Defining a strategy for the Validation and Qualification of Sterile Filtration Processes of Investigational Medicinal Compounds

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Traditional Definition of Sterilizing Grade Performance

- Sterilizing filtration is the process of removing microorganisms from a fluid stream without adversely affecting product.

- Demonstrate removal of a standard test organism (Brevundimonas diminuta)

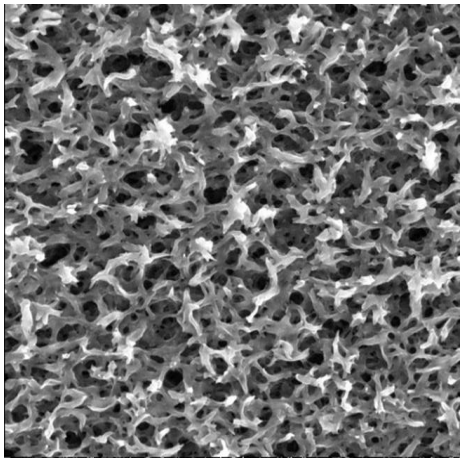
- At minimum concentrations of 10^7 cfu/cm^2

- ASTM F 838-05 is a standard TM inside which all sterilizing grade membranes can be compared

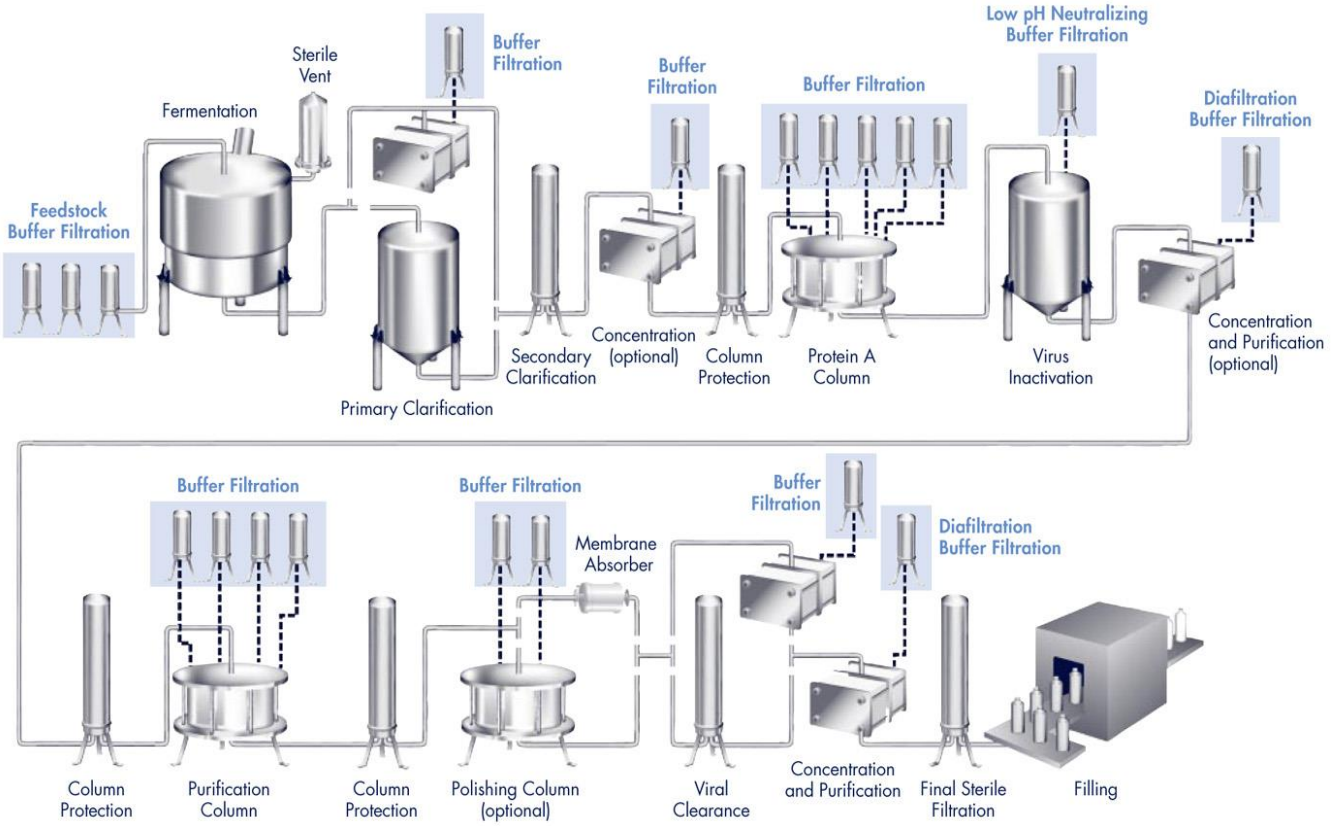
> "**A filter that reproducibly removes test microorganisms from the process stream, producing a sterile filtrate.**"
>
> *PDA® Technical report N°26, 2008*

Definition – Filter functionality

- Sterilizing-grade designation is not pore size dependent
  - It is a functional definition
- Functionality is firstly defined by **qualification testing**
  - Filter manufacturer
- Functionality is secondly defined by **validation**
  - Final user



Biotech Manufacturing Process



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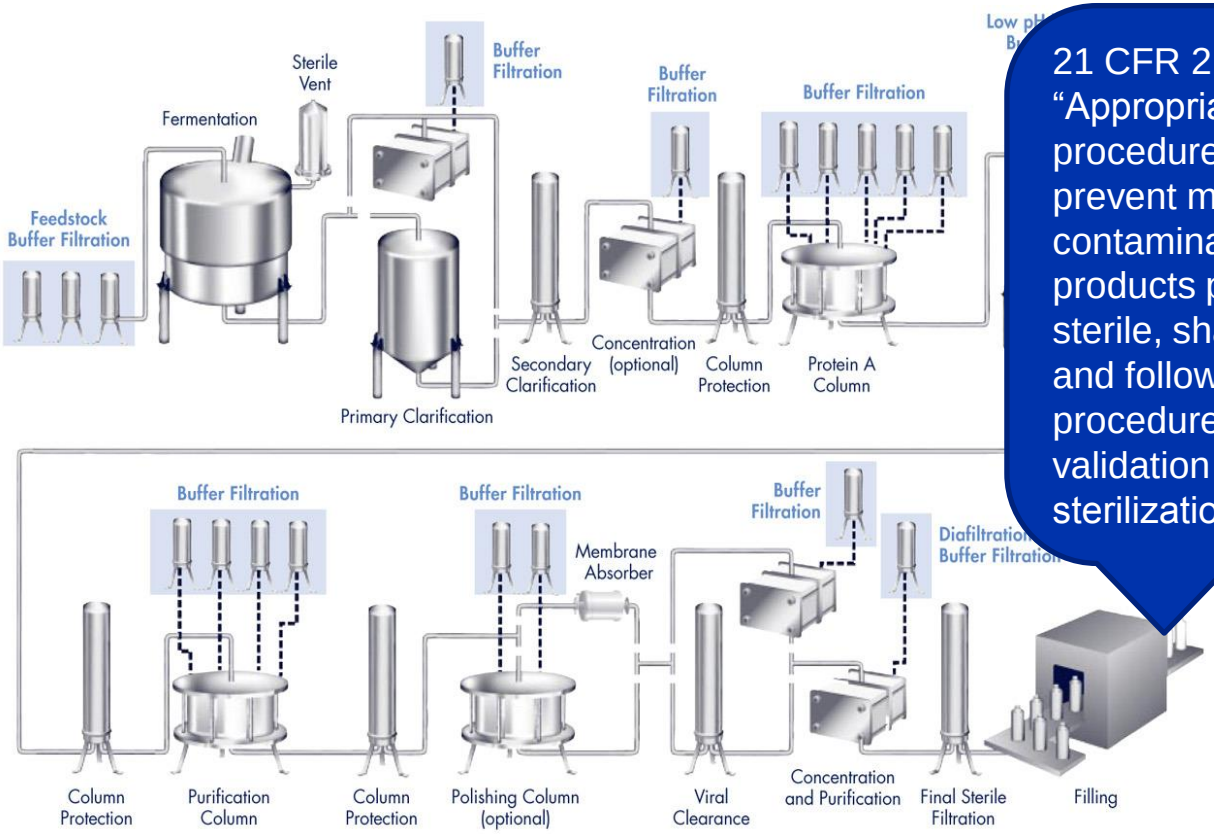
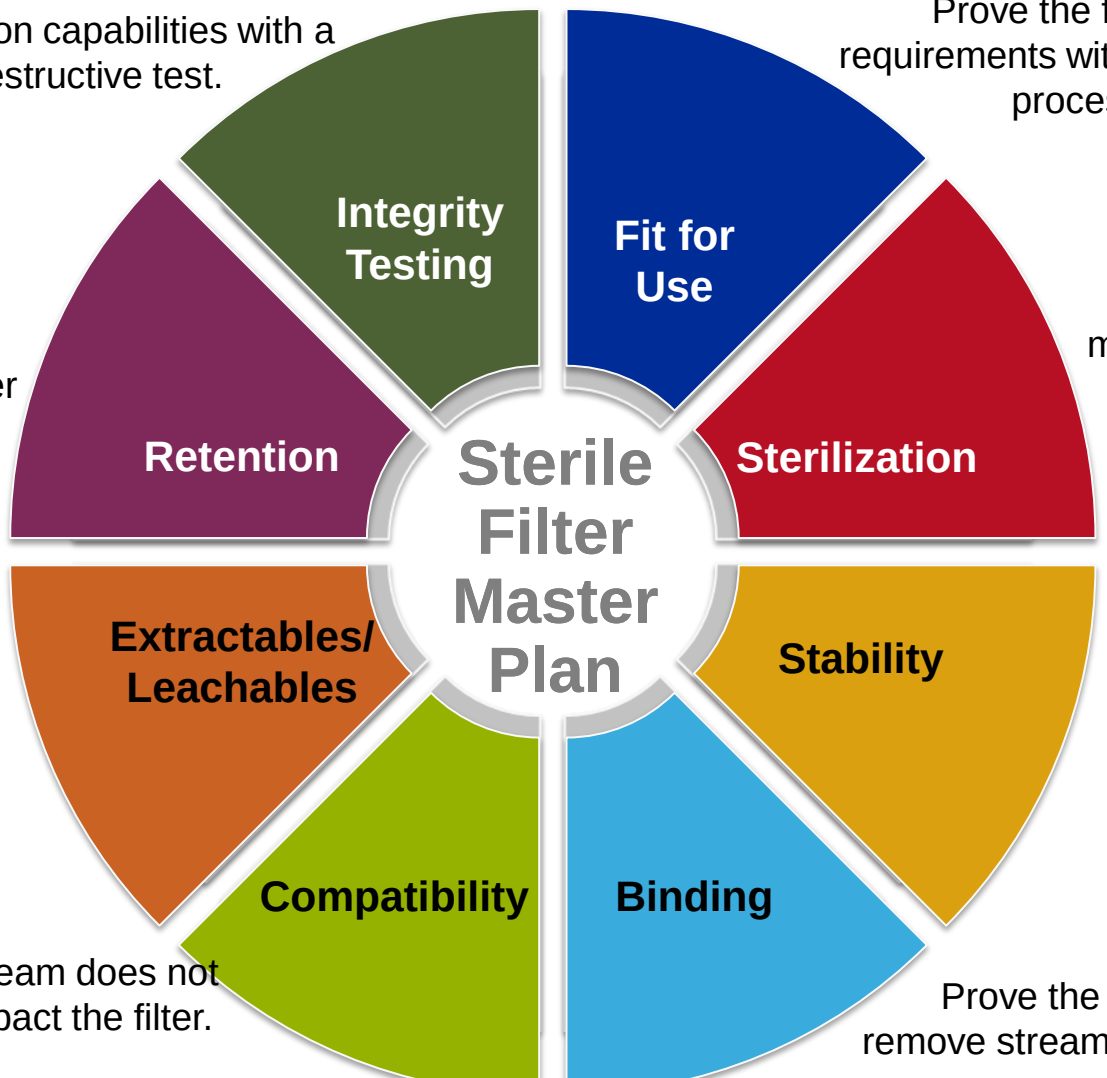


21 CFR 211.113(b) "Appropriate written procedures, designed to prevent microbiological contamination of drug products purporting to be sterile, shall be established and followed. Such procedures shall include validation of any sterilization process."

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.

Prove the stream does not adversely impact the filter.

Prove the filter does not remove stream components.

What standard to apply for development phase products ?

Phase 1 Guidance - FDA

FDA: Guidance for Industry CGMP for Phase 1 Investigational Drugs

C. Sterile Products/Aseptically Processed Products

Because product sterility is a critical element of human subject safety, you should take special precautions for phase 1 investigational drugs that are intended to be sterile. You should give thorough consideration to implementing appropriate controls for aseptic processing to ensure a sterile phase 1 investigational drug. **The guidance issued by FDA on aseptic processing is a good reference when using aseptic processing (Ref. 7)**. Particular manufacturing controls include:

Follows with a bullet list of controls (such as): media simulation, environmental monitoring, sterilization of components and devices, aseptic technique training, quality control requirements.

Early Phase Guidance - EU

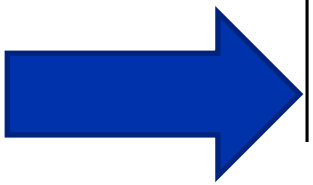
Medicinal Products for Human and Veterinary Use
Annex 13
Investigational Medicinal Products

17. Production processes for investigational medicinal products are not expected to be validated to the extent necessary for routine production but premises and equipment are expected to be qualified. **For sterile products, the validation of sterilising processes should be of the same standard as for products authorised for marketing.** Likewise, when required, virus inactivation/removal and that of other impurities of biological origin should be demonstrated, to assure the safety of biotechnologically derived

PIC/s Inspection Aide

Aide-memoire:
GMP PARTICULARITIES IN THE
MANUFACTURE OF MEDICINAL PRODUCTS
TO BE USED IN CLINICAL TRIALS
ON HUMAN SUBJECTS

PRODUCTION	Have critical parameters which were identified during development, been stated in writing?
Manufacturing operations	Have in-process controls which are primarily used to control the process, been identified in writing?
Field # 16, 17 and 18	Is due consideration by key personnel given to the key parameters, in-process controls, provisional production parameters gained from earlier development work and experience gained, in order to formulate the necessary instructions?
	Are the premises and equipment validated? List the protocol numbers and dates of the validation studies.
	For sterile products, are the sterilizing processes validated to the same extent as for sterile drugs authorised for marketing?



The stakes are high how do we get this right ?

Drug Development Objective

To develop a product that is:

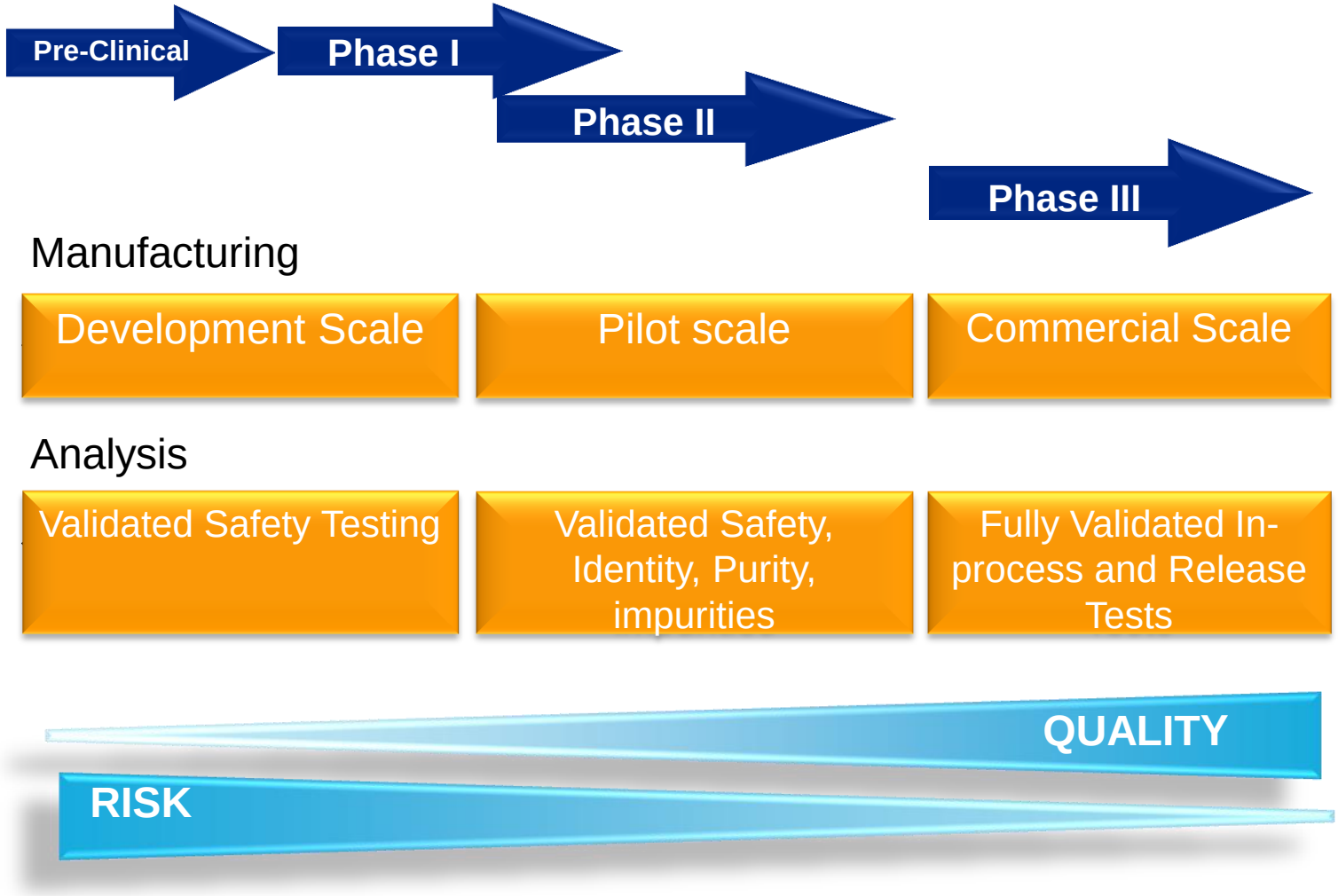
- High quality
- Approvable by Regulatory authorities
- Commercially viable

Quality will be achieved by getting

A characterized and consistent **PRODUCT**

A validated and reproducible **PROCESS**

Drug Development process



Early Phase Sterile Filter V&Q

Objectives

- Minimize the risk for patients
- Sterility is a critical element of safety
- Robust, reproducible and reliable results from clinical trials
- Commercial Viability - Gain knowledge to save time and money to design an optimized process for scale-up

Challenges

- Limited knowledge of product formulation
- Small amount of product available for testing
- Membrane chosen but device not definitive
- Process not well defined yet

How to overcome the challenges and meet the objectives?

Focus on These 3 Elements of Validation

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

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

Prove the stream does not adversely impact the filter.

Sterile Filter Compatibility

But, My process is not defined how can I approach this ?

I have no product available !

My formulation may change !

Compatibility Data Collection

Collect suppliers Information

- Manufacturer's compatibility tables
- Manufacturer's Validation Guides

	Guanidine Thiocyanate, 5M sol. aqueous solution	Helium gas	Hexane H.C. aliphatic	Hydrochloric Acid, 1 N (HCl) acid, inorganic	Hydrochloric Acid, 6N (HCl acid, inorganic	Hydrochloric Acid, conc. (HCl) acid, inorganic	Hydrofluoric Acid acid, inorganic	Hydrogen gas	Hydrogen Peroxide, 3% peroxide	Hydrogen Peroxide, 30% peroxide	Hydrogen Peroxide, 90% peroxide
Housing materials											
HDPE high density polyethylene	GR	R	LTD	R	R	R	R	R	R	R	NR
PP polypropylene	ND	R	NR	GR	TST	NR	NR	R	R	TST	R
PS polystyrene	ND	ND	NR	R	TST	NR	NR	ND	R	R	R
PVC polyvinyl chloride	ND	ND	NR	GR	TST	NR	NR	R	R	TST	R
MMA acrylic based copolymer	GR	ND	GR	GR	ND	ND	GNR	ND	ND	ND	ND
ABS acrylonitrile-butadiene-styrene polymer	ND	ND	GNR	GR	ND	ND	GNR	ND	ND	ND	ND
SAN styrene-acrylonitrile polymer	ND	ND	GR	ND	ND	ND	ND	ND	ND	ND	ND
PC polycarbonate	ND	R	NR	GR	TST	NR	NR	R	R	R	R
PET polyethylene terephthalate	ND	ND	R	GR	R	R	NR	R	R	R	R
EASTAR copolyester	ND	ND	R	ND	ND	ND	ND	ND	ND	ND	ND
Filter materials											
PP polypropylene	ND	R	NR	GR	TST	NR	NR	R	R	TST	R
PVC polyvinyl chloride	ND	ND	NR	GR	TST	NR	NR	R	R	TST	R
PC polycarbonate	R	R	R								
PTFE polytetrafluoroethylene	GR	R	R								
PVDF polyvinylidene fluoride	ND	TST	R								
MCE mixed cellulose esters	ND	R	GR								
PES polyether sulfone	ND	ND	GR								
NYL nylon	ND	R	R								

MILLIPORE

Validation Guide

Millipore Express® SHF and SHC Cartridge Filters

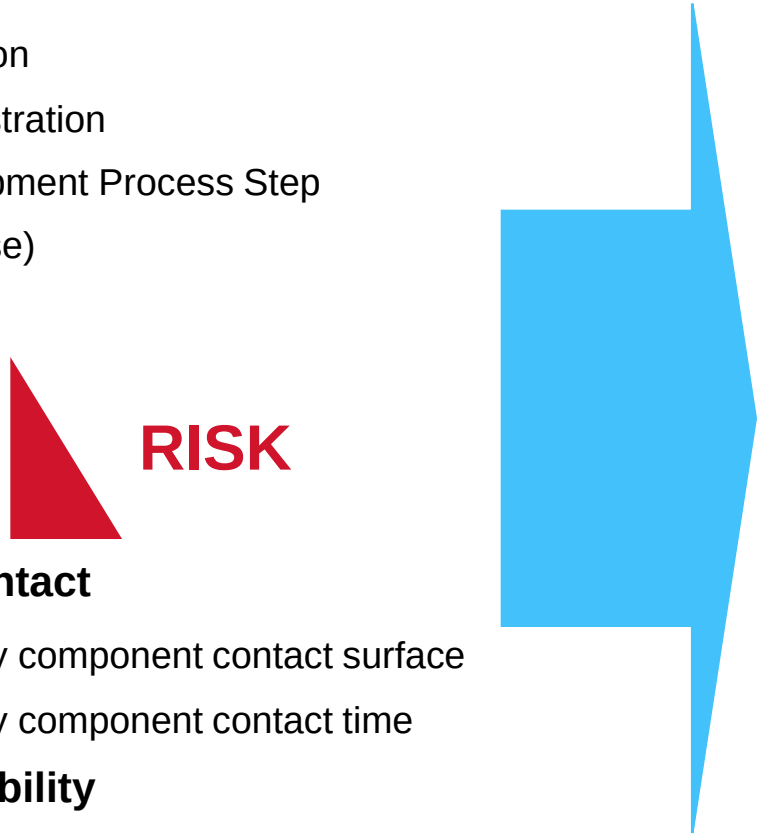
Opticap® XL and XLT Capsule Filters with Millipore Express SHF and SHC Membrane

Collect drug manufacturer's information

- Device fluid pathway
- Drug product solvents
- Key process parameters : Temperature, contact time

Risk Assessment per fluid pathway component

1. **Drug product**
   - Drug Indication
   - Drug Administration
   - Drug Development Process Step
   - (Clinical phase)
2. **Process step**
   - Upstream
   - Downstream
   - Final Fill
3. **Drug product contact**
   - Fluid pathway component contact surface
   - Fluid pathway component contact time
4. **Proof of compatibility**
   - Documented historic of similar conditions
   - Suppliers data availability



Certification

Any possible interaction between the selected components and The Drug Product formulation is assessed using qualification docs, compatibility charts, literature and past experience.

- Review of processing conditions
- Identification of pharmaceutical product solvent
- Scientific rationale and conclusion based on comparison of processing conditions and product solvent

* Membrane component: **Polyvinylidene fluoride (PVDF)**

	Recommendation	Presence in Product
Acetone	Not recommended	☐ Yes / ☒ No
Alconox > 1%	To be tested	☐ Yes / ☒ No
Ammonium Sulphate salt saturated	Not recommended	☐ Yes / ☒ No
Boric Acid	To be tested	☐ Yes / ☒ No
Butyl Acetate	To be tested	☐ Yes / ☒ No
Cyclohexane	Not recommended	☐ Yes / ☒ No
Cyclohexanone	Not recommended	☐ Yes / ☒ No
Diethyl Pyrocarbonate > 0,2%	To be tested	☐ Yes / ☒ No
Dimethyl Sulfoxide	Not recommended	☐ Yes / ☒ No
Dimethyl Acetamide	Not recommended	☐ Yes / ☒ No
Dimethyl Formamide	Not recommended	☐ Yes / ☒ No

Testing with Drug Product

Rationale :

- Test of process fluid pathway (see risk assessment step)
- Simulation of longest contact time and max temperature

Study design :

- Definition of test parameters per process component tested (bag, filter, connector, tubing…)
- Test methods definition and development

Test results assessment :

- Comparison before and after exposure
- Acceptance criteria review
- Visual examination

"**Chemical compatibility** testing should encompass the **entire device** and depends on the **fluid, filtration temperature, and contact time**."

PDA® Technical report N°26, 2008

Retention: What are the requirements

"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"

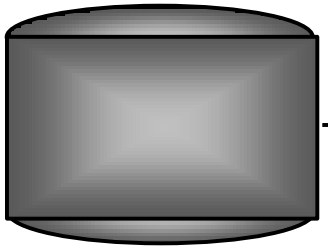
FDA Guideline on Sterile Drug Products Produced by Aseptic Processing (2004)

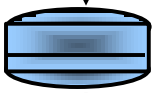
"The goal of bacterial retention validation studies is to have documented evidence demonstrating that the filtration process will consistently remove a high level of standard bacterium (or isolate)…under process condtions"

FDA Guideline on Sterile Drug Products Produced by Aseptic Processing (2004)

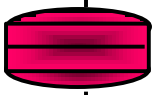
B. diminuta retention test process schematic

Actual drug product inoculated with *B. diminuta*





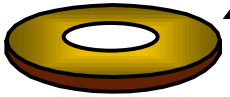
Sterilizing-Grade Test Filter (47 mm Durapore 0.22 µm disc)



Microbial Assay Filter (47 mm MEC)

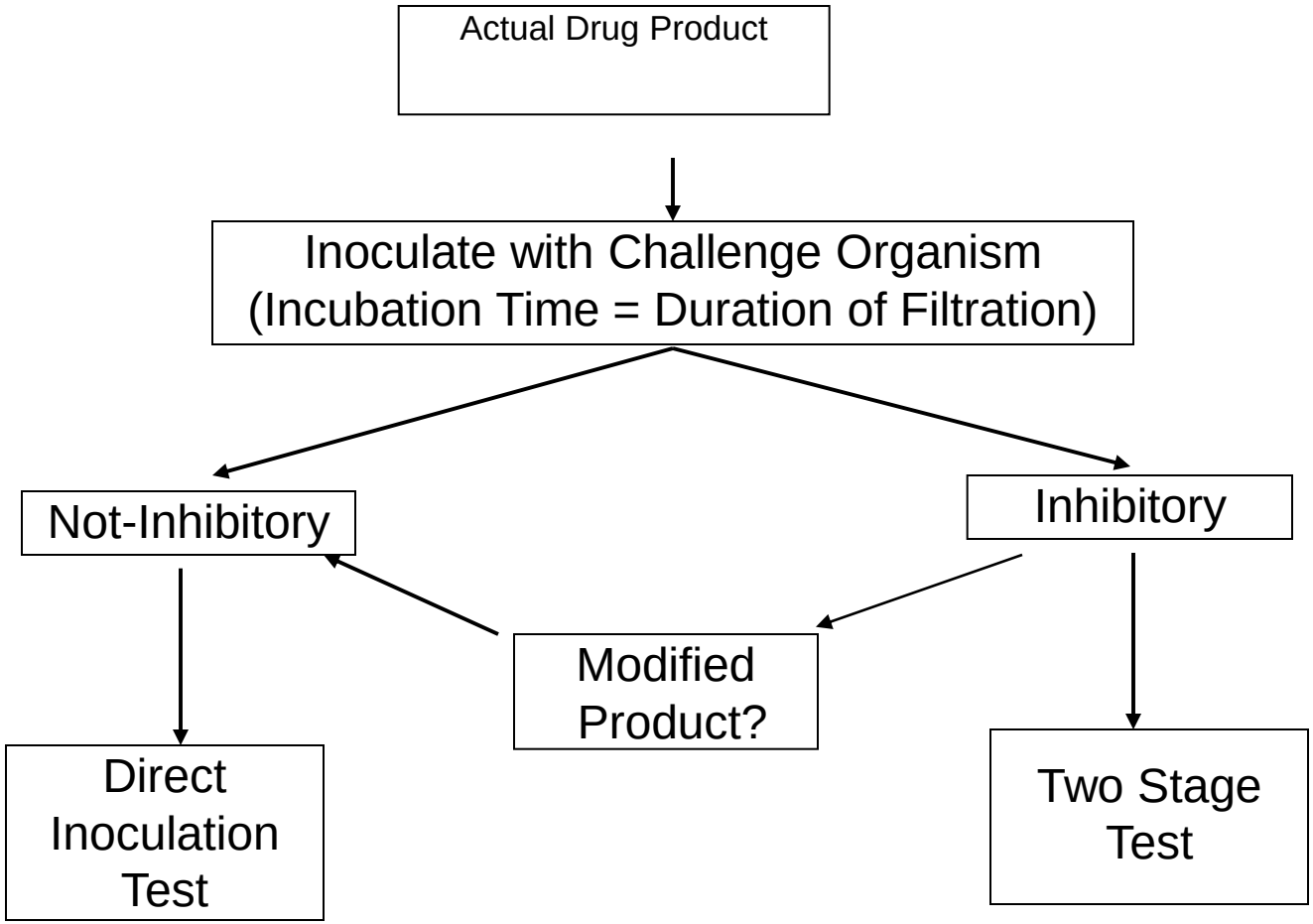
Waste

Plate MEC 47 mm disc on TSA



Incubate 7 days, Inspect for Growth

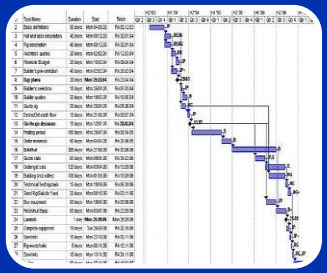
Test Design Considerations: Viability



Important: Identify YOUR situation

When **Required**

- Filter V&Q experience with highly similar forumulations / process parameters
- Leverage and risk assess – PDA TR26, The matrix approach (R. Levy)



As soon as **practical**

- Difficult to filter sterilize / have experience
- Not a challenging formulation / little experience

As soon as **possible**

- Difficult to filter sterilize products
- No Prior Experience

The value of manufacturing history:

You should be able to leverage historical success with similar formulations, filtration dynamics, membrane types, and process parameters.

- Using prior history of Validated and Efficacious Sterile Filtration to Assess Risk
- This could satisfy the FDA Phase 1 GMP Guidance
- May or May not fully satisfy EU Guidance but at very least will give a point of "defense" and demonstrate some diligence

Profiles of formulations that are difficult to filter sterilize:

- Oil and water emulsions
- liposomes
- Any nanoparticle or micelle containing solution
- Solutions containing a salt and a surfactant such as PEG or Tween 80 especially if other plugging ingredients like protein in the solution

Bacterial Retention Screening Studies

A screening study is a one disc retention study

- Those developing product formulations that are difficult to filter sterilize

Should,

- In addition to filter sizing and capacity testing conduct Bacterial Retention Screening

Why,

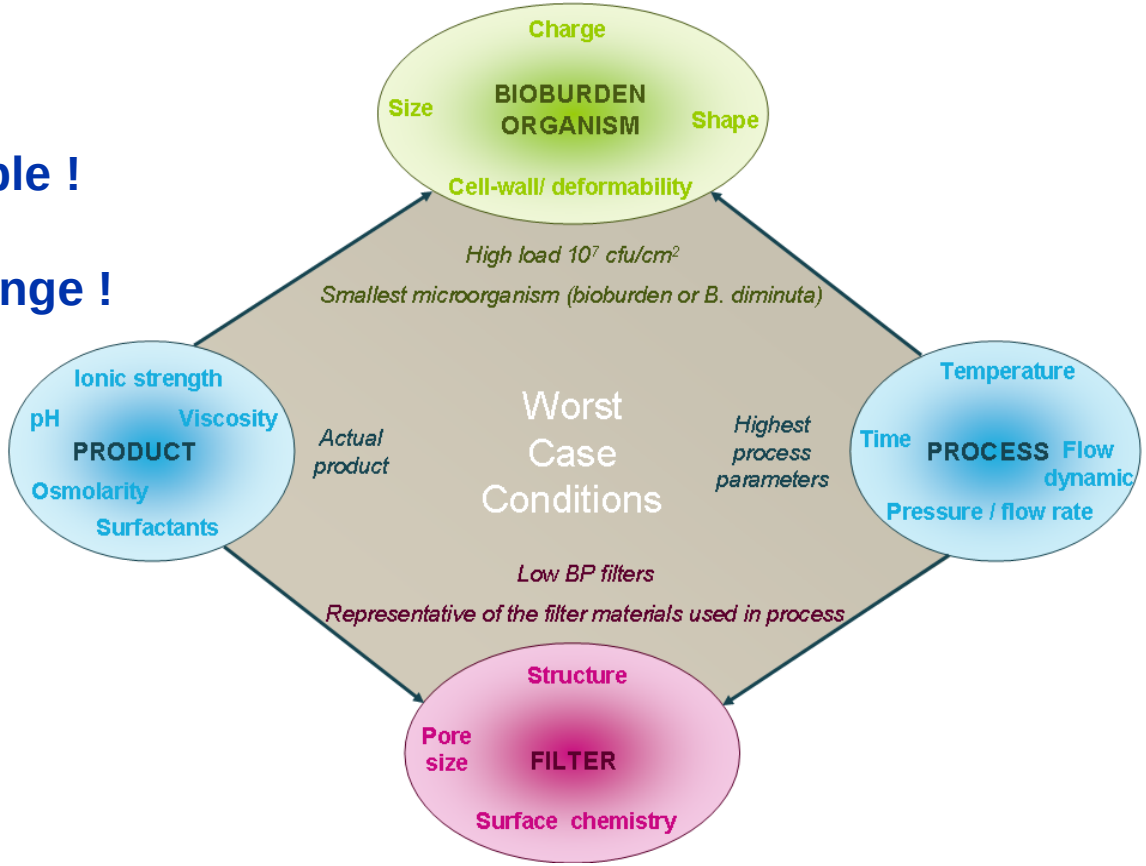
- Modifications to filter train or process parameters are easier to implement earlier in process development

Retention – Defining the Worst-case Conditions

But, My process is not defined how can I approach this ?

I have no product available !

My formulation may change !



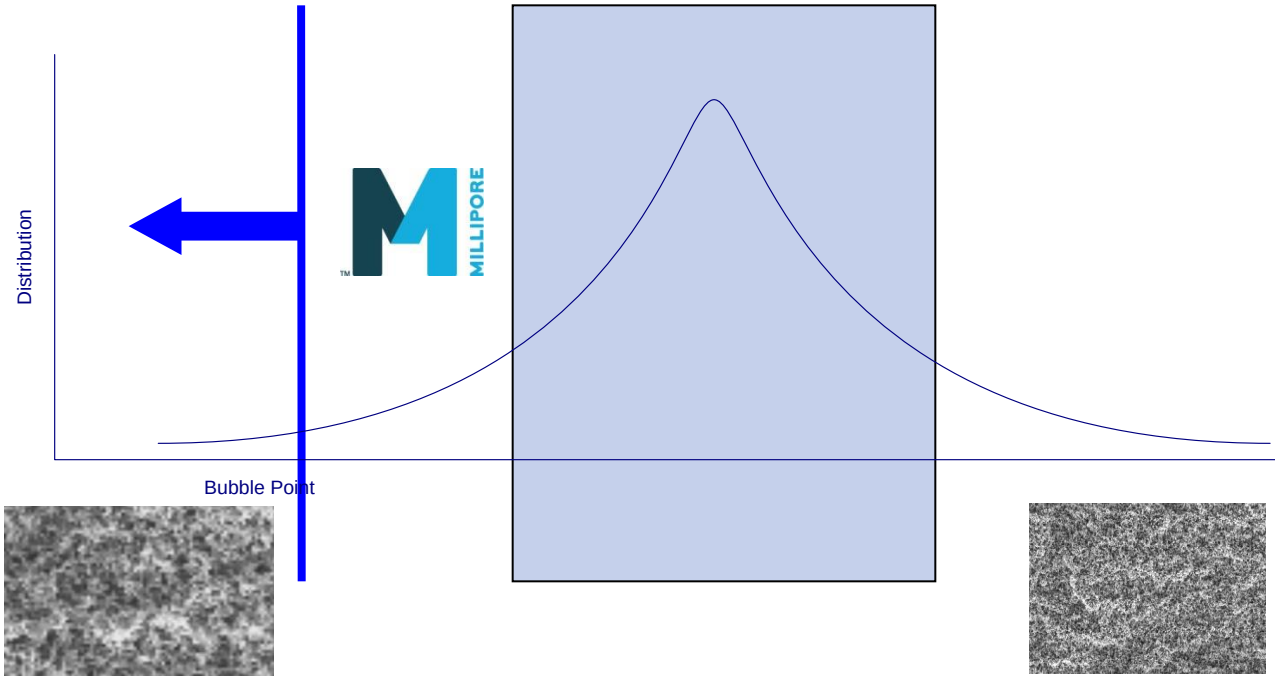
Filters - Worst case filters

Low BP Filters

Recent focus from Regulators and “Industry” on the validity of the 10%

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

Worst-Case Selection Threshold



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"

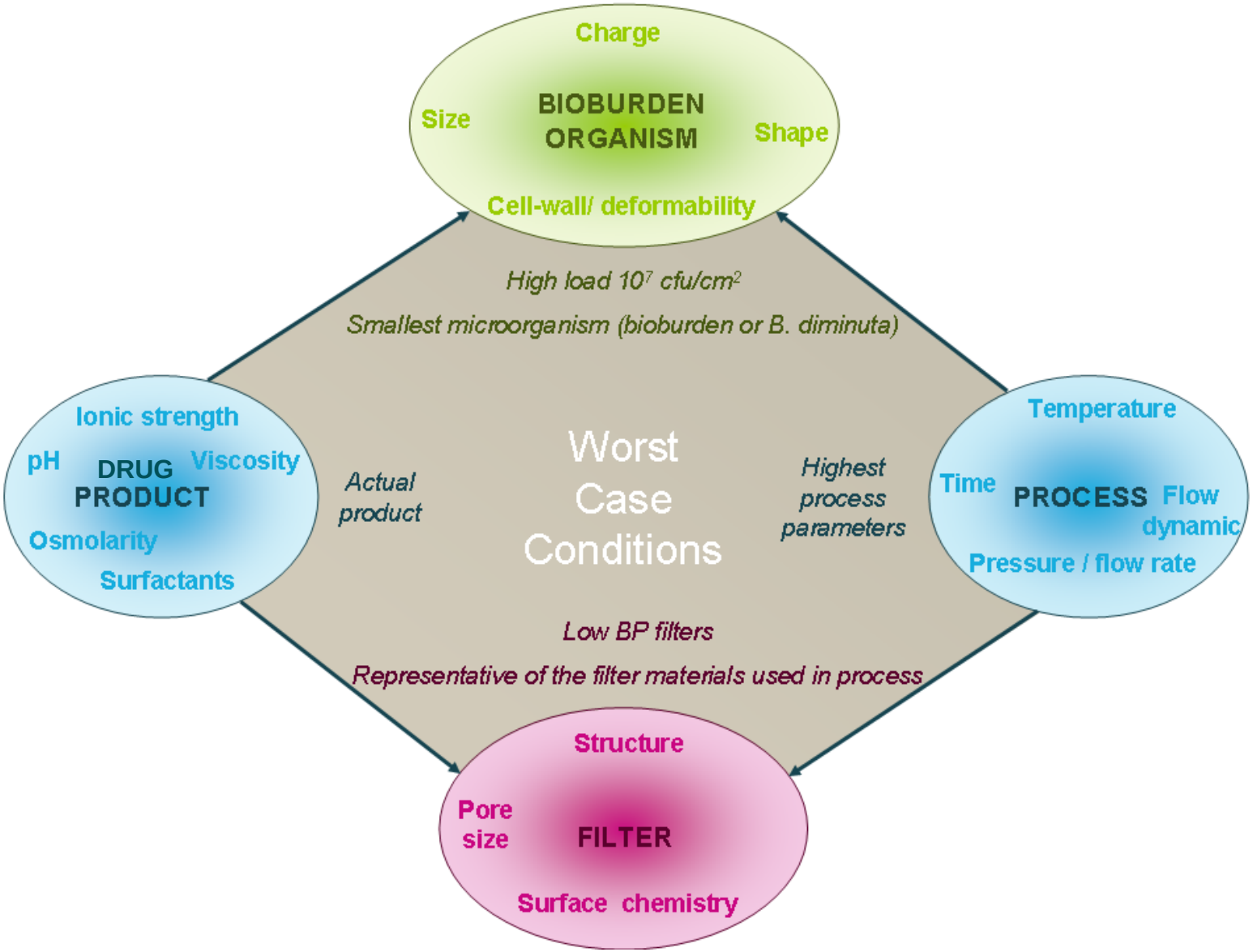
More and more observations & comments from FDA & EMEA auditors

Know your bioburden - Review environmental monitoring program results to identify small water-bourne 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

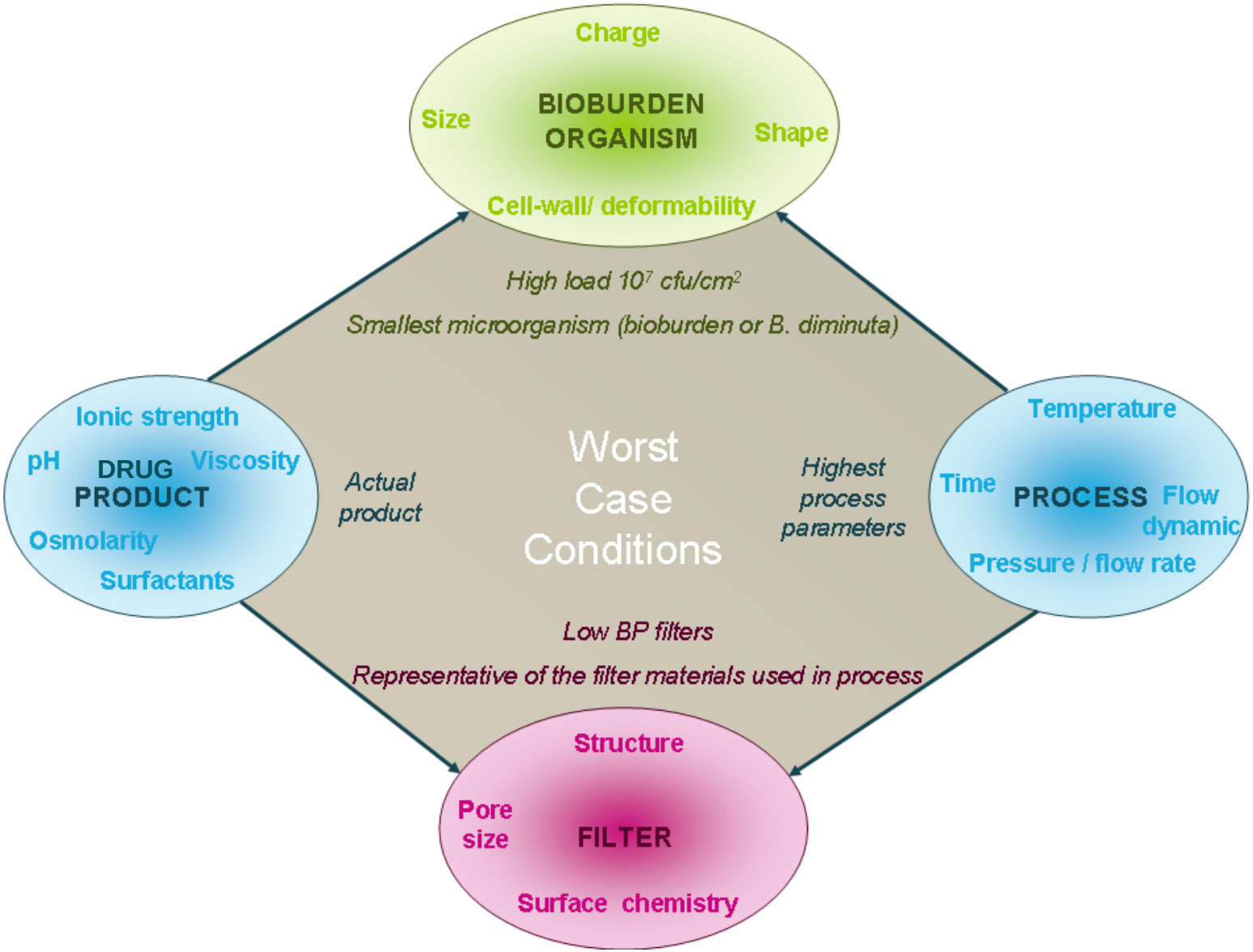
Defining the worst case conditions



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

Defining the worst case conditions



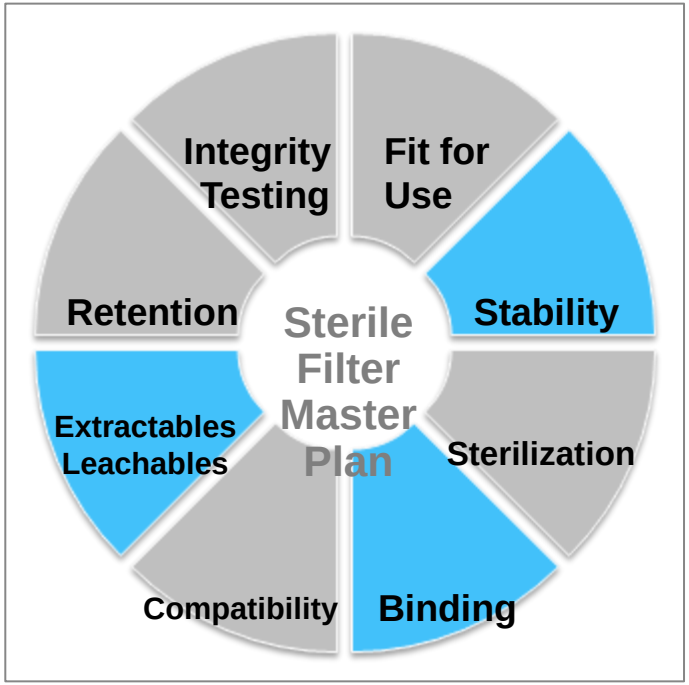
Process Parameters – Worst case conditions

	Main effect	Worst-case	
Pressure or Flow rate / capacity	Retention mechanism	Highest	→ Use Vmax to validate design space for capacity
Filtration time	Grow-through Bio-burden proliferation	Highest	→Include any static holding time as well as nonroutine interventions & events
Hydraulic shock	Blow-through	Highest	→ In-line integrity testing
Temperature	Membrane compatibility Bio-burden proliferation		

Reality: Retention study requires the MOST Product, a lab partner finds a solutions

150 Liters through a 4” filter	• 107 ml/cm^2 • 1.5 L per filter x 4 = 6 Liters
Recirculation	• Minimum working vol. 200mL/filter • Pump aggressive on sensitive molecules
Reporcessing	• Minimum working vol. 50 mL • System “open” higher risk of contamination

Extractables and Leachables: What are the 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

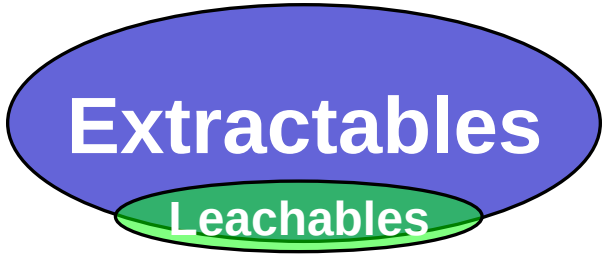
Definition - Extractable and Leachable Substances

Extractables

- Extracted from plastic or elastomeric materials in solvents under aggressive conditions.
- Determined under “worst-case” conditions (Model Stream approach)

Leachables

- Compounds that leach from the plastic or elastomeric materials into actual drug product under normal use conditions.
- Determined with the product under normal processing/storage conditions.



Extractables & Leachables Testing have Different Goals...

- **Extractables Studies**:

To identify and quantify as many compounds as possible that have **the potential** to become leachables

- **Extractables testing is quite attainable for development phase products because the model solvent approach is used**

- **Leachables Studies**:

To identify and quantify as many compounds as possible that migrate from the filtration process or storage systems into the actual drug product

- **Leachables evaluation starts with a well defined extractables study.**

Regulatory Agencies expectations

“CBER recommends **a risk-based approach** be taken in evaluating extractables and leachables where you take multiple aspects into account (e.g., indication, safety issues, product characteristics, dosage, formulation, and stability profile).

" **If there is no relevant risk** associated with the (material in question), "**vendor data can be cross referenced** and a detailed justification for the applicability of these data and a justification for no additional testing should be submitted,"

Where there is relevant risk, **the drug sponsor may have to determine toxicity based on maximum dosage** of potential leachables based on extractables data.

If the maximum dosage of potential leachables presents a **safety risk, leachable evaluation and testing may be necessary**.

Additionally**, if product quality could be affected** by potential leachables, studies may need to be performed **to assess the effect** on product quality, including efficacy."

Destry M. Sillivan - Senior Regulatory Review Officer, CBER

IBC's 7th International Single Use Applications for Biopharmaceutical Manufacturing Conference, la Jolla, CA, June 14, 2010

E&L Requirements for Final Filling Operations

- Operations downstream of Purification and Final Filling is generally considered greatest risk to patient
- Must demonstrate that patient is not at risk
- Must demonstrate product purity, efficacy, stability

"When possible, leachables should be evaluated when the final step in the production process is sterile filtration prior to filling." *PDA® Technical report N°26, 2008*

Recommended Steps for Drug Formulations in Development

- Incorporate Qbd by selecting well qualified and safe materials
- Generate extractables information in model solvents under worst-case conditions
- Perform risk assessment
- Conduct leachables studies as necessary
- Demonstrate non-toxicity

Extractable Substances Evaluation

Filter Extractables Study –

- Model solvent approach (no product necessary !)
- Worst-case conditions
  - Temperature
  - Time
  - Sterilization*
- Filters are static soaked. (no flushing)
- Generate a target compound profile
  - Total extractables quantified, individual compounds identified, linked to materials of construction

Summary

- **Patient Safety is more than satisfying the regulators**
  - *Clearly some regulatory inconsistencies exist*
  - *But, patients are served by "Designing with the end in mind"*
- **Traditional Challenges can be overcome**
  - *By focusing on what is most important (Comp. Retention E&L) one can overcome the traditional challenges of: process definition, product volume constraints*
- **A paradigm shift from "point in time" to life cycle effort**
  - *Helps to ensure that quality is designed into the process and verified at the earliest opportunity not a pre-defined "gate".*
  - *Process Understanding – extends into other products and your existing knowledge has VALUE and can be leveraged*
- **It helps to have a value added partner who can consult and advise**

Questions ?

and,

Discussion