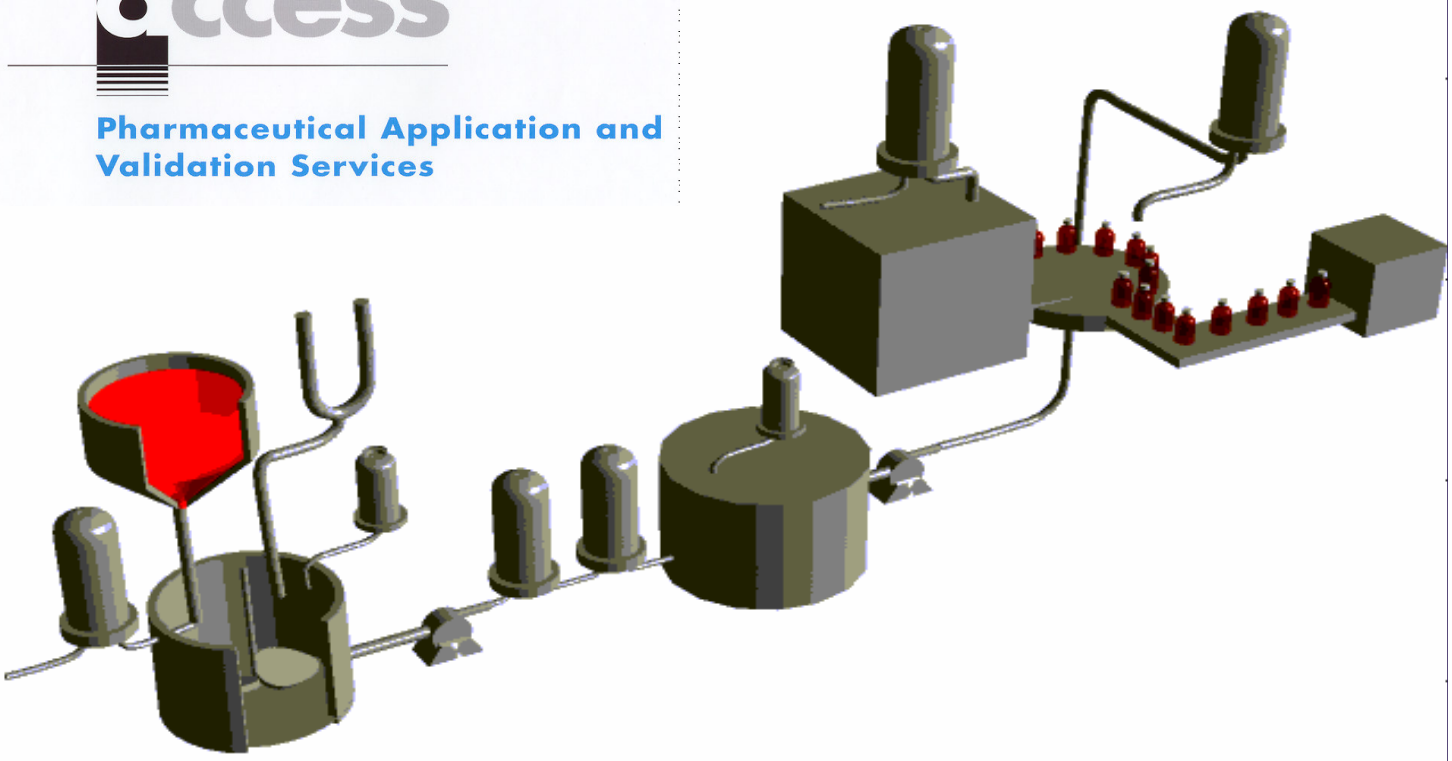
Validation Master Plan for Sterilising-Grade Filters

access℠

Pharmaceutical Application and Validation Services



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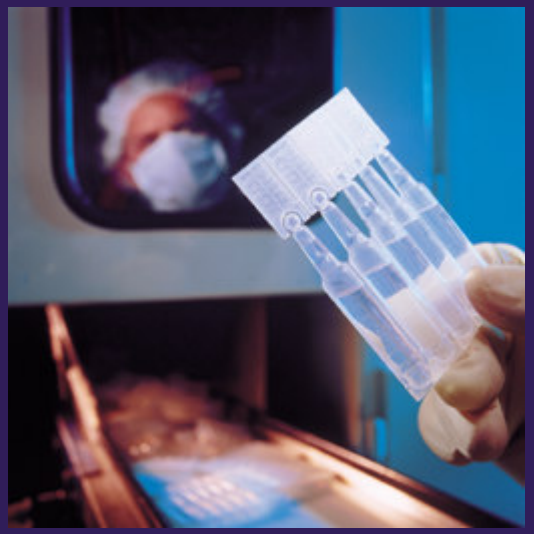
Factors Influencing Sterility Assurance Level

- Filter performance
- Filtration process design
  - System sizing and engineering
  - Standard Operating Procedure
- Validation of the filtration process
- Training of operators
- Process control and monitoring



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Perspectives

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focuses on increasing Sterility Assurance Level

- Reliable sterilizing-grade filters
- Rigorous QA/QC system
- Application expertise and validation services

Drug manufacturer

focuses on Potency Efficacy Purity Safety Compliance

- High quality filtration products
- Robust filtration process
- Sterility assurance

Sterilising-grade filter
Definition

- FDA Guideline on Sterile Drug Products Produced by Aseptic Processing

  1987

  - A sterilizing filter is one which, when challenged with the microorganism *Brevundimonas diminuta*, at a minimum concentration of 10^7 organisms per cm^2 of filter surface, will produce a sterile effluent.
  - Correlate filter performance with filter integrity testing.

  2004

  - A filter which, when appropriately validated, will remove all microorganisms from a fluid stream, producing sterile effluent.
  - A product filter's integrity test specification should be consistent with data generated during bacterial retention validation studies.

- PDA technical report 26 1998
  - A physical integrity test is meaningful only when it can be related to specific filter retention characteristics

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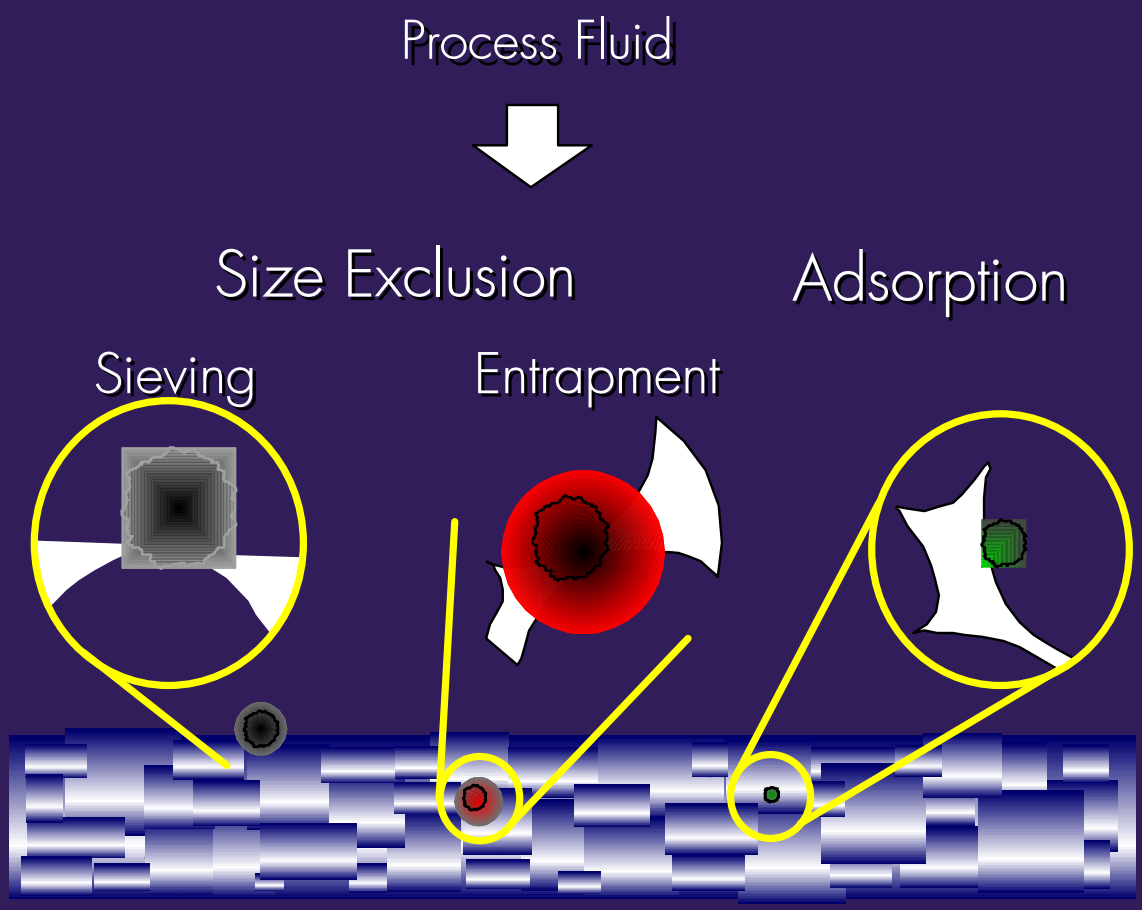
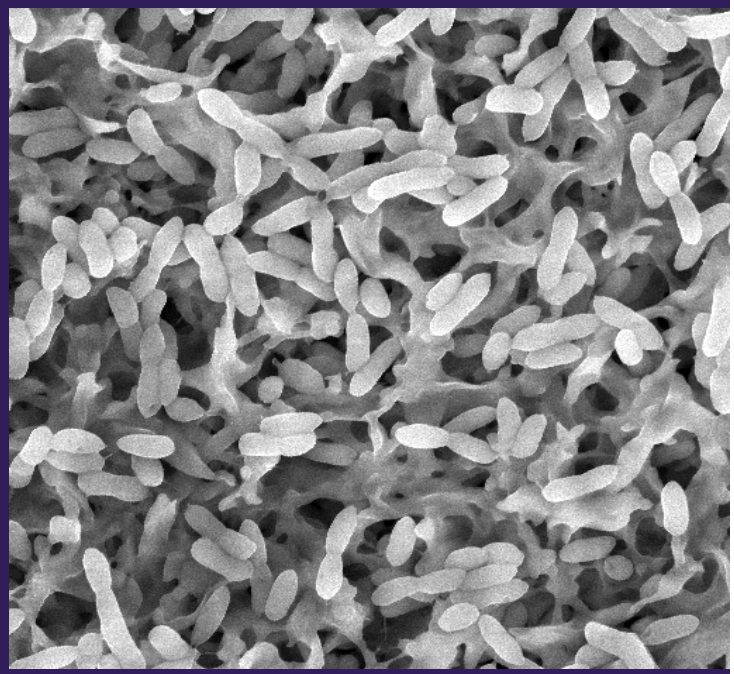
Sterilising-grade filter

How does a membrane retain ?

Retention Mechanisms





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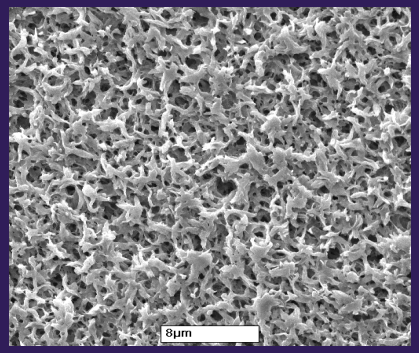
Sterilising-grade filter

Single layer & controlled pore size

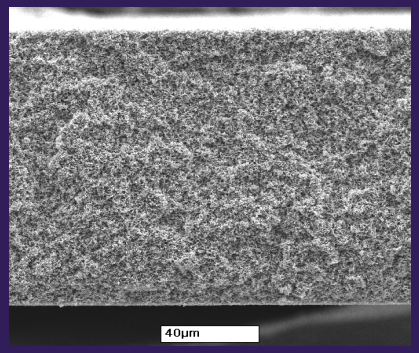
Size exclusion

controlled pore size distribution

less dependant on process conditions



Surface view

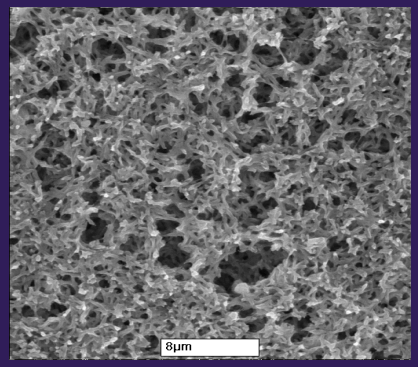


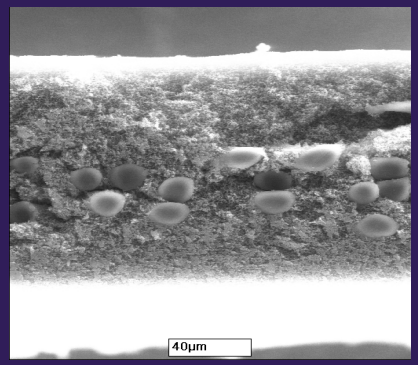
Cross section view

Adsorption

added thickness

double layer structure





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Validation Master Plan

- Validation of filter performance
  - Qualification of sterilising-grade filter
  - Specific validation study
- Validation of filtration process
  - Filter sterilisation
  - Filter integrity testing
  - Process control and monitoring
- Training and certification
- Quality Control & Quality Assurance system

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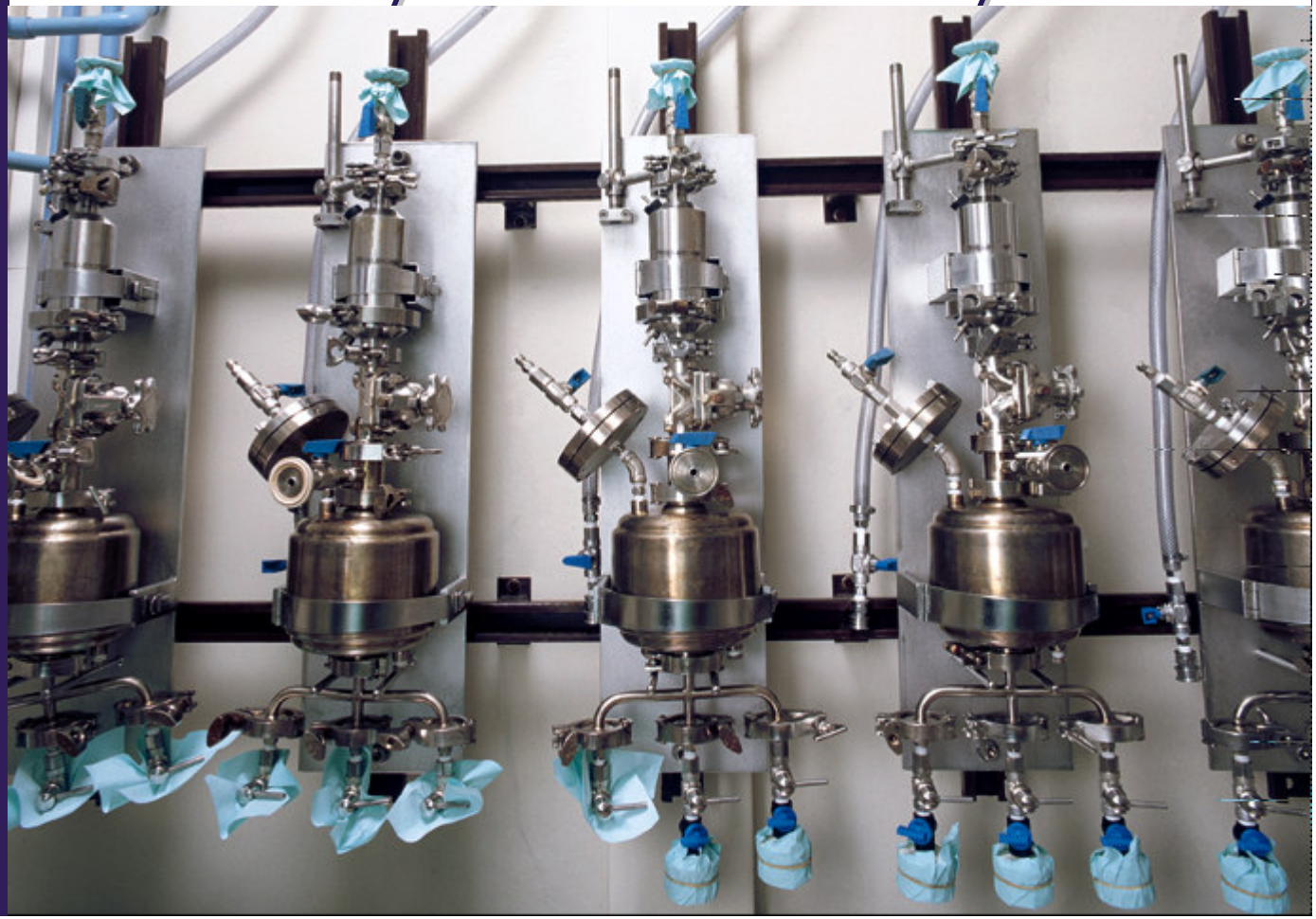
Manufacturing & Quality Assurance System



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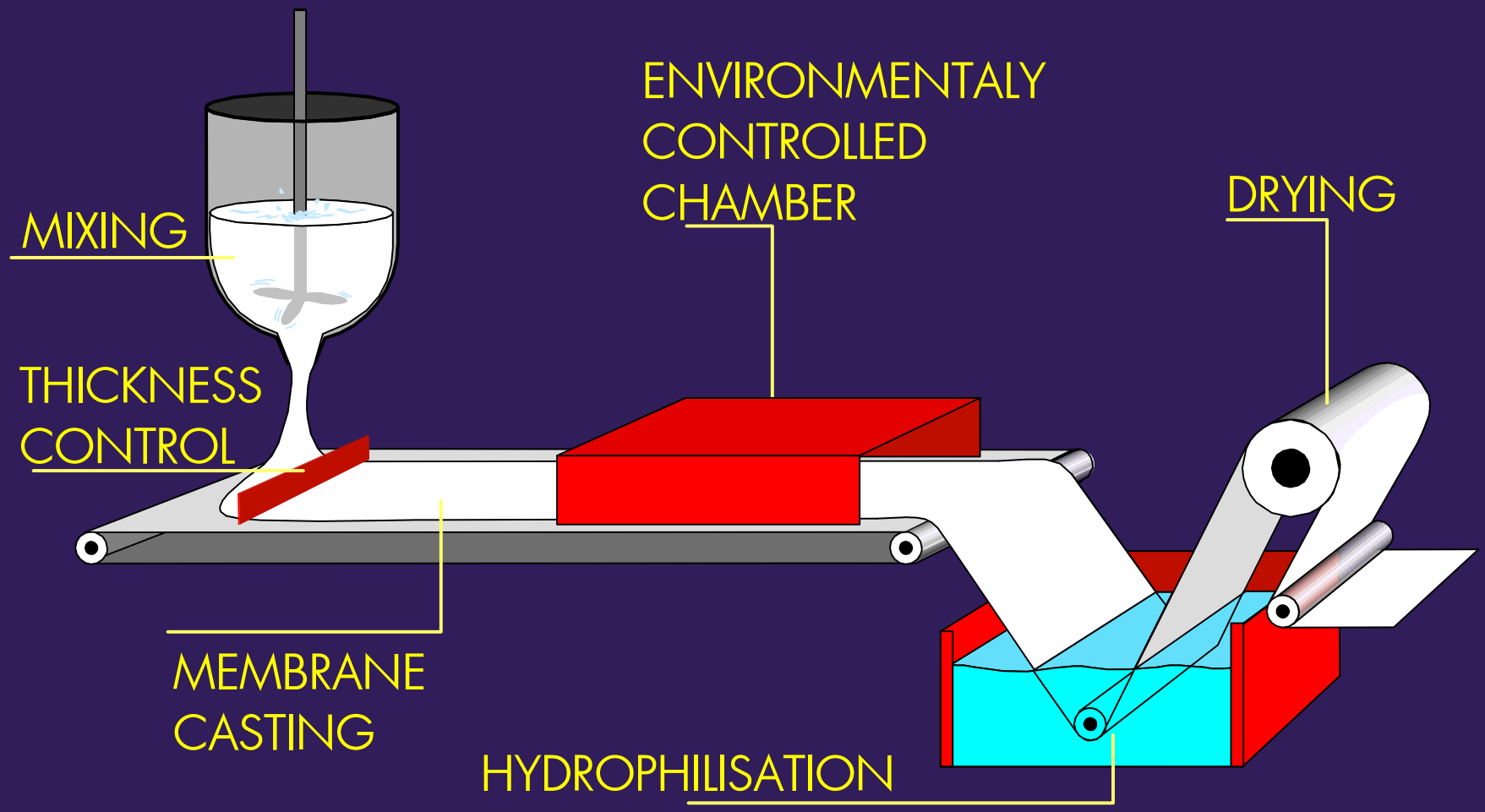
Membrane Casting



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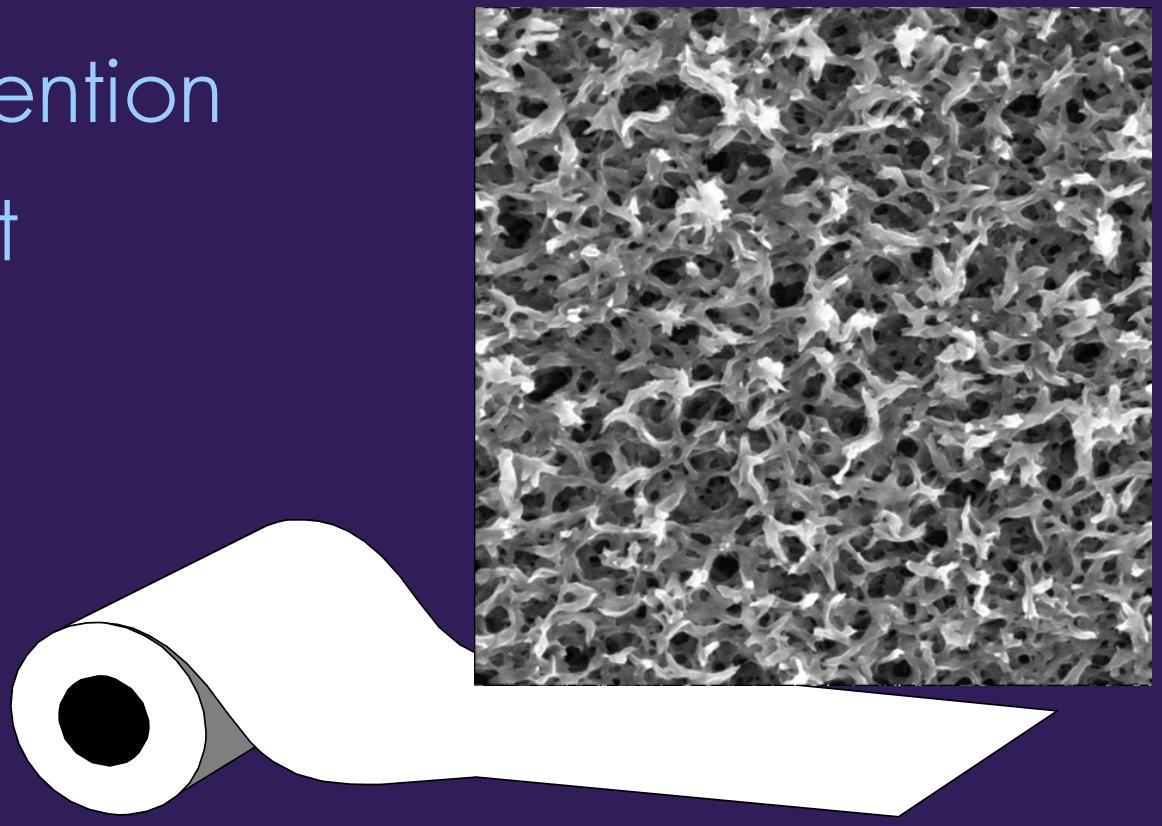
Membrane Quality Assurance

- Bacterial retention
- Bubble point
- Thickness
- Flow time
- Pyrogenicity
- Toxicity



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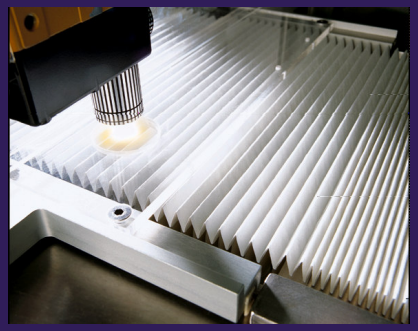
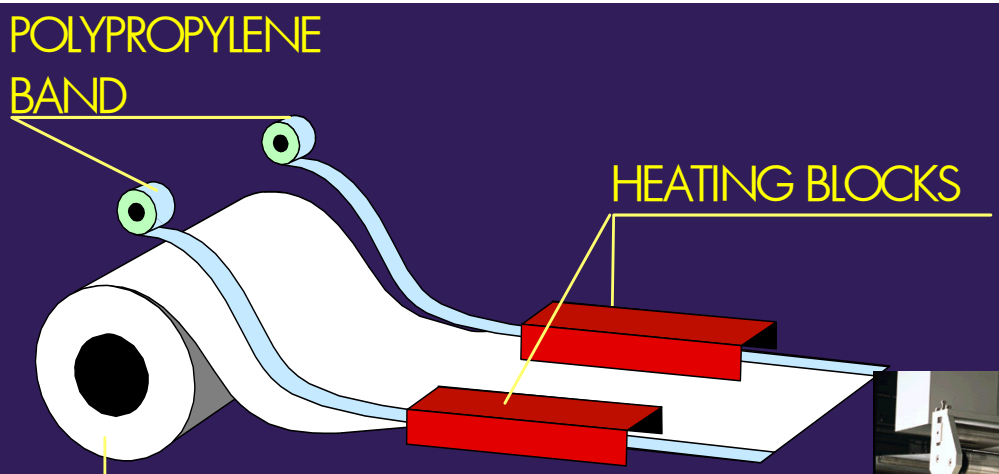
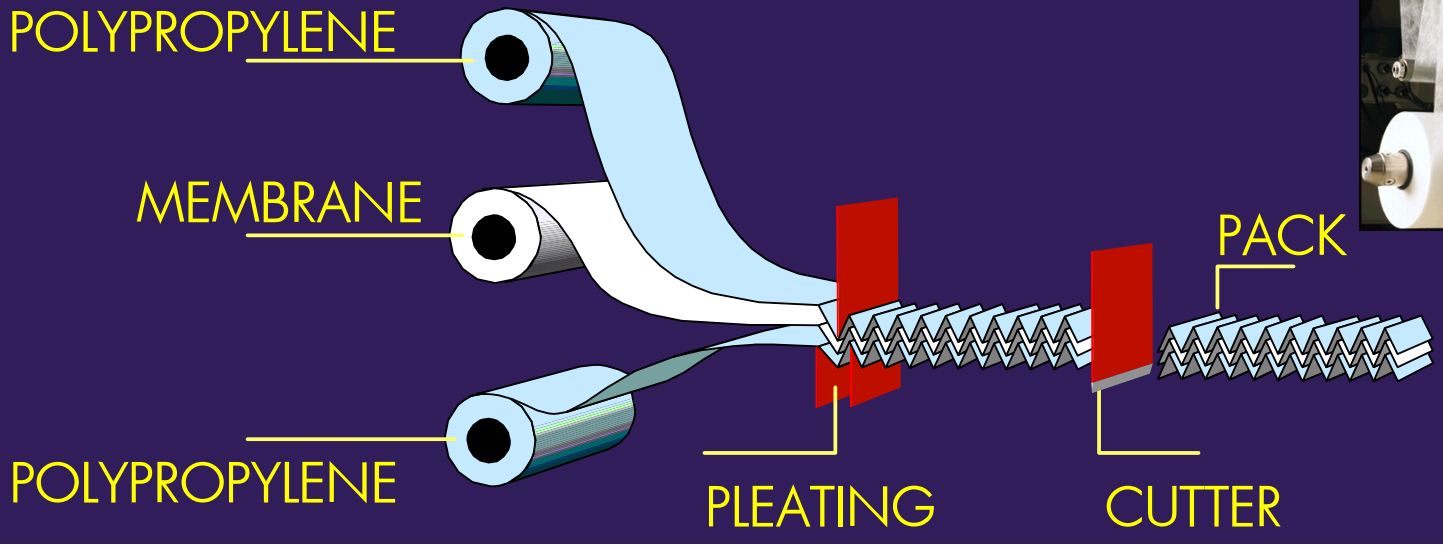
Lamination & Pleating







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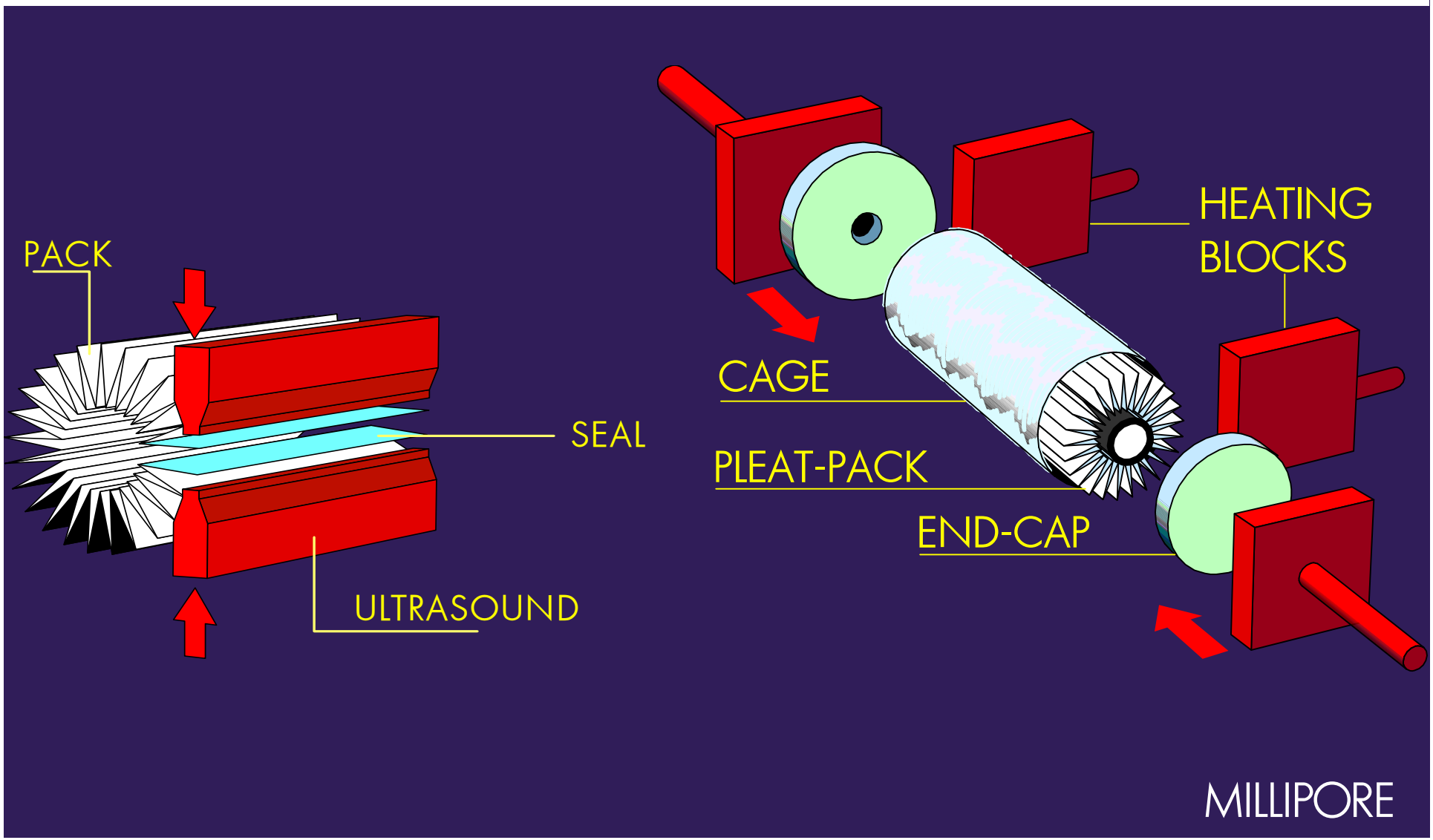
Seaming & End capping



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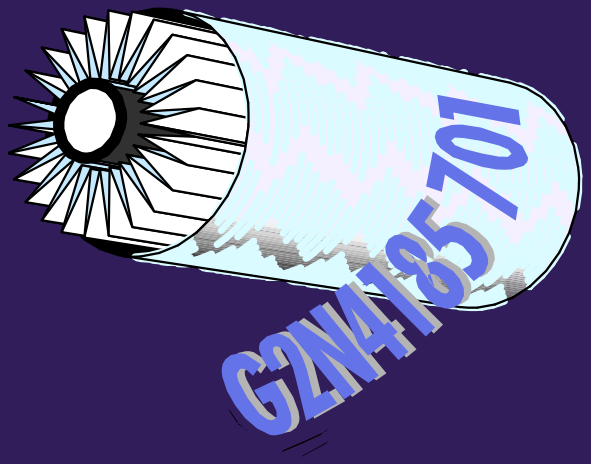
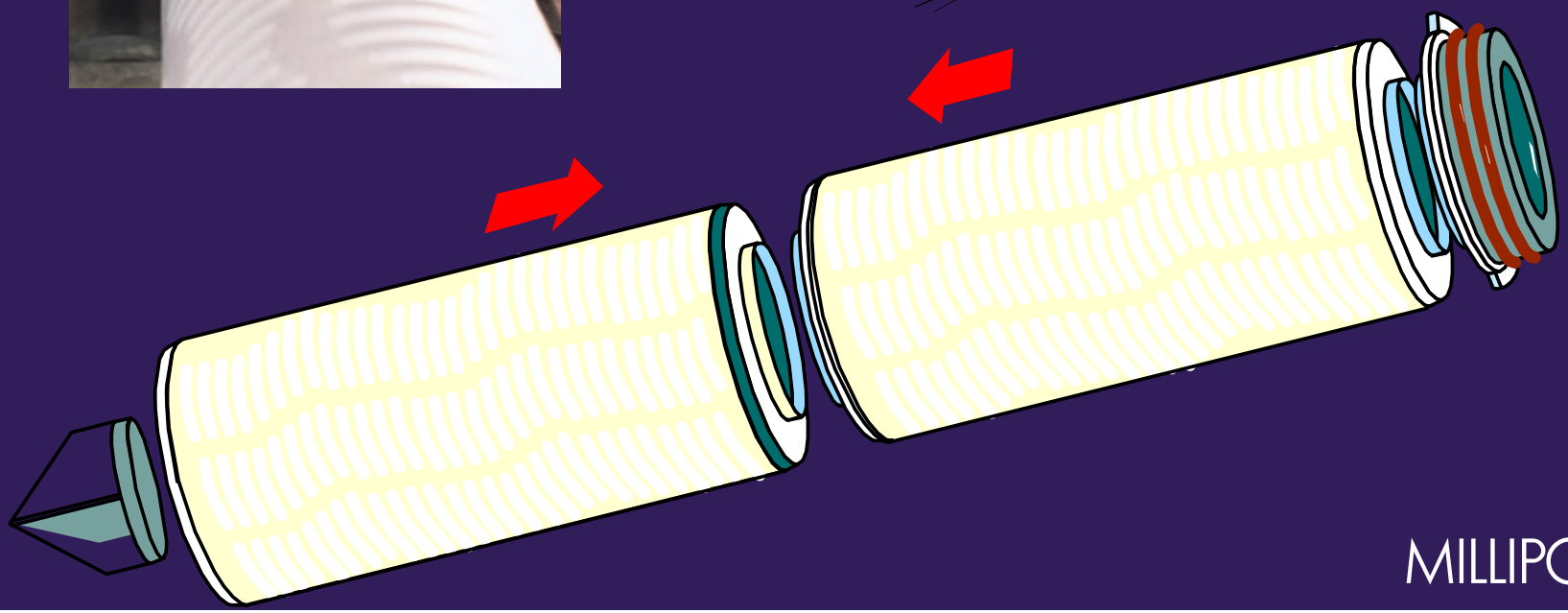
Serial numbering for complete traceability & Stacking





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Device Quality Assurance

- Bacterial retention
- Bubble point
- 100% device integrity testing
- Liquid flow rate
- Extractables
- USP bacterial endotoxin
- Mechanical stress (thermal, hydraulic)
- Steaming resistance

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Position Statement

Millipore ensures sterilising-grade performance for filters by using a three step integrity testing strategy:

1. All membranes used in Millipore sterilising-grade filters are BP tested
2. After filter devices are fabricated, Millipore performs a proprietary integrity test on all products
3. Finally, Millipore provides customers with integrity test specification

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100 % In-process Device Integrity Testing

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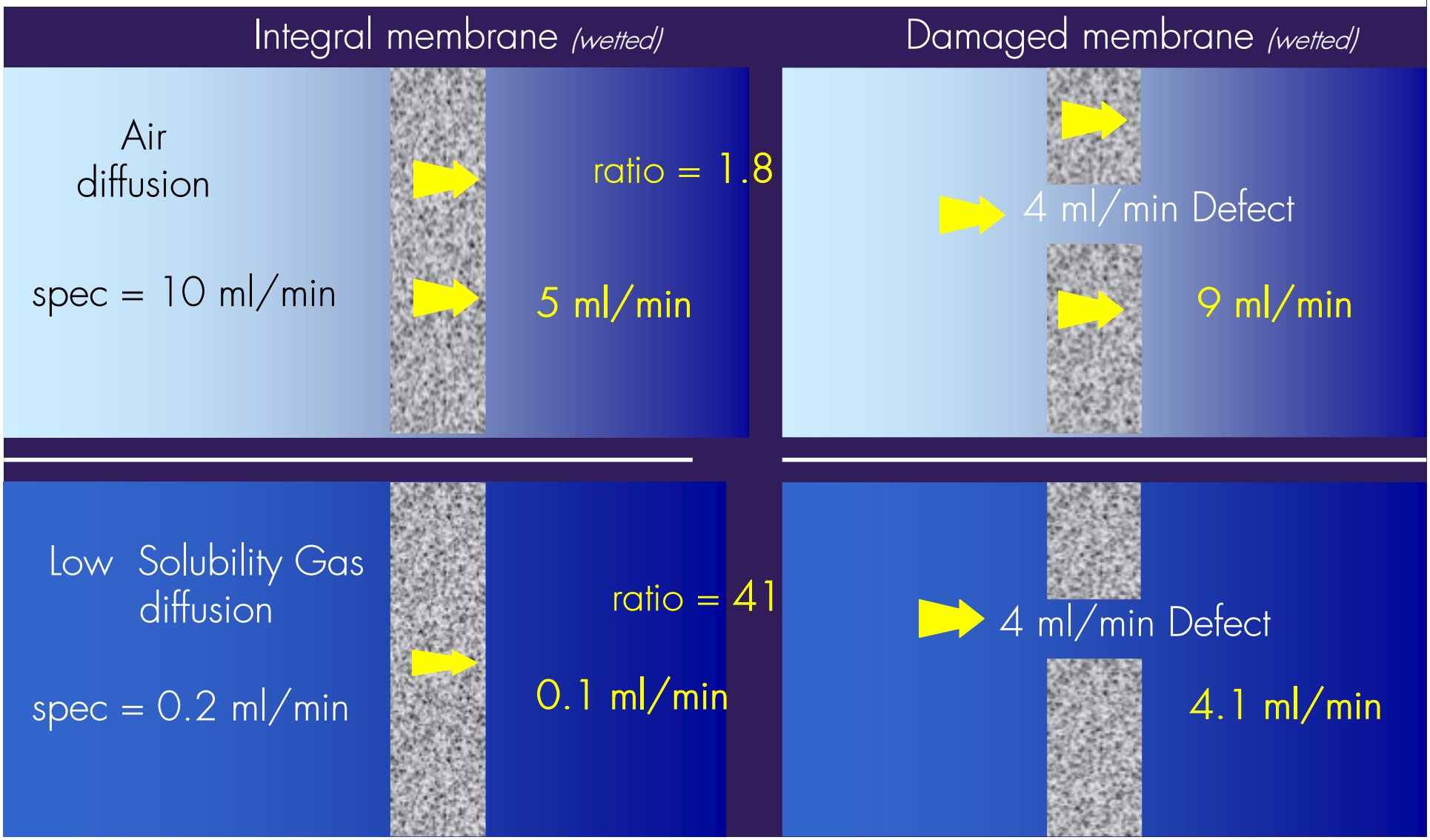

Requirements for increased SAL

- PDA TR n° 26
  - "Integrity testing alone is insufficient to assure the sterility of the filtrate. At least two other elements must be in place:
  - the production controls and quality assurance systems used by the filter manufacturer…,
  - and the validation studies used to show that a particular combination of product, processing conditions and sterilizing grade filter will meet the requirements of the bacterial challenge test".

Specific Validation Study

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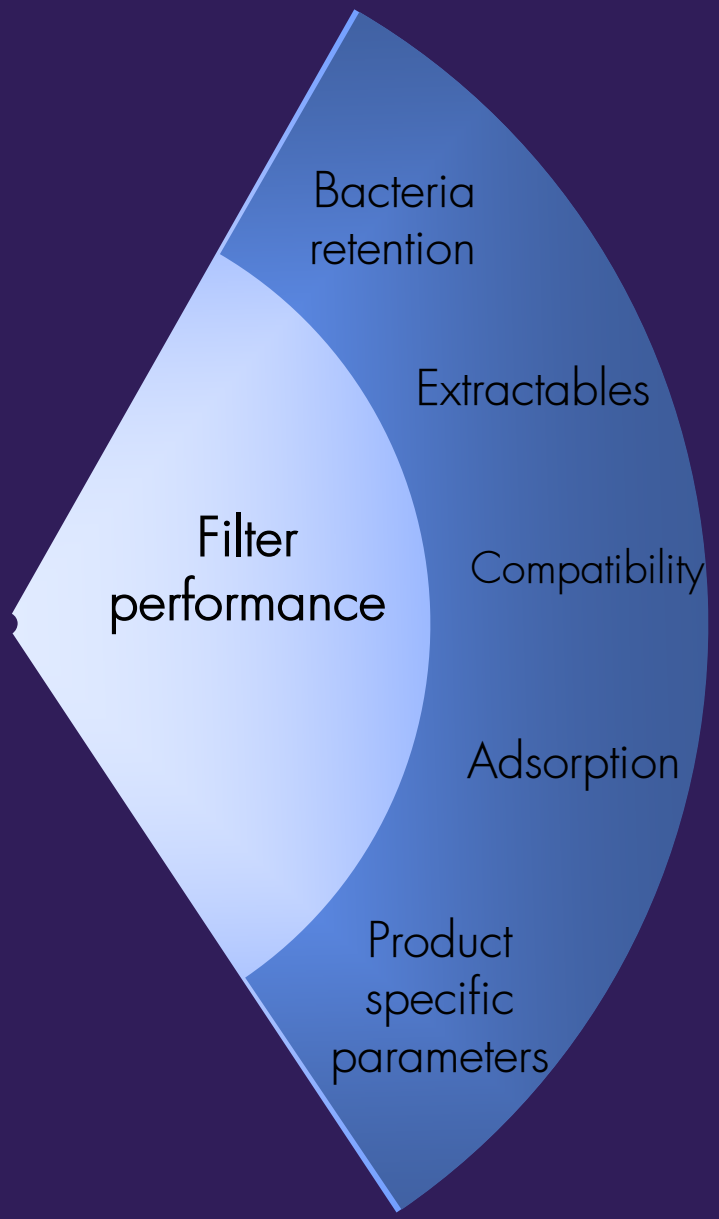

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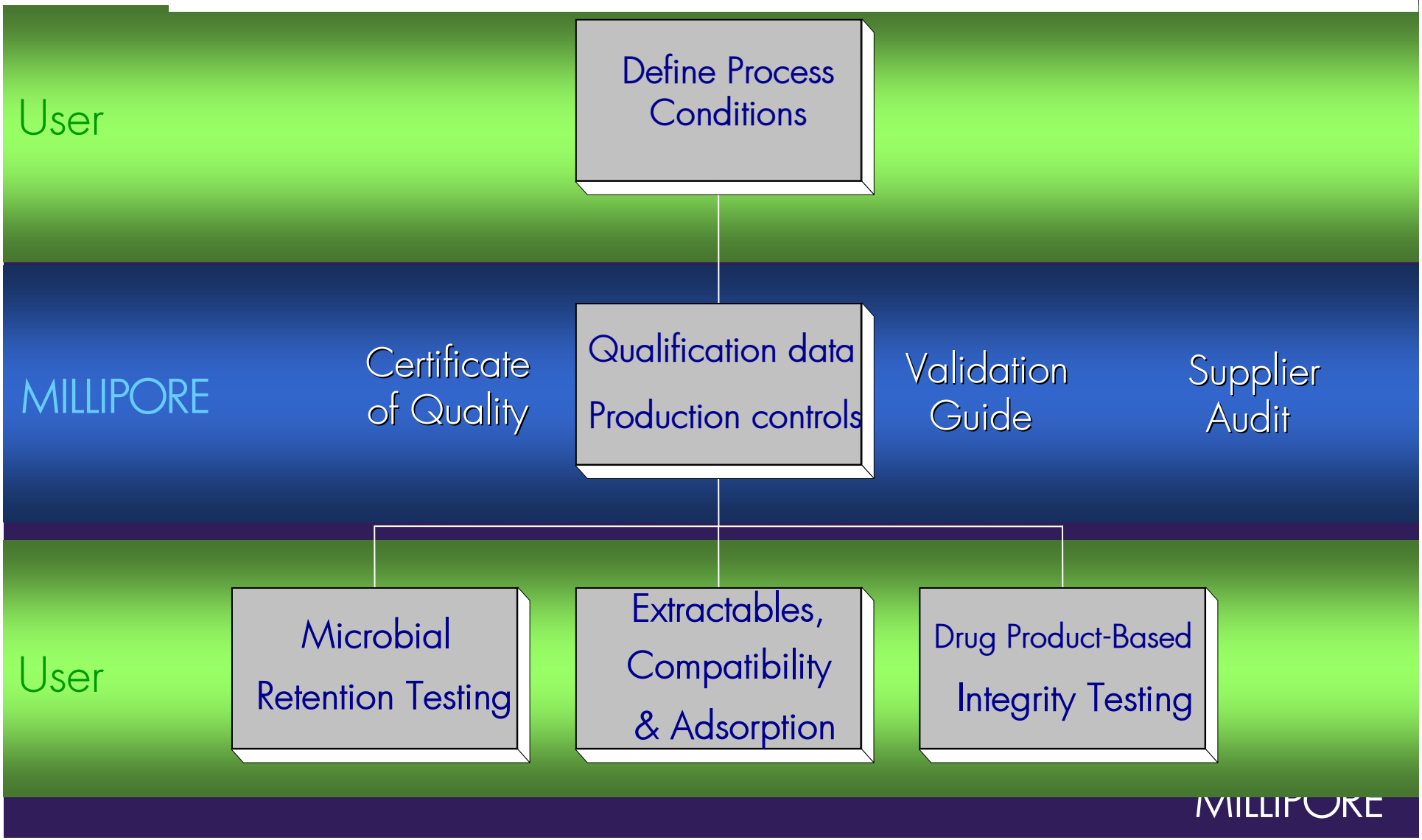
Validation of Filter Performance



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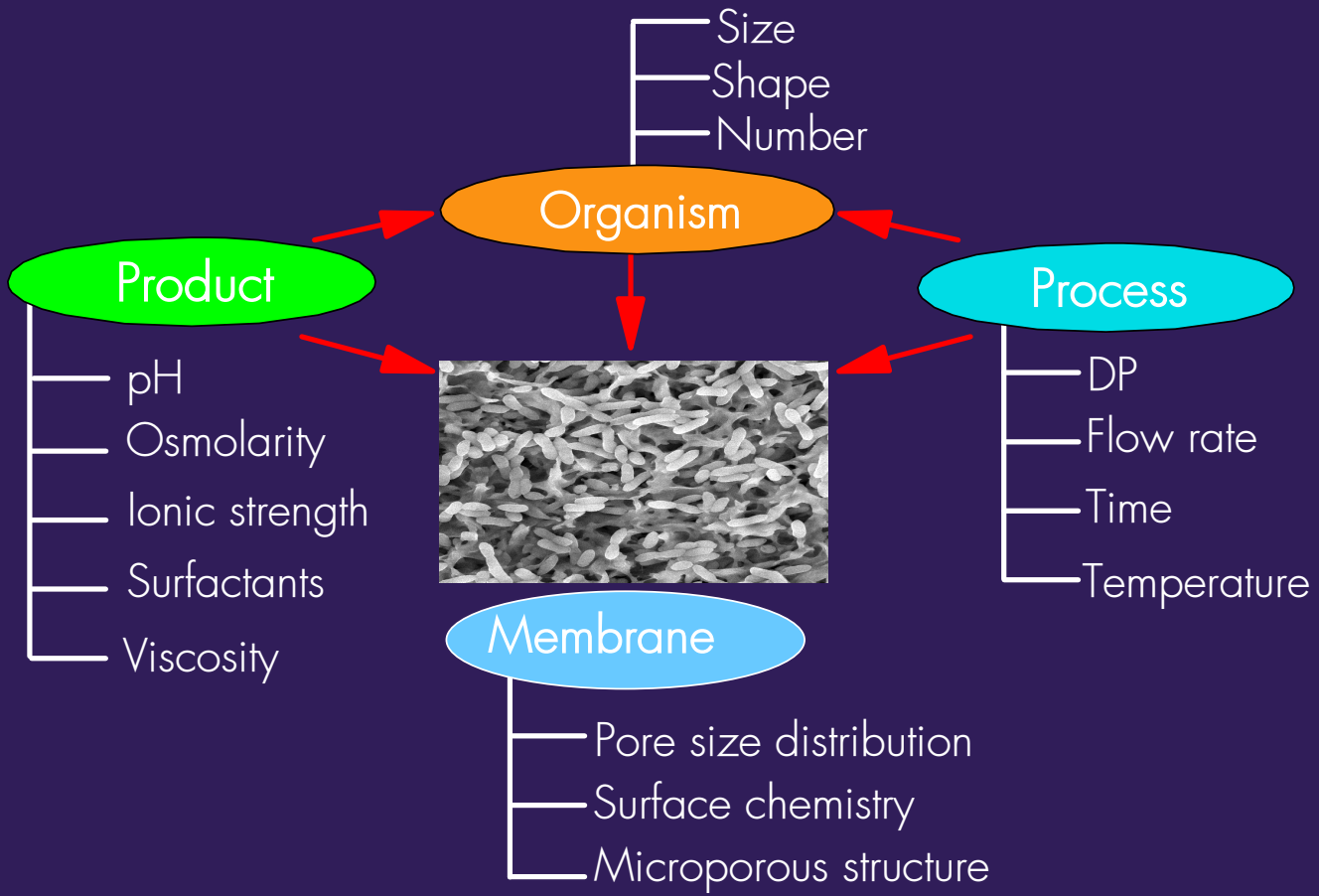
There is NO absolute filter

Factors that can influence filter retention



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Bacteria retention testing
Regulatory requirements

- FDA Guideline on Sterile Drug Products Produced by Aseptic Processing 1987, 2002
  - Validation should include microbiological challenges
  - Acceptable challenge is at least 10^7 cfu/cm^2
  - The micro-organism should simulate the smallest micro-organism that may occur in production
  - Laboratory experiments should simulate production conditions: flow rates, pressures, temperature, time

Bacteria retention testing
cGMP advice

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PDA technical report 26

- Filter membrane lots used for bacterial retention should have a pre-filtration water wet physical integrity test value at or near the filter manufacturers production limit
- The integrity test will help establish the similarity of the test filters to the filters validated to retain a bacterial challenge under process-related conditions

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Extractables testing
Regulatory requirements

- FDA Guideline for Submitting Documentation for Sterilization Process Validation
  - Any effects of the filter on the product formulation should be described (adsorption or extractables)

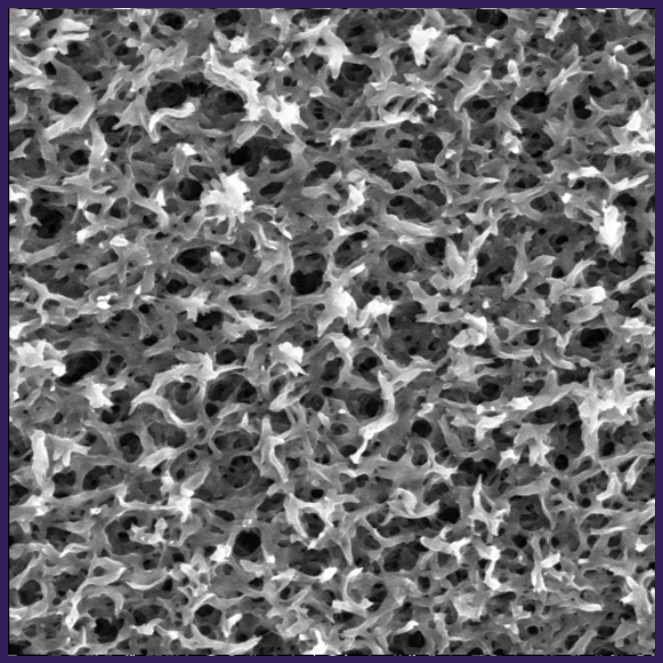
- FDA Human Drug cGMP Notes 9/94
  - Extractables cannot be detected because drug product interferes with methods and quantities are very low
  - Use appropriate methods and solvents to obtain the amount of extractables per filter.
  - Show the identity, quantity, and toxicity of the extractables.

Filter integrity testing

- Water is the standard wetting fluid
  - Drug component binding reduce surface tension
  - Post-use test failures
- Testing with the drug product as the wetting agent
  - Facilitates pre-use post-SIP testing
  - Avoids rinsing the membrane after filtration
  - Reduces the risk of post-use integrity testing failures

Compatibility & Adsorption

- Expose filters to the drug solution and the processing conditions
- Evaluate adsorption
  - Analytical assay for final product release
- Check compatibility
  - Confirm filter integrity
  - Also confirmed during
    - Microbial retention
    - Extractables testing



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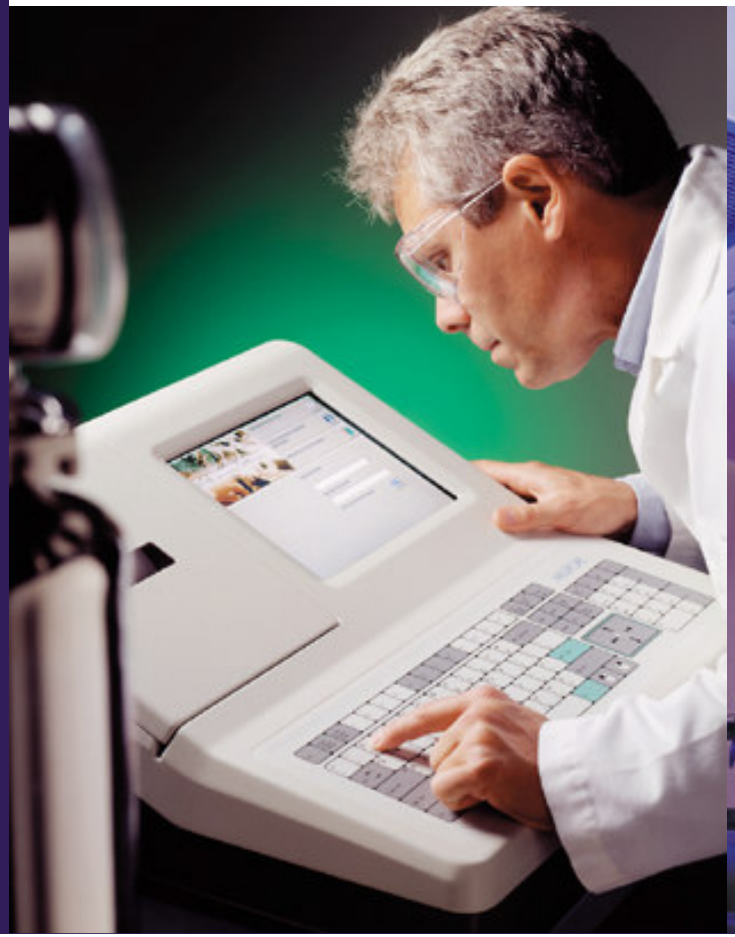
Validation of the Aseptic Process



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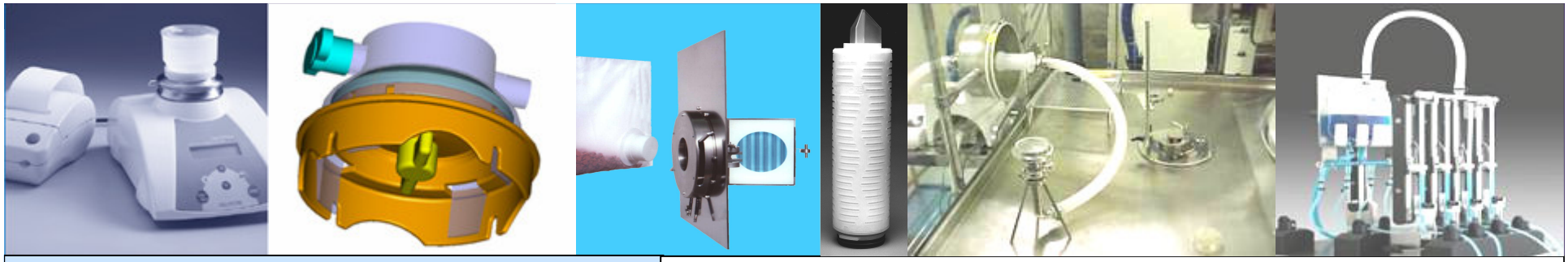

Grade C

Grade B

Filter performance

Operators & Aseptic connections

Grade A

SIP
Integrity testing

Autoclaving
Integrity testing

Microbial limit tests

Product Bioburden

Sterile transfer

Sterility testing

Environmental monitoring

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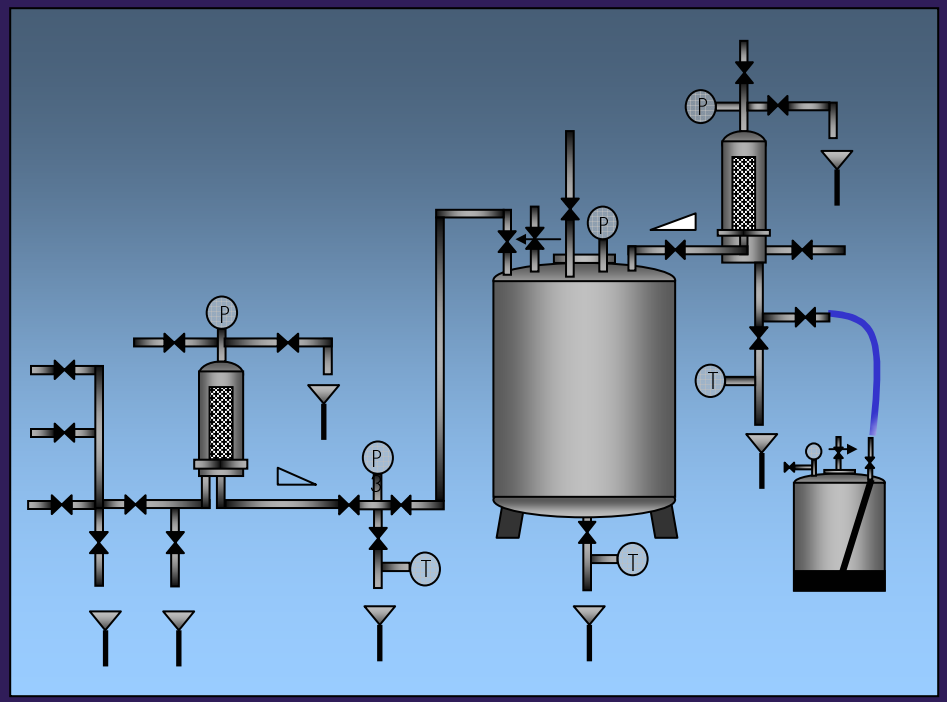
Design of filtration process

- Design of filtration system
  - P&ID and flow schematics
  - Functional description
- Development of SOPs
  - Filter SIP & autoclaving
  - Filter integrity testing
- Installation qualification
- Operational qualification
- Performance qualification



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Validation of filter integrity tester
Regulatory requirements

- EU GMP
  - Equipment which are critical for the quality of the products shall be subjected to appropriate qualification
- FDA Guideline on general principles of process validation
  - The manufacturer shall validate computerized systems that monitor and/or control the manufacturing process

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Validation of filter sterilisation
Regulatory requirements

- FDA Aseptic guideline 1987
  - In-line filters cause a significant pressure differential and temperature drop
  - Use suitable biological indicators at appropriate downstream locations
  - Filter SIP validation should also include measurements of temperature and pressure

- EU GMP Annex1 1997
  - … Any sterilisation process … should be demonstrated by thermometric means and by biological indicators where appropriate

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Bioburden monitoring
Regulatory requirements

- FDA Aseptic guideline 1987
  - Assure that actual bioburden does not contain micro-organisms of a size and/or concentration that would reduce sterility assurance
- FDA Recommendations for submitting documentation for sterilization process validation
  - Describe the program for routinely monitoring bioburden
  - Give information concerning the number, type, and resistance of bioburden organisms

Bioburden monitoring
EU Regulatory requirements

- Manufacture of the finished dosage form
  EU Guideline 3AQ2a
  - For sterilisation by filtration the maximum acceptable bioburden…in most situations, 10 cfu's/100 ml
  - If this requirement is not met, it is necessary to use a pre-filtration through a bacteria-retaining filter to obtain a sufficiently low bioburden

Validation of bioburden monitoring

- Equipment / device / media

  Qualification

- Method validation

- Monitoring program

- Maximum microbial limits

Environmental

Product bioburden

Personnel

(Sterility testing)

- Absence of bioburden

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Process controls

- FDA Aseptic guideline 1987, 2002
  - The total time for product filtration … should be limited to an established maximum
- EU GMP Manufacture of sterile medicinal products Annex 1 1997
  - The time taken to filter a known volume of bulk solution and the pressure difference to be used across the filter should be determined during validation and any significant differences from this should be noted and investigated

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Training

- EU GMP
  - Provide training for personnel whose activities could affect the quality of the product
  - Personnel should receive training appropriate to the duties assigned to them
- US GMP
  - Each responsible person shall have the training and experience to perform the assigned functions

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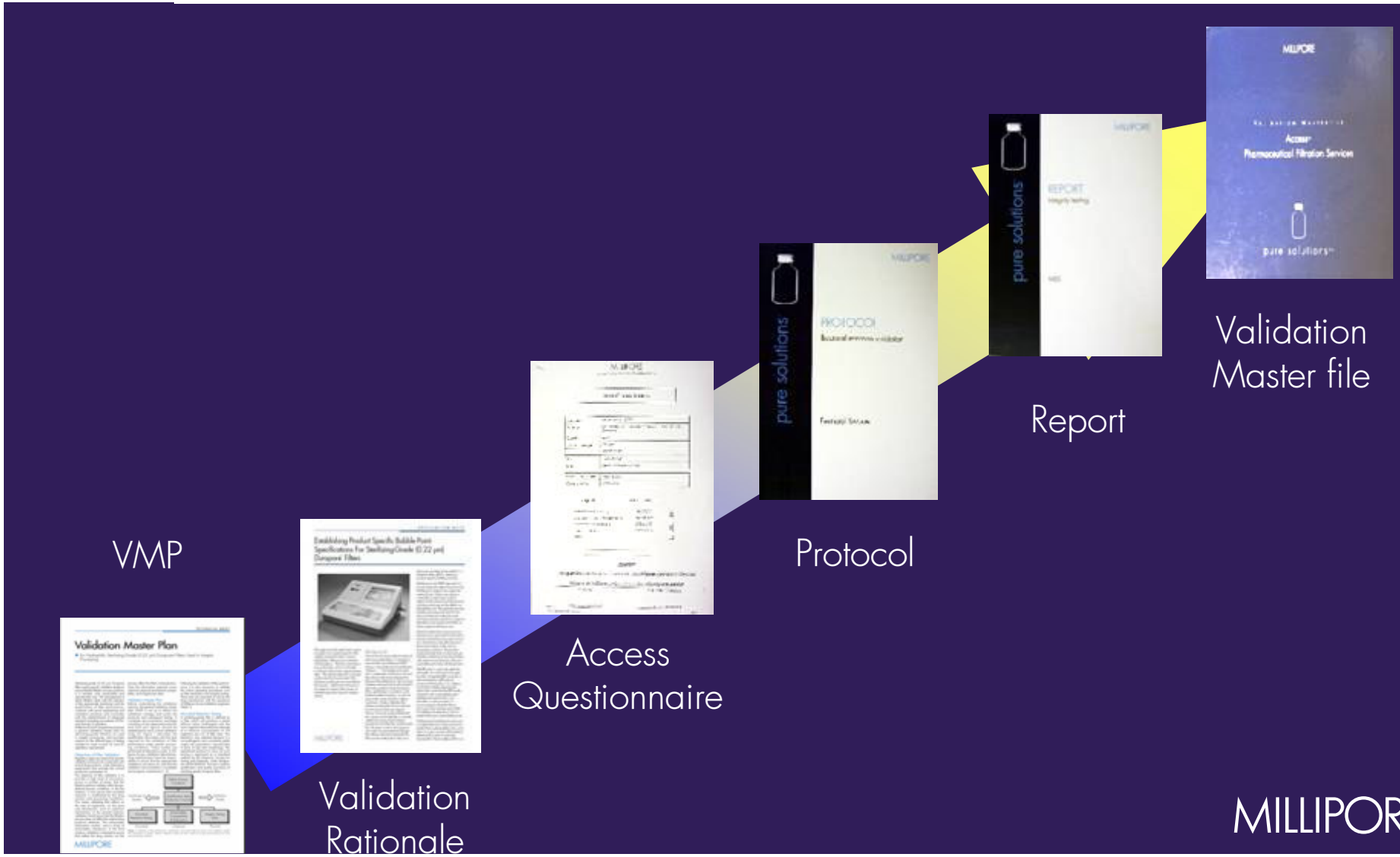
Validation documentation



Sterile filtration validation
Responsibilities

Test type	Millipore access services	Drug manufacturer
Microbial retention testing Extractables Compatibility Product-specific integrity-test data	Protocol Laboratory execution Report	Approve protocols Maintain documentation Process controls
Adsorption	Protocol	Execution, report
Integrity testers IQ/OQ	Protocol Field execution & report	Approve protocols Maintain documentation
Validation of integrity-testing PQ, SOP, training	Operator training and certification	PQ protocol Field execution, report
Validation of filter-sterilisation PQ, SOP, training	Protocol Operator training	Field execution, report Documentation

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Bioburden monitoring validation
Responsibilities

Test type	Millipore access services	Drug manufacturer
Method development Product bioburden Sterility testing	Protocol Laboratory execution Report	Approve protocol Maintain documentation
Method validation Equipment IQ/OQ Microbiological procedures Training	Protocol Lab execution & report (Documentation) Certification	Approve protocols (Lab execution & report) Maintain documentation

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Qualification route

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Filter sizing & scale up

Training & certification

Filter validation

Process validation

R&D

Process design

Production

Clinical Phase

Registration

Process development

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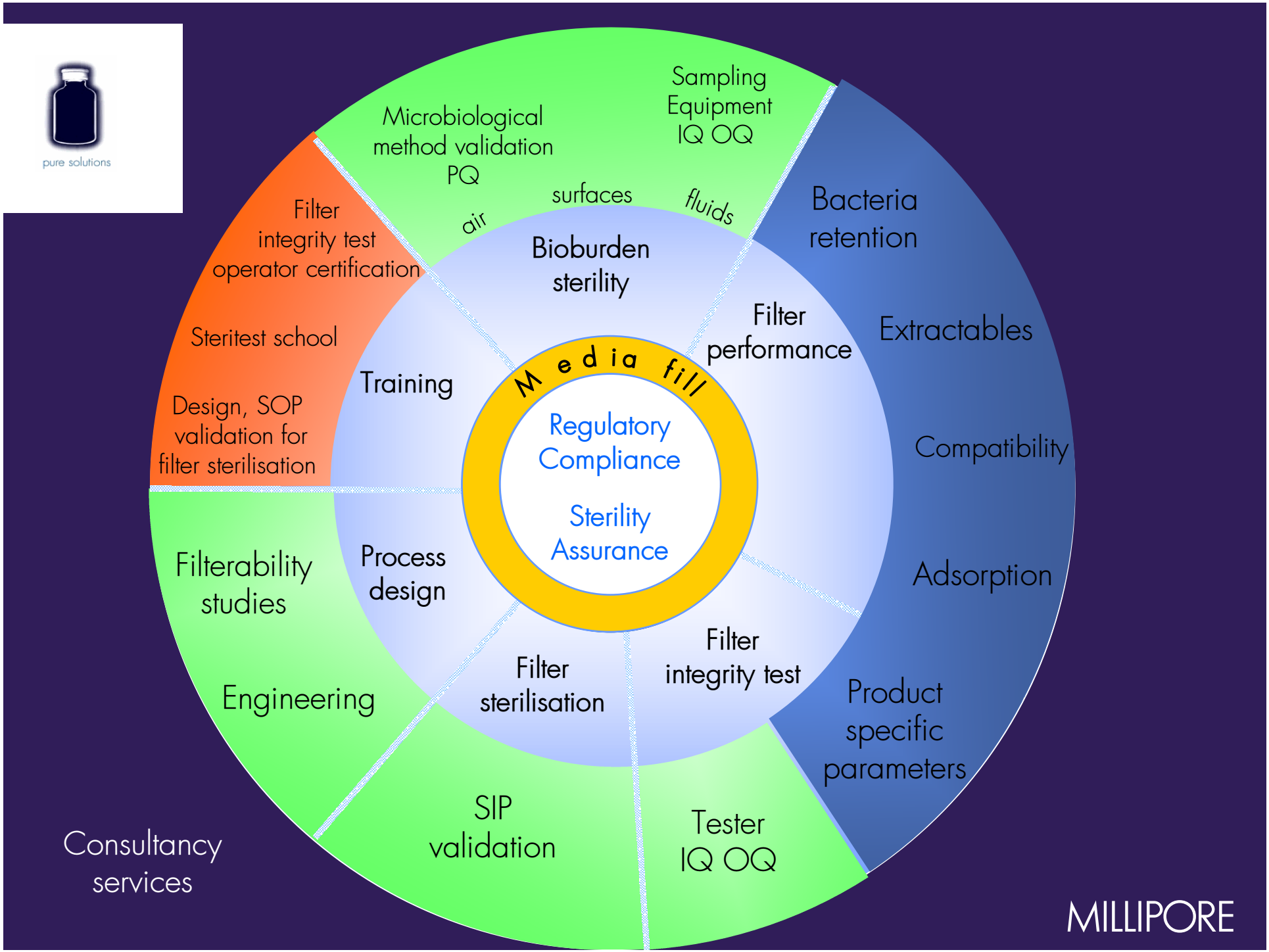
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Microbiological method validation PQ
air
surfaces
fluids
Sampling Equipment IQ OQ
Bacteria retention
Extractables
Compatibility
Adsorption
Product specific parameters
Tester IQ OQ
SIP validation
Filter sterilisation
Filter integrity test
Process design
Filterability studies
Engineering
Consultancy services
Design, SOP validation for filter sterilisation
Steritest school
Filter integrity test operator certification
Training
Bioburden sterility
Filter performance
Media fill
Regulatory Compliance
Sterility Assurance
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References

EMEA		eudraportal.eudra.org www.emea.eu.int
FDA	Aseptic guideline HcGMP notes	www.fda.gov
US GMP	21CFR212	www.access.gpo.gov
EU GMP	Eudralex volume 4	http://pharmacos.eudra.org/F2/home.html
PDA	Technical report 26	www.pda.org

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