtaining additional ongoing product attribute data. This may include measuring the product surface tension periodically and comparing it to an established standard or periodically measuring the bubble point ratio. In some applications, mixing the process fluid with the wetting fluid should be avoided,

Good to have value established at a temperature (± °4C) at which you intend to perform the test on shop floor

# Product adsorption

## 4.5.3 Adsorption

Adsorption is a mechanism of product binding to the membrane and may affect the product composition and concentration. Adsorptive filter materials include membrane, hardware and support materials. Flow rate, product concentration, contact time, preservative concentration, temperature and pH are some of the factors that can affect the level of adsorption. For filtration processes in which the level of adsorption is tolerable but still relatively high, it may be helpful to pool the product prior to filling so that the mass of material adsorbed is minimal in comparison to the mass of the material in the upstream process volume. During process development, adsorption tests are typically performed at small scale and confirmed at large scale. These tests can also be used to establish potential pretreatment (e.g., buffer flush, soaking) options, operational parameters or membrane polymer choices.

# Bacterial retention

After the test organism's viability within the product has been established, the challenge methodology and protocol should be developed. Bacterial challenge test conditions should simulate the production process. Since bacterial challenge tests are generally performed in a laboratory, the methodology should be scaled accordingly. The flux should be scaled to an equivalent flow rate per unit area, as expressed in (ml/min)/cm² of filter surface area. If filtration is regulated by pressure, the challenge test pressure should be at least equal to the maximum processing pressure. If questions

# What are Extractables & Leachables?

**Oligomers**
PVDF, PP, PE
Etc.

**Additives and Degradants**
Antioxidants, UV stabilizers,
Slip agents, etc.

**Residual Solvents**

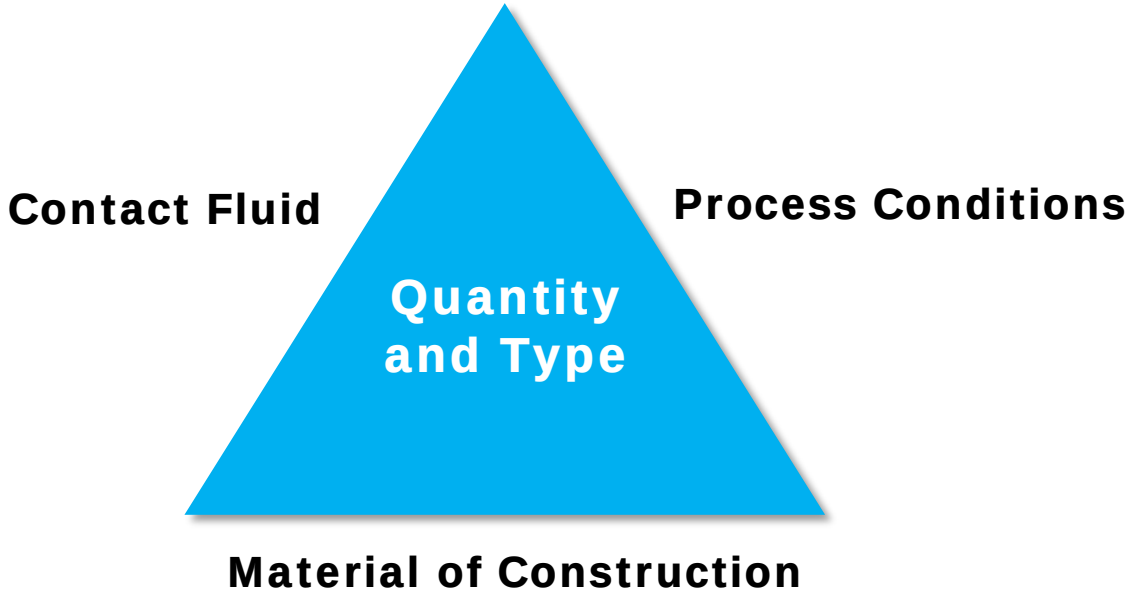
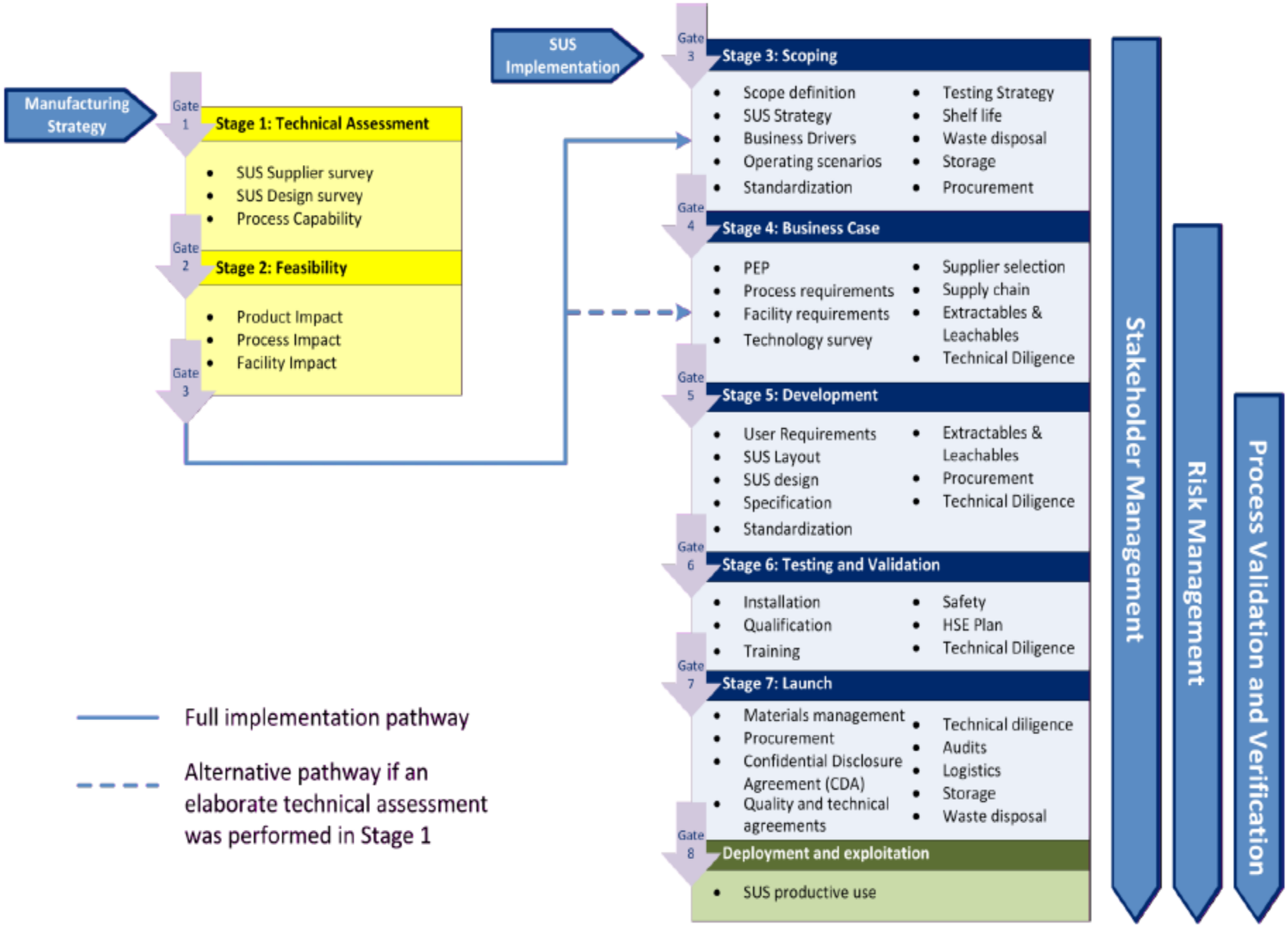
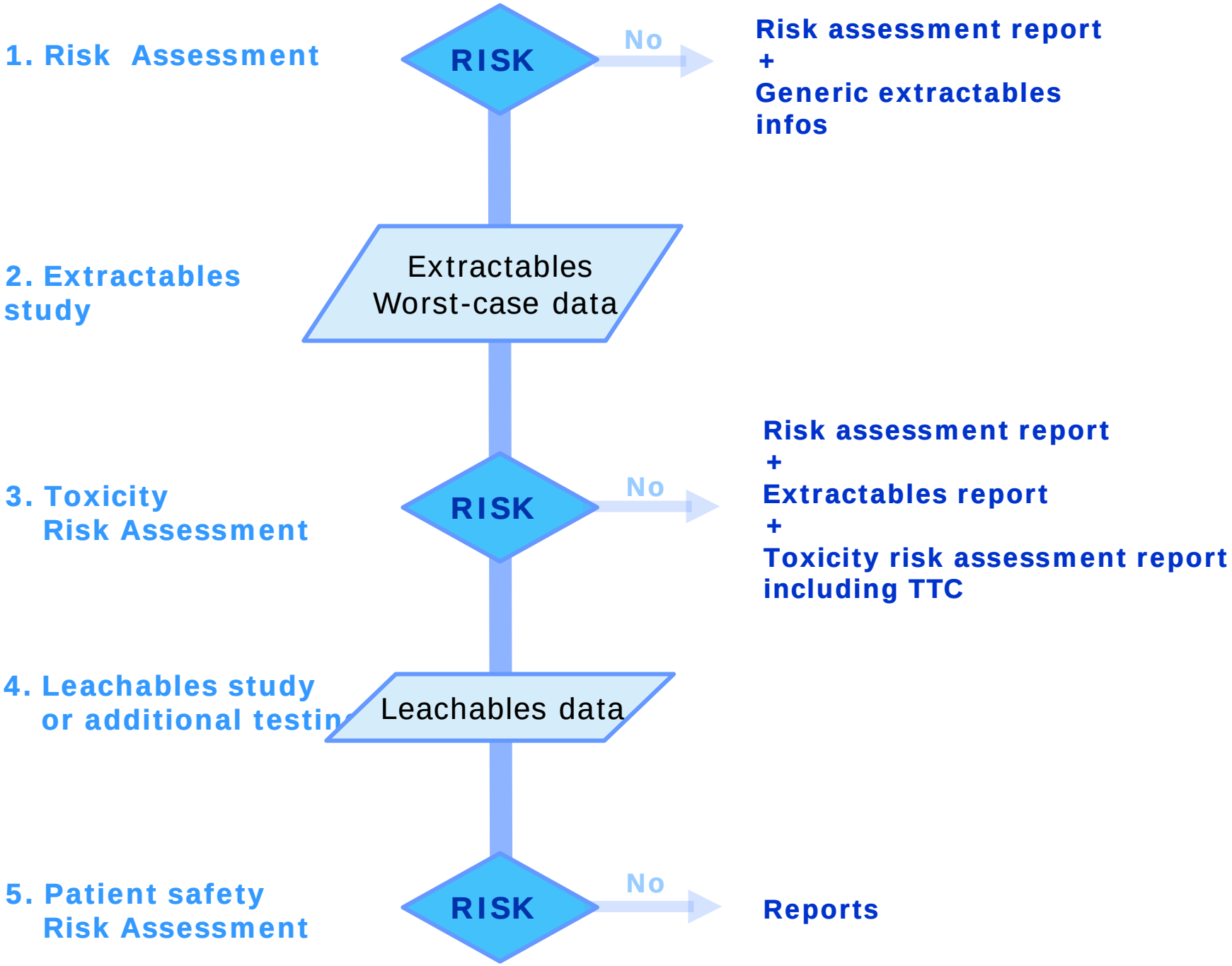


**Figure 7.1-1** SUS Implementation Road Map




1. Risk Assessment
RISK
No
Risk assessment report
+
Generic extractables
infos
2. Extractables
study
Extractables
Worst-case data
3. Toxicity
Risk Assessment
RISK
No
Risk assessment report
+
Extractables report
+
Toxicity risk assessment report
including TTC
4. Leachables study
or additional testin
Leachables data
5. Patient safety
Risk Assessment
RISK
No
Reports

# Conclusion

- Defining the 8 elements of aseptic filter validation makes the validation
- Defining the “worst case” parameters to be validated
- Ensuring the verify the parameters during the scale up / exhibit batches to prove the correlation between the validated and practices on the shop floor

# Some Useful Regulatory References

**FDA**

Quality Systems Approach to Pharmaceutical Current Good Manufacturing Practice Regulations

Sterile Drug Products Produced by Aseptic Processing - Current Good Manufacturing Practice

**PICS**

PE 009-7 GMP Guide (especially Annex 1 and Annex 20)

**WHO**

WHO Guideline on Quality Risk Management (Draft Working copy) (2010)

WHO Technical Report Series 908, Annex 7 (2001)

**ICH**

Q10 Pharmaceutical Quality System

Q9 Quality Risk Management

**PDA**

TR44 Quality Risk Management for Aseptic Processing

TR26 Sterilizing Filtration of Liquids

TR40 Sterilising Filtration of Gases

**PQRI (Product Quality Research Institute)**

Post Approval Changes for Sterile Products Working Group - Final Report April 19, 2007

# Thank You for your Attention!

Ramesh.raju@merckgroup.com