

Quality by Design (QbD) Principles in Aseptic Processing

Have you minimized your sterile filtration risk?

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Introduction

As a drug manufacturer, safety of your final product is critical. You are required to follow industry best practices and regulatory guidelines. Additionally, it is your responsibility to validate a sterile effluent in the intended application under worst case processing conditions. You are not in this alone. It is your filter supplier's responsibility to demonstrate the sterilizing filter can consistently and robustly remove all bacteria in a single process step.

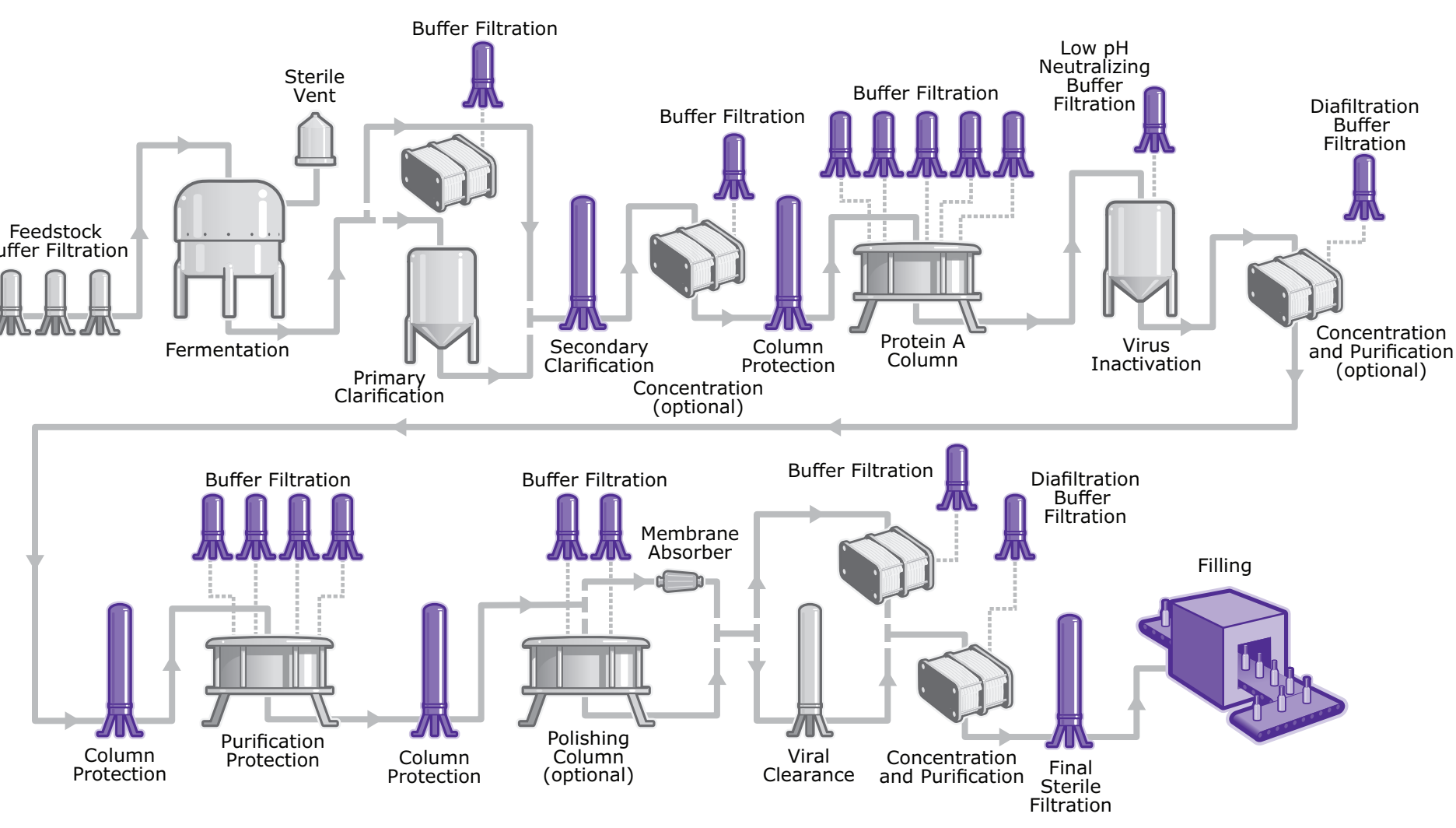
In this poster you will learn how we employ Quality by Design (QbD) principles to ensure our products will meet your expectations.

Key Principles: FDA's Initiative on Quality by Design (QbD)

- The product is designed to meet patient requirements
- The process is designed to consistently meet product critical quality attributes
- The impact of product components and process parameters on product quality is understood
- Critical sources of process variability are identified and controlled
- The process is continually monitored and updated to assure consistent quality over time

Sterile filtration is used at multiple steps in your process

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Regulatory Guidance

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Filter Manufacturing
validated, audited,
controlled and monitored

Validate Filter Efficacy
"worst case", process
simulation, and testing



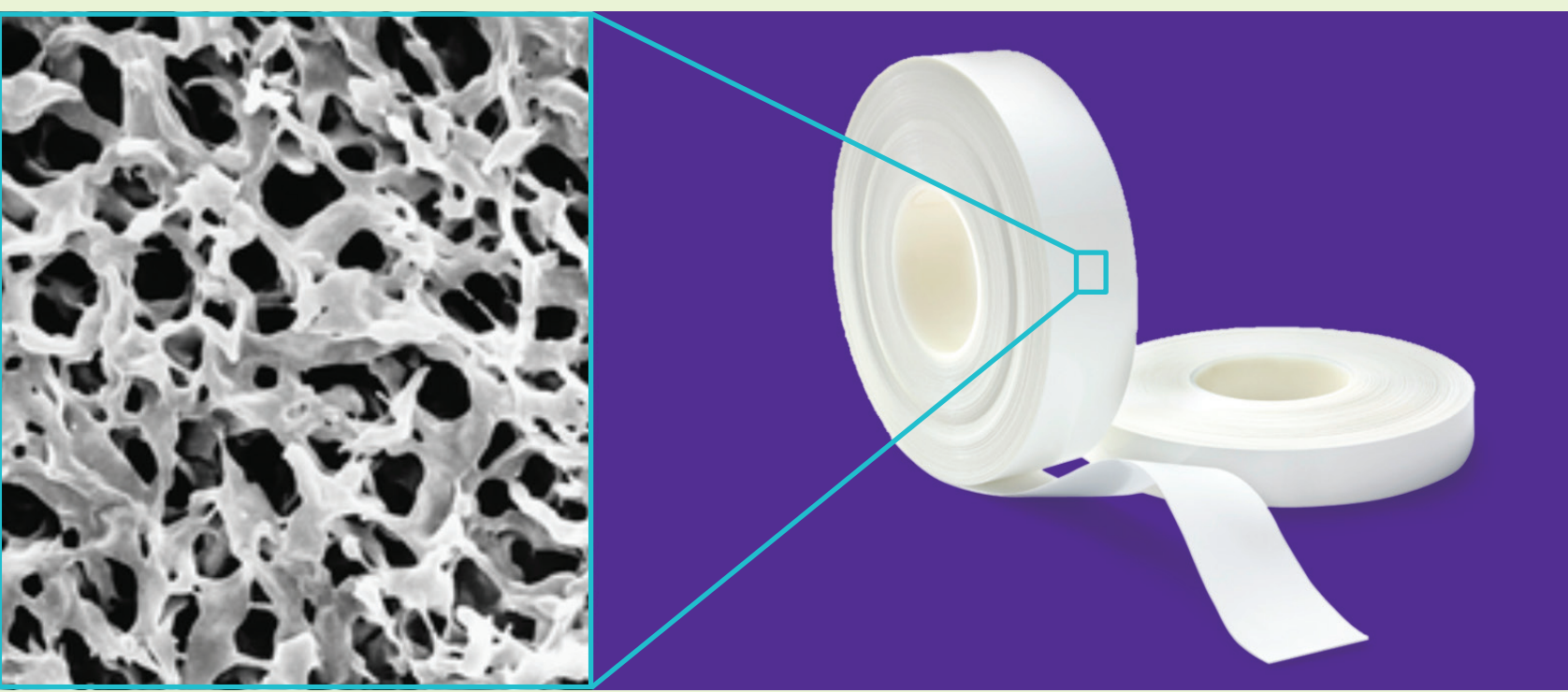
User Integrity Testing
Specifications consistent with
data generated during validation

The life science business of Merck operates as MilliporeSigma in the U.S. and Canada.

Our QbD Approach: Filters Designed and Validated to Assure Sterility

Membrane Designed for Sterilizing Applications

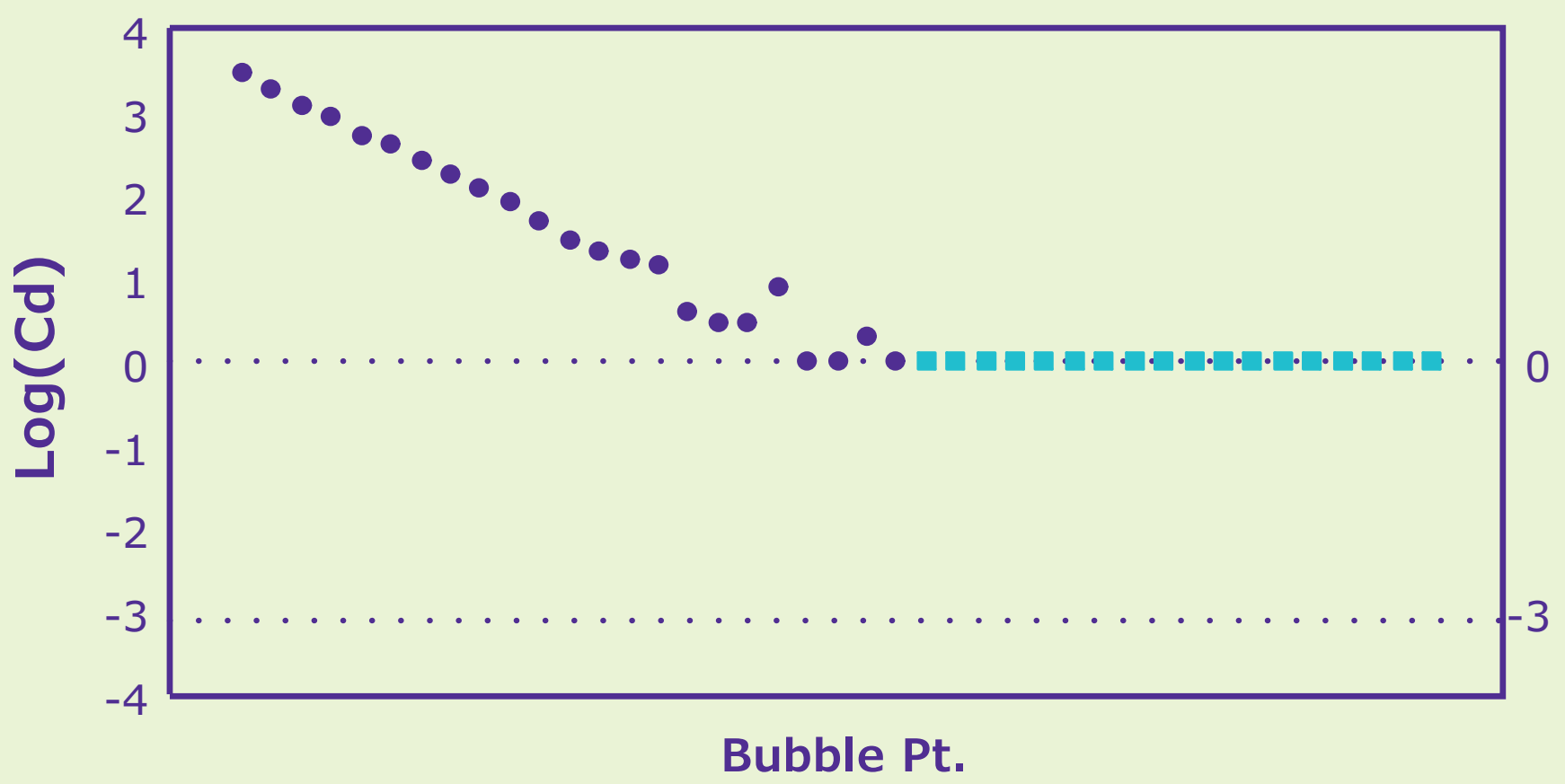
- Retentive at predetermined assurance level
- High permeability and capacity
- Low extractables
- Easy to water wet
- Sterilization stable (gamma, SIP)
- Strong for device fabrication



Pore size is the primary characteristic defining retention based on size exclusion

Logarithm of colony forming units (CFU) in a filtrate vs. bubble point can be used to quantify retention assurance

- $\text{Log (CFU)} = a + b \times \text{bubble point}$

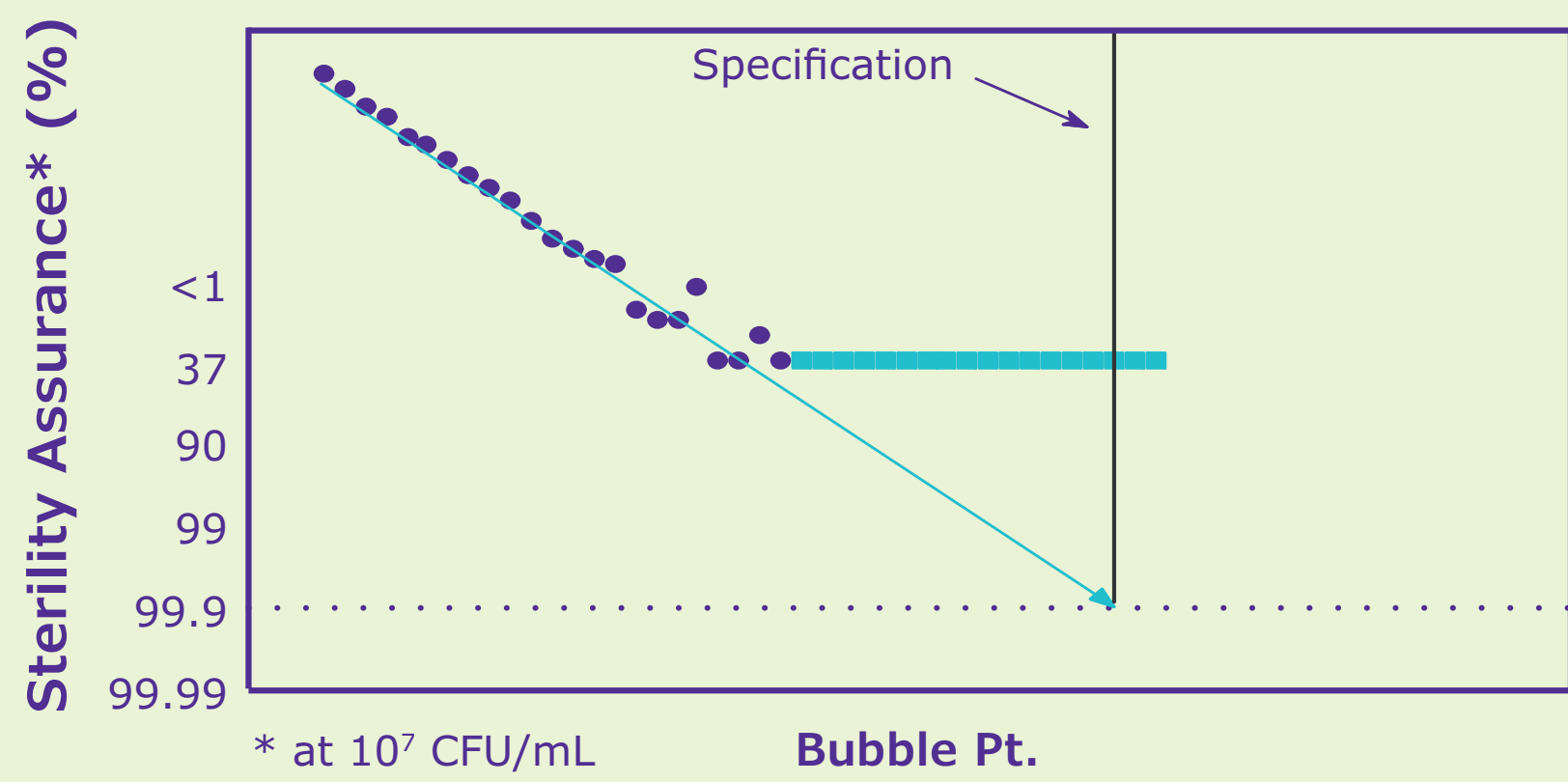


Filter specification set with high capability retention at ASTM® F838 conditions

- Retention assurance >99.9% at 10⁷ CFU per cm²

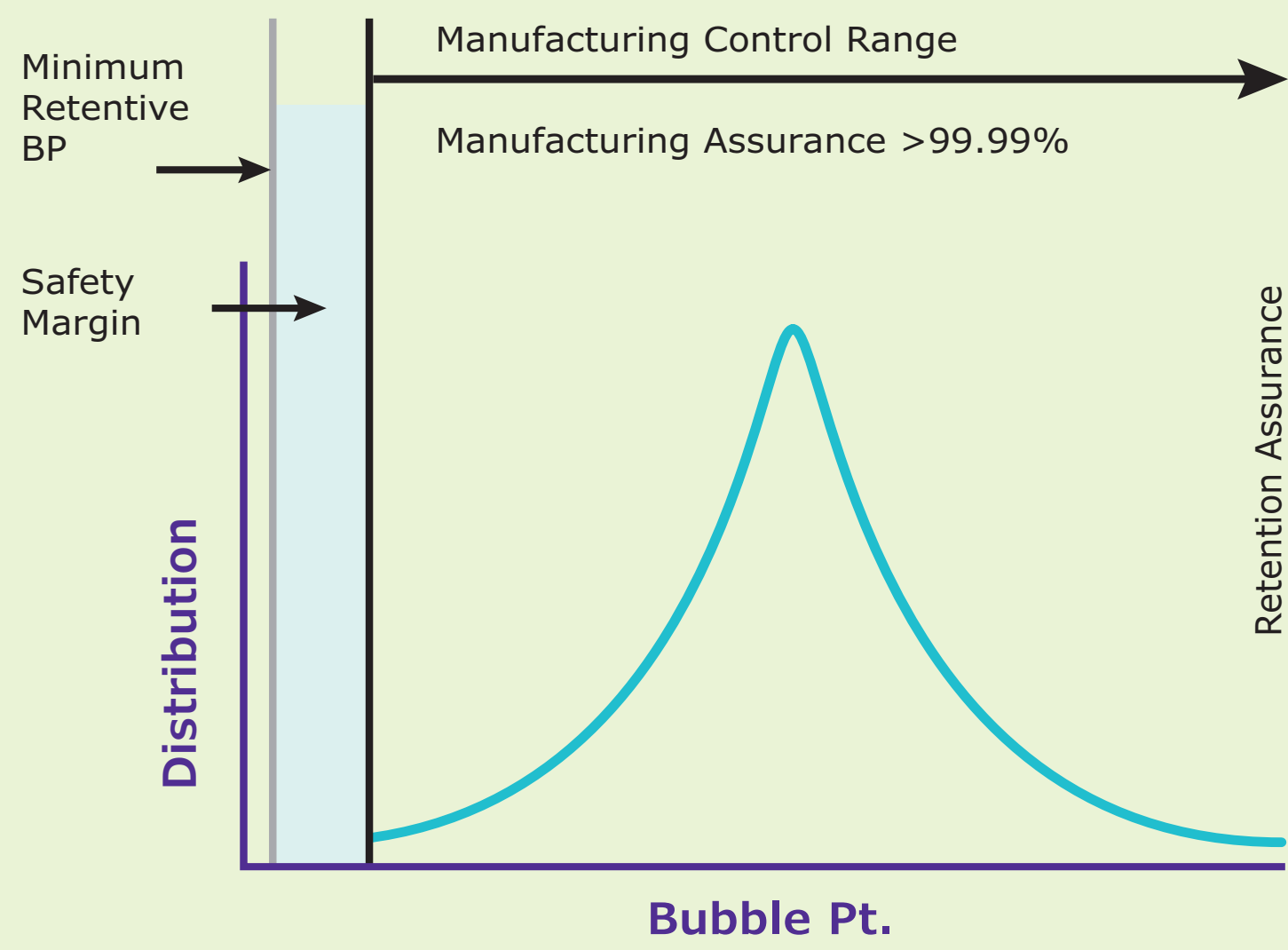
Using log (CFU) vs. bubble point, the specification is established with a safety margin

- When log (CFU) = -3, average CFU is zero with 99.9% confidence.



We reduce your risk by minimizing ours

Our sterilizing-grade membranes are manufactured with >99.99% sterility assurance at a bacterial load of 10⁷ per cm²



On-going Process Monitoring



Membrane Lot Release Testing

- ASTM® Retention tested
- Endotoxin tested
- Integrity tested
- Application based tests

In-Process Integrity Testing

- 100% device testing (proprietary high sensitivity test)

Device Lot Release Testing

- ASTM® Retention tested
- Endotoxin tested
- Thermal stress tests
- Hydraulic stress tests
- Integrity lot tests
- Application based lot tests

STERILITY ASSURED. No one does more to assure sterility and compliance

End-User Validation and Testing

Device Lot Release Tests

Device 100% In-Process Integrity Test

Membrane Lot Release Tests

**Membrane and Device
Product Design and Process Validation**

Conclusion

We design sterilizing grade filters to meet the regulatory and industry requirements of our pharmaceutical customers. We follow a scientifically based quality by design process to develop, validate, and control critical design properties. Membranes are designed with a high and well characterized safety margin for bacterial retention, with further safety margin and control provided in manufacturing. This work is an element of our comprehensive on-going quality program.

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