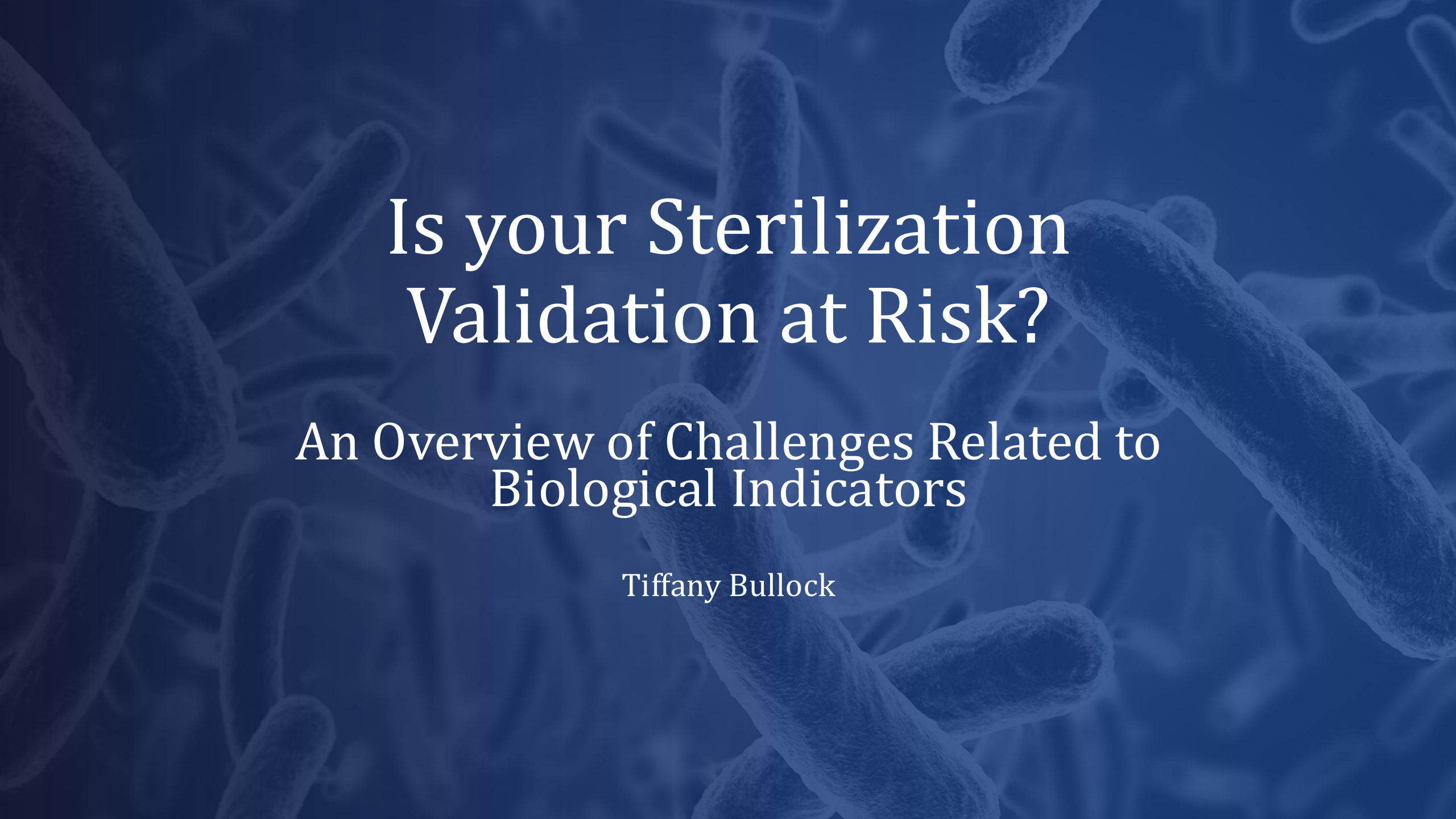
Sterility Assurance & Quality Risk Management Conference

PDA®
Parenteral Drug Association
Midwest Chapter



Is your Sterilization Validation at Risk?

An Overview of Challenges Related to Biological Indicators

Tiffany Bullock

Goal

- Minimize risk of failure to comply with sterilization validation requirements

Current Situation

- Limited guidance
- Conflicting information
- Resources

Agenda Topics

- Guidance Documents
- Key Terms
- Performance Characteristics
- Responsibilities
- Population Verification
- Minimizing Risk

Audience Benefits

CONSERVATIVE APPROACH

ALIGNMENT OF RESOURCES

MINIMIZE RISK

Guidance Documents

Key Guidance Documents

- USP <55> Biological Indicators – Resistance Performance Tests
- USP <1229.5> Biological Indicators for Sterilization
- USP <1117> Microbiological Best Laboratory Practices

- ANSI AAMI ST79 – Comprehensive Guide to Steam Sterilization and Sterility Assurance
- EN 285 Sterilization
- AAMI TIR13 – Principles of Industrial Moist Heat Sterilization

- 2004 FDA Guidance for Industry, Sterile Drug Products Produced by Aseptic Processing — Current Good Manufacturing Practice (CFR 211)
- EU GMP Annex 1, Manufacture of Sterile Medicinal Products

International Organization for Standardization

ISO 11135	Ethylene Oxide Sterilization
ISO 11138	Biological Indicators
ISO 17665	Moist Heat Sterilization
ISO 20857	Dry Heat Sterilization
ISO 14161	Guidance for Selection, Use, and Interpretation of Results

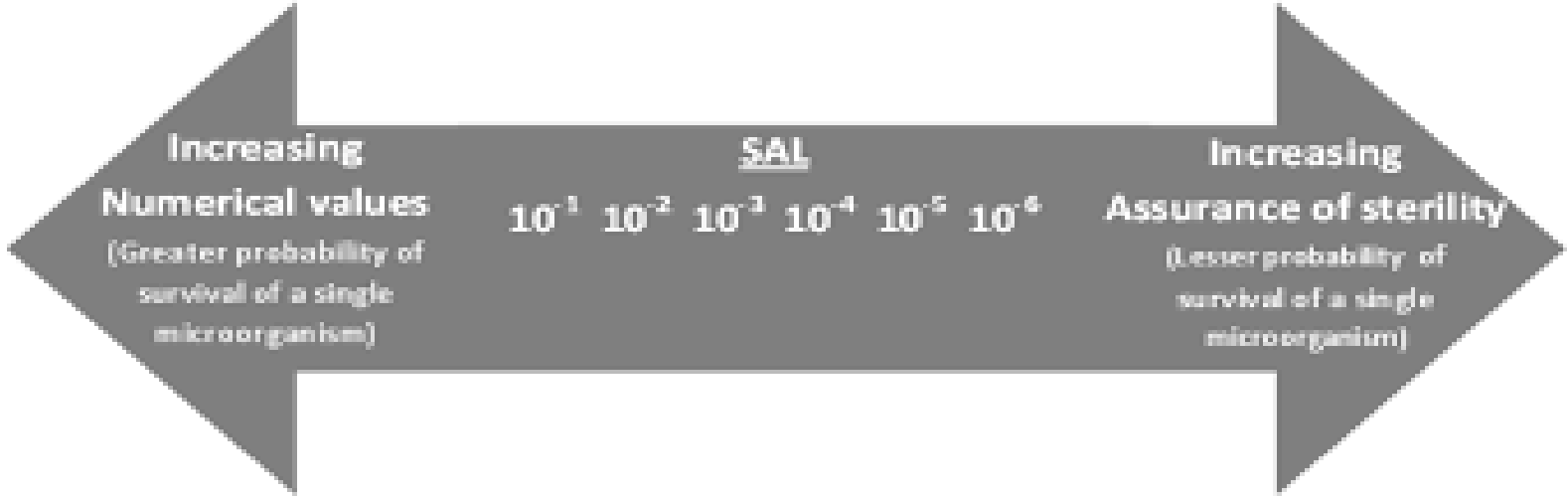
Key Terms

Key Terms

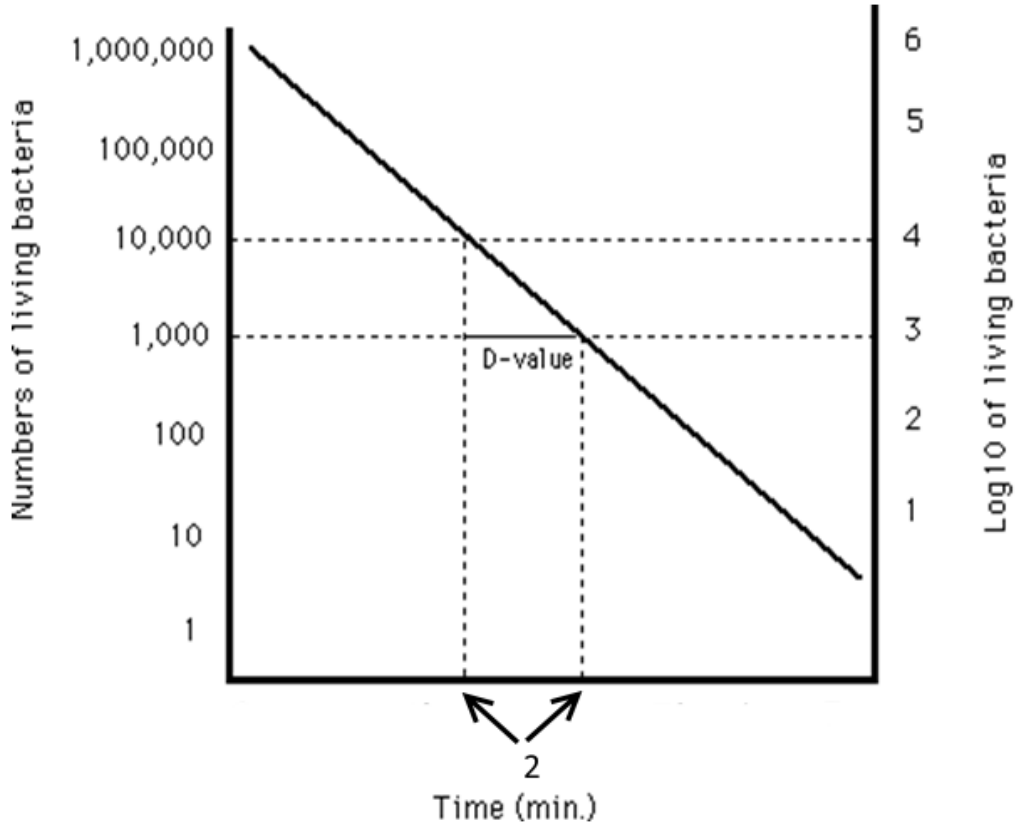
Biological Indicator - test system containing viable microorganisms providing a defined resistance to a specified sterilization process

Key Terms

- Sterility Assurance Level (SAL) – the probability of a single viable microorganism remaining on a sterilized item, expressed as a negative exponent (10^{-3},10^{-6})

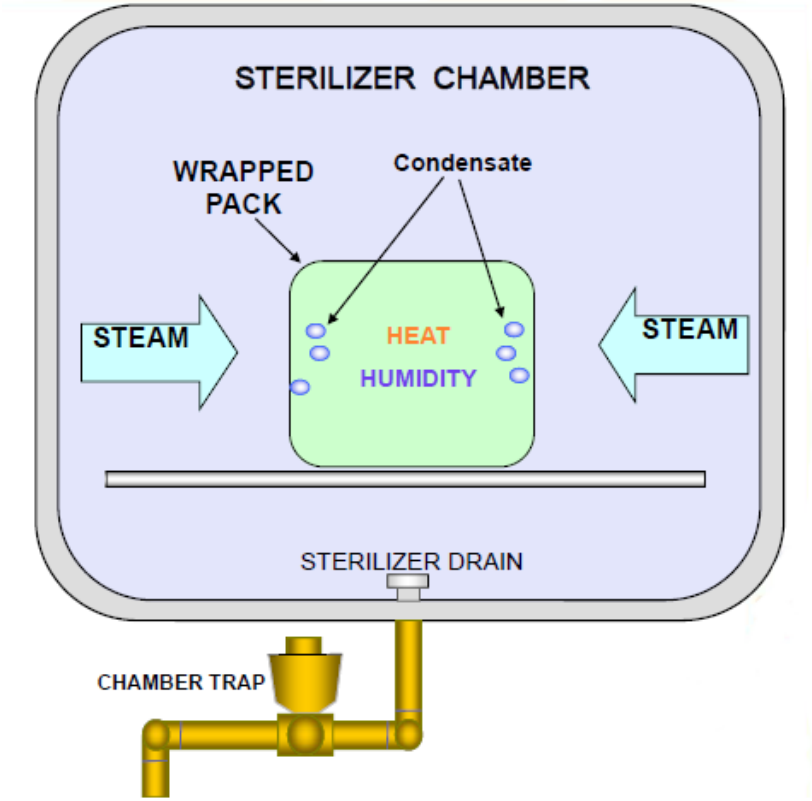


Key Terms



D-value - the time required at a specified temperature to reduce a population of microorganisms by one log or a 90% reduction in count

Key Terms



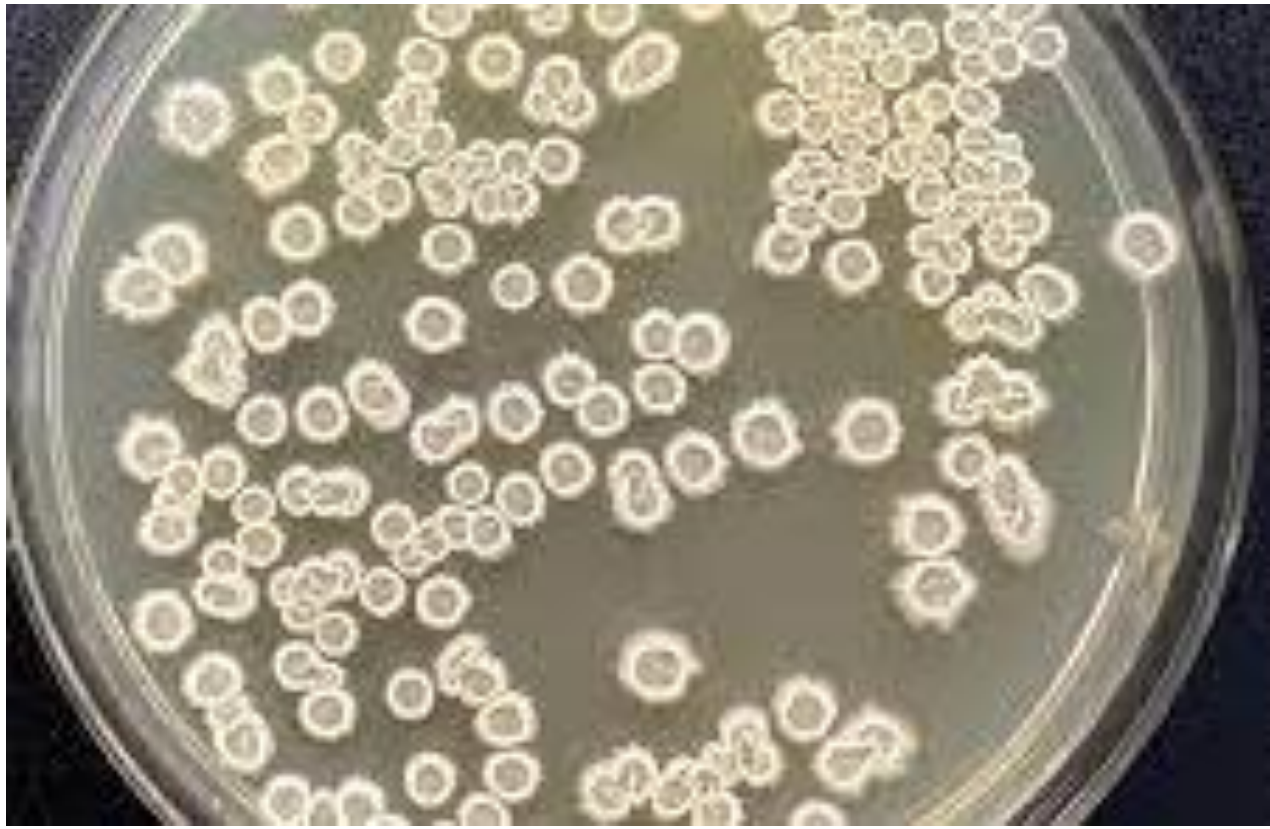
- Sterilization – validated process used to render the product free from viable microorganisms

Performance Characteristics

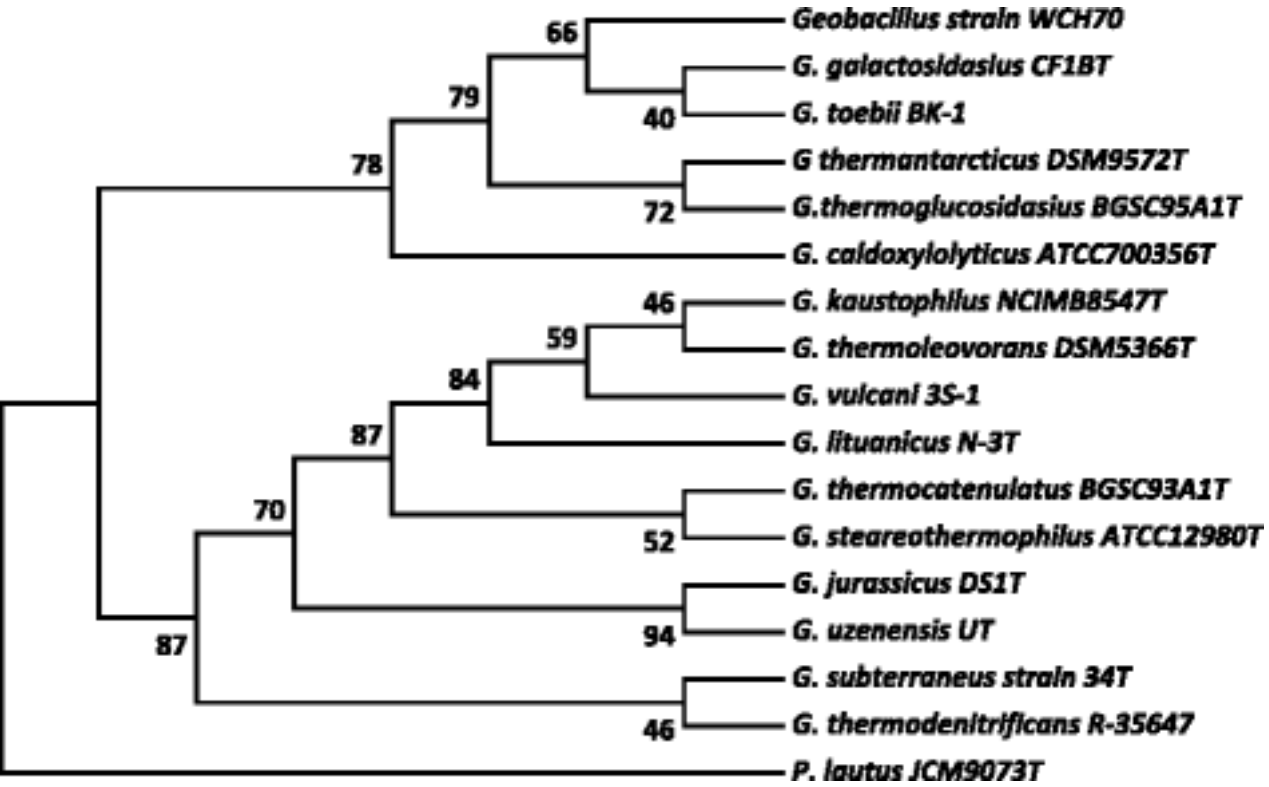
Biological Indicator Quality

Performance Characteristics

- Population – Determination of Viable Count
  - BI population selection required for SAL



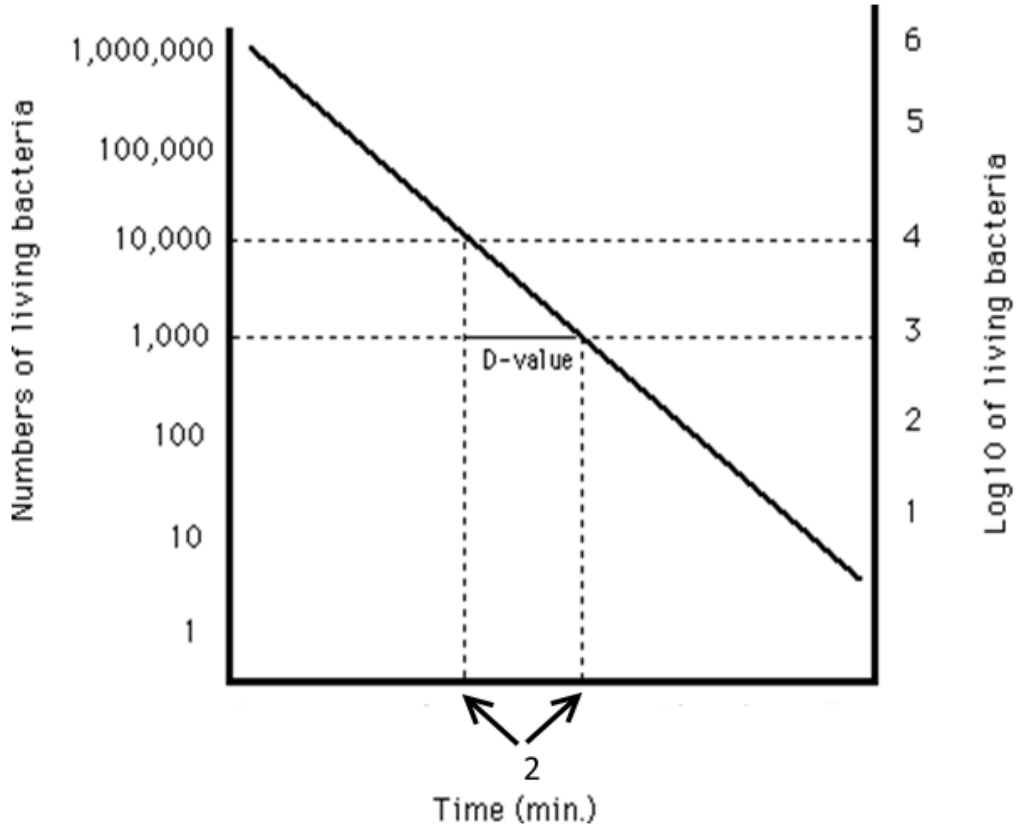
Performance Characteristics



- Identity - Microbial Identification
  - Verified to the strain
  - Traceable to the reference culture
- Purity – no evidence of contamination with other microorganisms

Performance Characteristics

- D-value – qualified for mode of sterilization – resistance specifications are provided by ISO for example,
  - With a D-value of 2 minutes at 121°C, it will take 12 minutes to achieve a 6 log reduction of challenge microorganism



Performance Characteristics

***Bacillus atrophaeus* NRRL B4418:**

Mean Population Recovery* (CFU): **2.4 x 10^6**

D_{EO} Value** (Min.***): **2.8**

D_{DH} Value** (Min.***): **1.1**

Incubate at 30°C to 35°C for 7 days

Survival Time (Min.): 12.3

Kill Time (Min.): 29.0

Survival Time (Min.): 4.9

Kill Time (Min.): 11.4

- Survival-Kill
  - extent of exposure to a sterilization process under defined conditions where there is a transition from all biological indicators showing growth to all biological indicators showing no growth

Responsibilities

Responsibilities

- The manufacturer is responsible for providing results for each of the required performance characteristics

STERIS

BIOLOGICAL INDICATOR CERTIFICATE OF PERFORMANCE

CATALOG NUMBER: NA008 **PRODUCT NAME: Spordi Strip**

PRODUCT LOT NUMBER: 261223 **SUBASSEMBLY LOT NUMBER: 1745**

EXPIRATION DATE: December 23, 2026 **DATE OF MANUFACTURE: August 5, 2025**

MANUFACTURE LOCATION: 9325 Pinecone Drive, Mentor, OH 44060

***Geobacillus stearothermophilus* 7953:**

Mean Population Recovery* (CFU): 2.6 x 10^6 Survival Time (Min.): 4.9

D_T Value** (Min.***): 2.0 Kill Time (Min.): 16.8

Incubate at 55°C to 60°C for 7 days

***Bacillus atrophaeus* NRRL B4418:**

Mean Population Recovery* (CFU): 2.4 x 10^6 Survival Time (Min.): 12.3

D_{160} Value** (Min.***): 2.8 Kill Time (Min.): 29.0

D_{121} Value** (Min.***): 1.4 Survival Time (Min.): 4.9

Kill Time (Min.): 11.4

Incubate at 30°C to 35°C for 7 days

* Colony forming units determined after a preliminary heat treatment.
** Saturated Steam, 121±0.5°C or 600±30mg/L EO using 100% EO, 54±1°C, 60±10% RH or 160±1°C Dry Heat
*** Determined at time of manufacture by fraction negative procedure after graded exposure to sterilization conditions.

Store at 2°C to 24°C and between 30% to 80% RH. **DO NOT** use after the indicated **expiration date.**
Dispose of as you would any other microbiological waste (121°C for a minimum of 30 minutes).

This document certifies that the biological indicator product listed above meets STERIS' quality assurance specifications and the performance criteria suggested by the current revision of the United States Pharmacopeia.

Quality Systems Representative: _____ Date: 8-6-25

Reviewed By: Maggie Lillardino Date: 8-6-2025

LIMITATION OF LIABILITY AND INDEMNITY

Nothing in this Certificate of Performance shall, or is intended to, alter, expand, or diminish the terms and conditions of sale governing your purchase of the Biological Indicator Product from STERIS. In no event, whether as a result of breach of warranty, or tort (including negligence and strict liability) shall STERIS or its suppliers be liable as a result of any statement or information contained in this Certificate of Performance. In addition, STERIS shall not be liable for any consequential or incidental damages including, without limitation, loss of use or damage to your products or equipment, cost of substitute products, or down time costs, allegedly caused by the Biological Indicator Products. The responsibility of STERIS for damages due to injuries or death caused by the Biological Indicator Product shall be limited to that portion of such damages as might be attributable to the negligence or strict liability or other tortuous conduct of STERIS.

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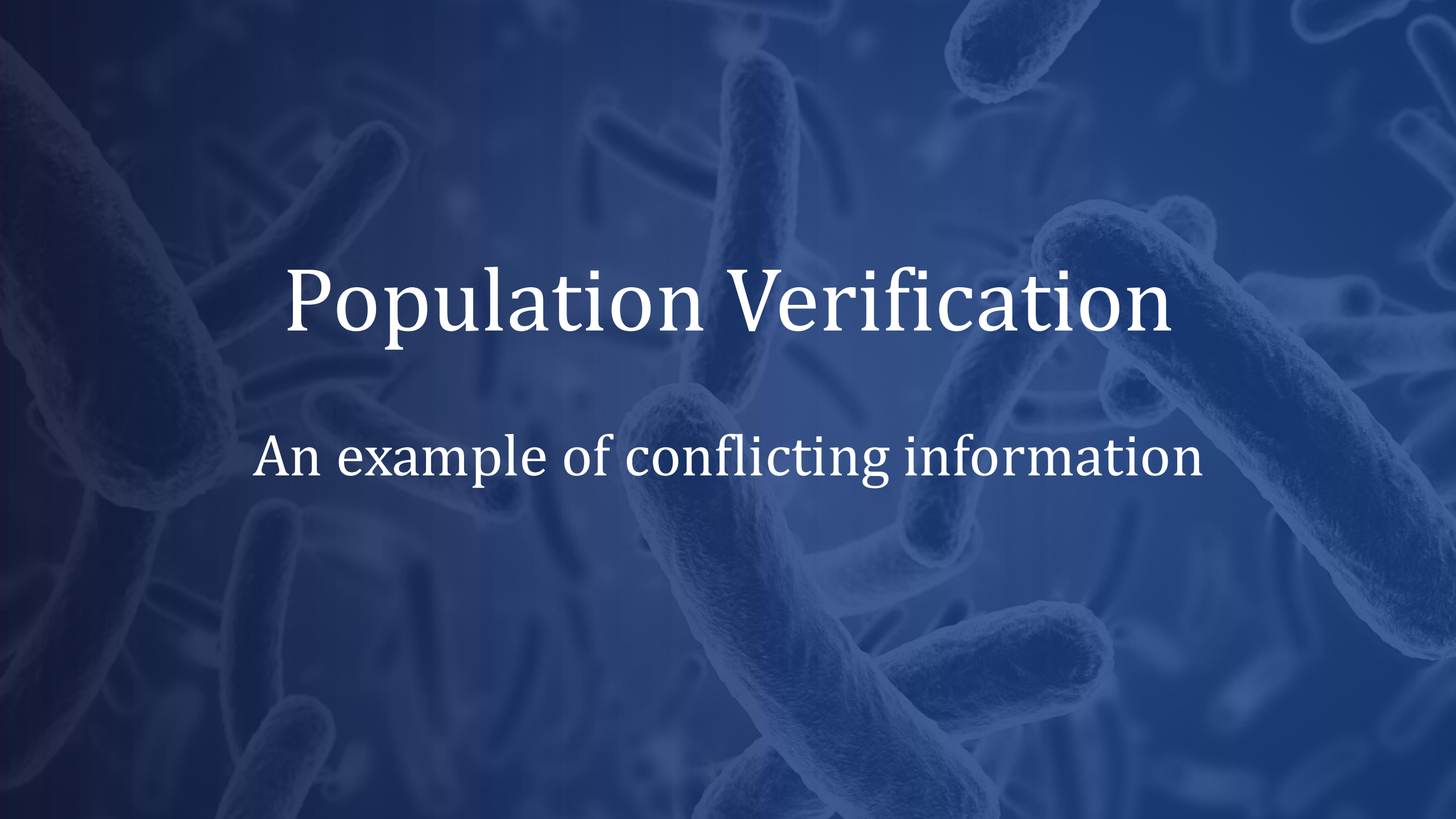
UNCONTROLLED WHEN PRINTED

Responsibilities

- End users are responsible for confirming results of **population verification** and **Identity/Purity**
  - Verify appropriate D-value during sterilization validation
  - Determine D-value when using a BI in an application outside of that validated by the manufacturer



Population Verification

An example of conflicting information

Sample Sizes – Population Verification

ISO 11138 minimum of 4 units

USP minimum of 3 units prior to Aug 1, 2016 –

Manufacturer (example) minimum of 10 units

- Current minimum aligned with ISO

ISO 11138-1 Annex A

1. Elute
2. Dilute
3. Plate
4. Incubate
5. Enumerate

USP <55>

1. Elute
2. Heat
3. Ice
4. Dilute
5. Plate
6. Incubate
7. Enumerate

Manufacturer

1. Elute
2. Dilute
3. Heat
4. Ice
5. Plate
6. Incubate
7. Enumerate

Test Methods – Population Verification

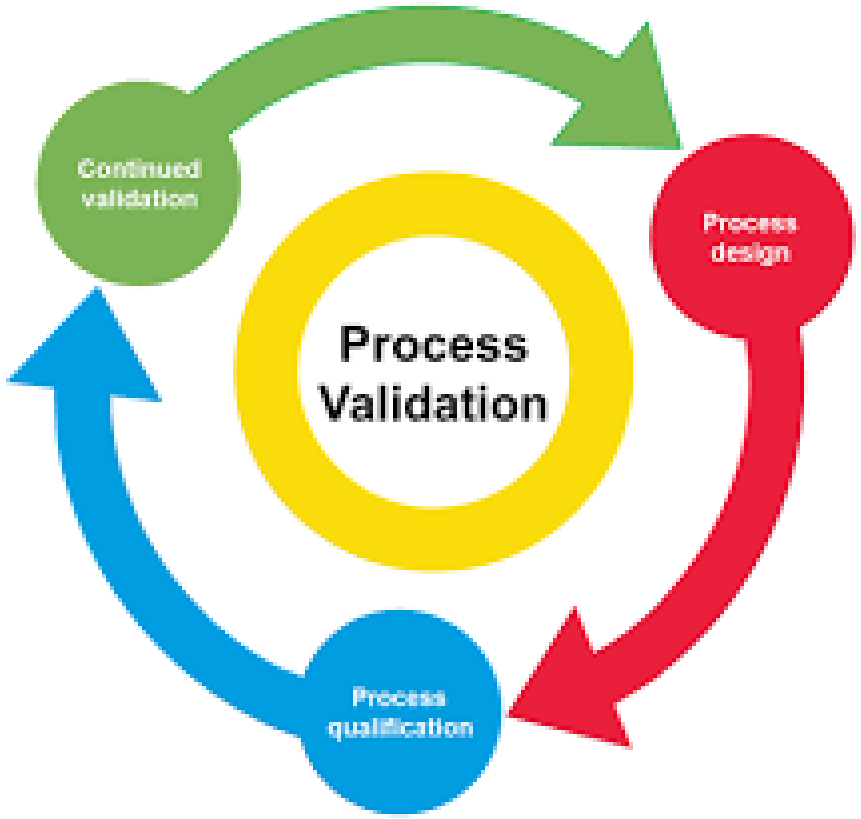
Population Verification

- Key Differences
  - Sample size
  - Eluting – variety of options – requires validation
  - Dilution – before/after heat shock

  - Variability in test methods leads to variability in test results

Minimizing Risk

Minimize Risk

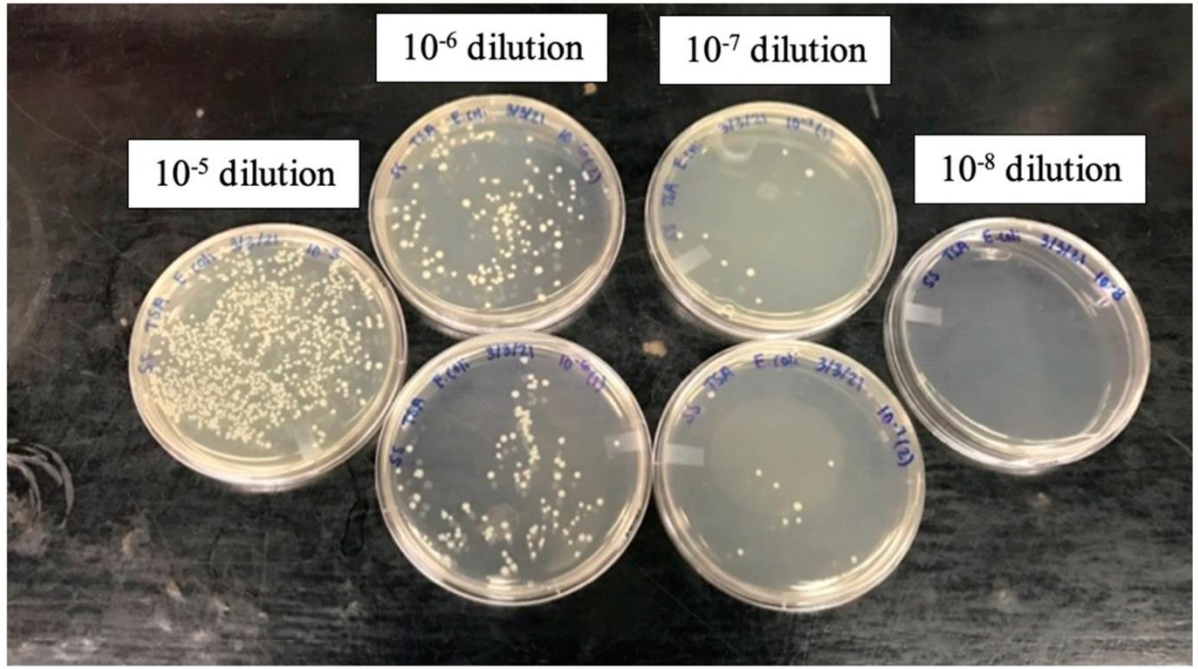


"The biological indicator manufacturer should be consulted to ensure that the same techniques and procedures are used, because variations in testing procedures can affect the population determination results." ISO 14161

"If the user applies a different method from that recommended by the manufacturer, the method should be validated." ISO 14161

Minimize Risk

- Reduce variability by increasing sample size for averaging results
  - This applies to sample size as well as replicates plated for incubation and enumeration

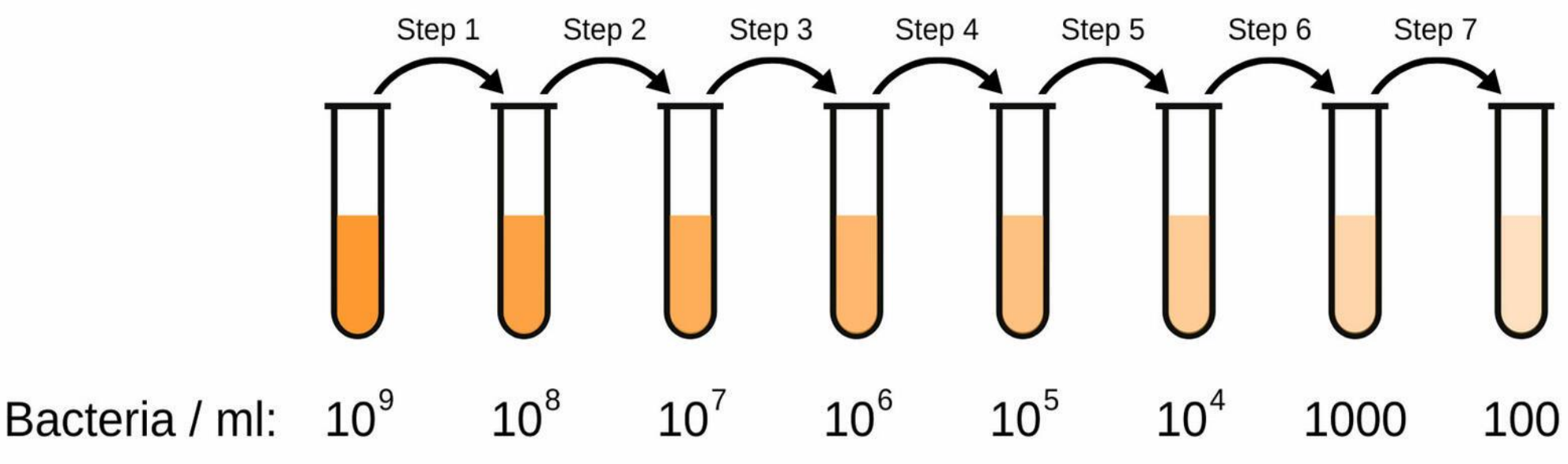


Minimize Risk

- Validate the method used for elution
  - Various options might work better for variety of BI's

Minimize Risk

- Validate the method used for dilution, including when to dilute spore suspensions – before or after heat shock and ice bath



Minimize Risk

- **Proactively** understand the purpose of the BI's and the importance of using validated test methods and acquiring BI's from a trusted manufacture

Facility Audit

Technical Support

Quality BI Product

Minimize Risk

- Understanding D-value and how that relates to your validated sterilization cycle
- Is your sterilization validation based on SAL, overkill, bioburden, or a combination
- What is the potential product/patient impact of a BI failure

Minimize Risk

- Alignment with the manufacturer

Technical Services

Validated Test Methods

Troubleshooting Guides

Conclusion

- Guidance Documents
- Key Terms
- Performance Characteristics
- Responsibilities
- Population Verification
- Minimizing Risk

CONSERVATIVE APPROACH

ALIGNMENT OF RESOURCES

MINIMIZE RISK

Thank you!

Questions…