Misconceptions with Moist Heat Sterilization

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11 October 2018

A Famous Quote from *The Big Short*

"It ain't so much the things we don't know that get us into trouble. It's the things we know that just ain't so."

-Mark Twain

-Will Rogers, Charles Kettering, Eubie Blake, Walter Mondale, Yogi Berra

-NYT attributes it to either Josh Billings, Kin Hubbard, Artemus Ward

Misconceptions

- Everyone has them
- Need to address student misconceptions before they can learn
- Harvard graduates and seasons
  - YouTube: Harvard misconceptions seasons
- Colleagues, customers, auditors familiar with aseptic processing but not as familiar with terminal sterilization

Summary of Common Moist Heat Misconceptions

1. A Highly Resistant BI (*G. stearotheromophilus*) Must be Used to Develop/Qualify Sterilization cycles
2. Terminal Sterilization is "The Big Eraser"
3. BI Positives in Requalification = Undetected Product/Process Change
4. Porous Hard Goods, Liquid Loads – It's all the Same!
   A. Equilibration Time is Relevant to Liquid Loads
   B. Air – Removed with Porous Hard Goods/Added for Liquid Loads
   C. Risks of Moisture with Porous Hard Goods
5. The Sterility Test is Sensitive/Capable of Confirming Sterility
6. Parametric Release is a New Concept
7. Parametric Release is Not in Widespread Practice
8. Top Reasons (Excuses?!?) for Not Adopting Parametric Release
9. Parametric Release is Difficult to Achieve
10. Alternate Load Monitor Case Study

Math Warning

Term	Definition
$D_{121°C}$ value	Time at 121°C required for destruction of 90% of organisms.
F_0	Lethality from time and temperature of product during sterilization expressed as “minutes @ 121°C (z=10)”.
N_0	Initial population prior to process (Time = 0)
N_F	Final population after process
PNSU	Probability of a NonSterile Unit
SLR	Spore Log Reduction = Log(organisms killed)
Parametric Release	Achieving validated parameters of time, temperature, etc to assure sterility *in lieu* of a sterility test.

A Highly Resistant BI (*G. stearotheromophilus*) Must be Used

Let's assume that we have adequate data to support that our bioburden spore count is **<1 CFU per unit** with a **$D_{121°C}$ value of 0.4 minutes***

Step 1: ID Biological Indicator (BI) to Represent Product Bioburden (Bb)

Recommendation: *Bacillus subtilis* 5230: Minimum $D_{121°C}$ = 0.4 minutes

Step 2: Determine Minimum Physical Lethality (F_0) Required for 10^{-6} Probability of a Non-Sterile Unit (PNSU)

F_0 = (Bb $D_{121°C}$ value) **x** [Log (Bb Spores/Unit) – Log (Bb Surviving Spores/Unit)]

F_0 = 0.4 min. **x** [Log (10^0) – Log (10^{-6})]

F_0 = **2.4** minutes –> will provide PNSU of 10^{-6}**

*Note: This is a very conservative assumption for a well-controlled pharmaceutical or medical device manufacturing operation.

**Recommend addition of safety factor approximately 2 x D_{121} or 0.8 minutes for this example.

A Highly Resistant BI (*G. stearotheromophilus*) Must be Used

Step 3: Calculate PNSU Using BI Inactivation Data

-Assume Complete Inactivation of 10^6 *Bacillus subtilis* 5230 = **6 Spore Log Reduction**

log(PNSU) = Log (Bb Spores/Unit) – (Spore Log Reduction)
log(PNSU) = Log (1) – (6) = 0 – 6

PNSU = 10^{-6}

Step 4: Demonstrate 6 Spore Log Reduction

Use cycle developed in Step 2 to achieve ≥ 6 SLR of BI

If we understand the heat resistance of the bioburden, we can design a cycle without having to use a highly resistant spore or thermophile.

Terminal Sterilization is the “Big Eraser”

- Process design needs to assume bioburden Numbers and Resistance
- Need to have a state of control as defined by the design space
- Terminal sterilization does not remove BET or particulate contaminants.
- If bioburden is out of control, it indicates that something else is out of control, e.g., raw material quality, housekeeping, training, sanitization….
- Need to have container integrity to assure sterility throughout shelf life.

BI Positives in Requalification = Undetected Product/Process Change?

Developed an Overkill process that delivered F_0 = 12 minutes. What would the survivor level be for a BI with population of 10^6 spores and D_{121C} of 1.5 minutes?

Semi-log Survivor Curve Equation:

$$\log N_F = \frac{-F_0}{D_T} + \log N_0$$

$$\log N_F = \frac{-12\ minutes}{1.5\ minutes} + \log 10^6$$

N_F = 10^{-2} or 1 in 100 units positive

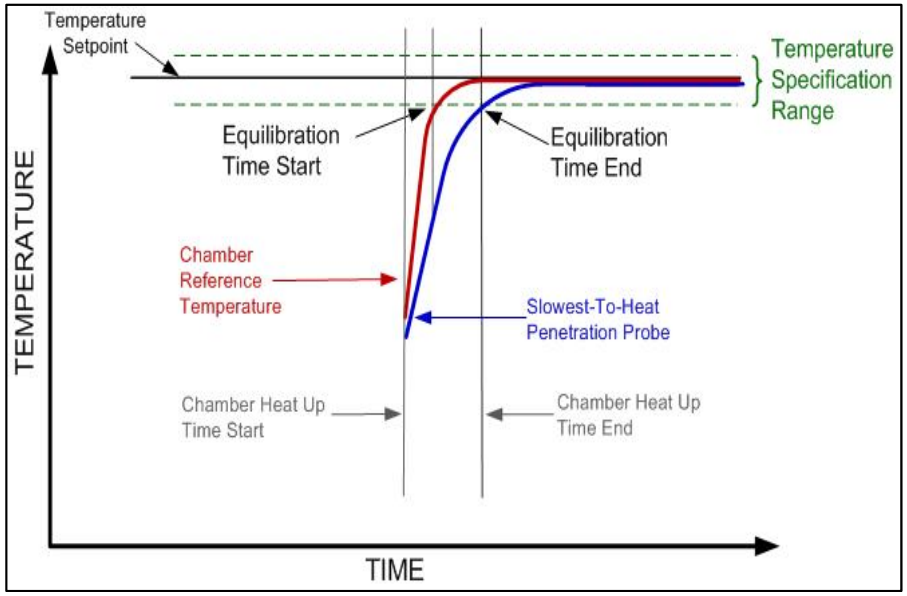
Now it is time for annual requalification and the BI selected for use contains a population of 10^6 spores and D_{121C} of 2.4 minutes. What is the expected survivor level?

$$\log N_F = \frac{-12\ minutes}{2.4\ minutes} + \log 10^6$$

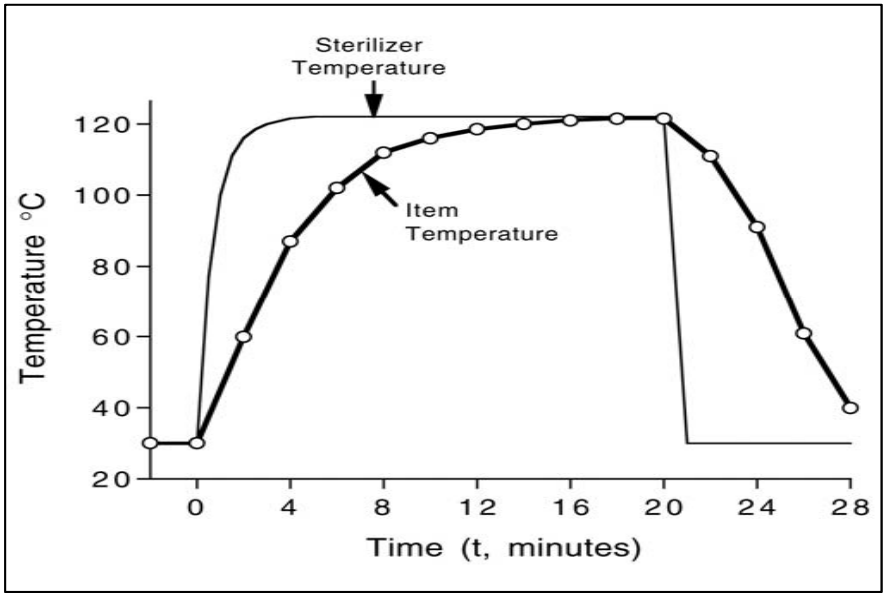
N_F = 10^1 or an average of 10 spores per unit = 100% positive!!

Porous Hard Goods, Liquid Loads – It's all the Same!

Porous Hard Goods Loads: Equilibration Time



Liquid Load: Temperature Lag Mass Dependent

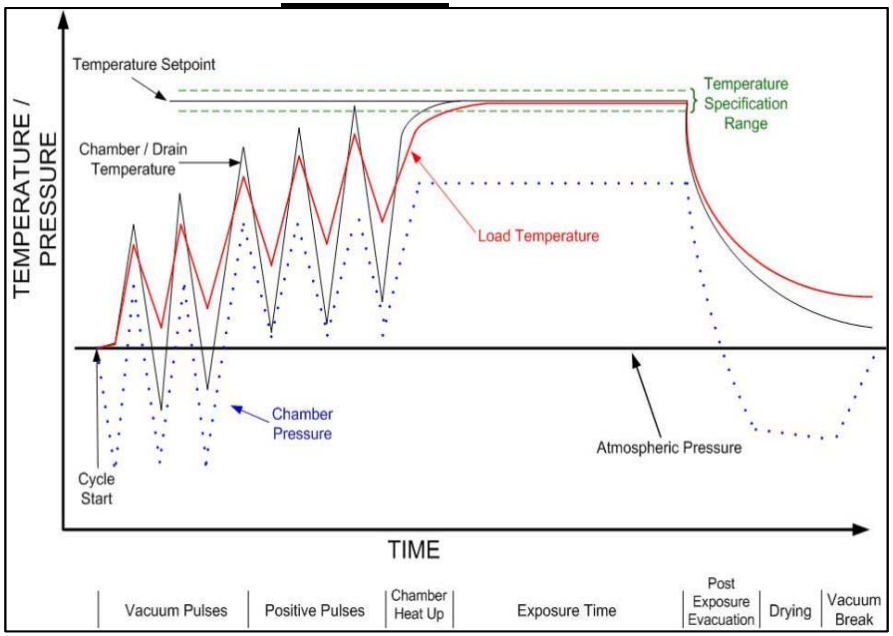


Taken from PDA TR No. 1 2007 Revision

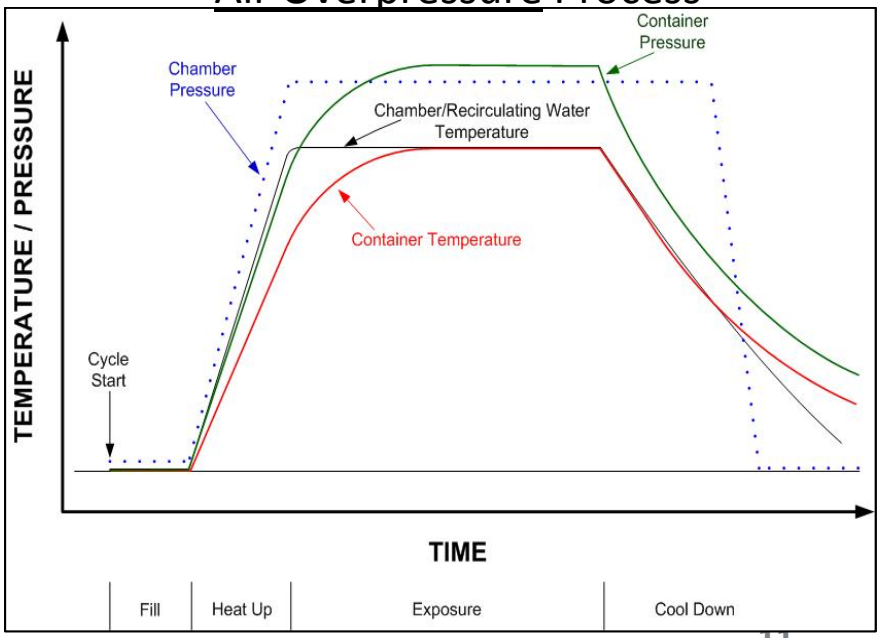
Porous Hard Goods, Liquid Loads – It's all the Same!

Air – Removed with Porous Hard Goods/Added for Liquid Loads

Porous Hard Goods: Pre-vacuum Air Removal Process



Liquid Loads: Superheated Water spray Air Overpressure Process



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Porous Hard Goods, Liquid Loads – It's all the Same!

Risks of Moisture with Porous Hard Goods (PHG)

- Liquid loads sterilized via conduction of energy through sealed container
  - Container integrity
    - Assures no contact with heating medium
    - **No risk of moisture on exterior of primary packaging**
- PHG sterilized with direct contact with saturated steam
  - Latent heat from steam transferred during condensation on sterile surfaces
  - Packaging must be porous → air removal, steam penetration, moisture removal
    - Tyvek >> Medical grade paper
  - Post sterilization –
    - **Moisture can cause wicking of microorganisms = Sterility Risk**
- Top 5 Recommendations for Dry Loads
  1. Steam trap positioned/working properly immediately before inlet to sterilizers
  2. Steam quality testing for Dryness Fraction
  3. Position heaviest items on bottom shelves of carts
  4. Prevent accumulation of condensate – invert containers
  5. Maximize Post-Dwell Evac Rate -Maximum heat under vacuum

The Sterility Test is Sensitive/Capable of Confirming Sterility

Sterility Test Shortcomings

- Statistically Limited
  - Detection Sensitivity (n = 20 samples)

True Batch Contamination Rate	Probability of One Sterility Test Positive
1.0	1.0
0.1	0.88
0.01	**0.18**
0.001	0.02
10^{-6}	1.9×10^{-5}

Note: The 20 Sample Sterility Test is only capable of detecting a contamination rate of 0.01 (Equals SAL of 10^{-2} While 10^{-6} Required for Sterility) only 18% of the time!

The Sterility Test is Sensitive/Capable of Confirming Sterility

And if Statistical Limitations Weren't Enough…

Additional Shortcomings of the Sterility Test

- Less than 1% of all microorganisms are culturable!
- Typically Employs SCD Broth at 20-25°C and FTM at 30-35°C for 14 Days
  - All Organisms do not Grow at These Conditions
  - Incubation Conditions (Temperature, Aerobic/Anaerobic, Gasses)
  - Time Required for Visual Indication of Growth
  - Test Medium (pH, Salt Content, Nutrients)
  - State of the Organisms (i.e., Spores, Injured)
  - Potential for False Positives (heat labile organisms)

Parametric Release is a New Concept

History of Parametric Release
-Moist Heat Sterilized Drug Products

- First Drug Parametric Release Submission in the United States in 1981
- Approval Granted in January, 1985, Prior to Issuance of Formal Guidance to the Industry
- The Initial Submission Served as the Model for Future Requirements
- FDA Compliance Policy Guide 7132a.13 issued in 1987
- No Further Parametric Release Approvals Until the mid-90's
- FDA Submission Guidance (February, 2010)
- Updated FDA CPG—Enforcement Guide (August 2012)

Parametric Release is Not in Widespread Practice

Current Baxter Parametric Release Locations

- Australia
- Brazil
- Belgium for US
- Canada
- China (Trial Complete)
- Ireland (also Pan-EU)
- Mexico
- Singapore
- Spain
- Thailand
- United Kingdom
- United States

Green = Recently Implemented Red = In Development

Top Reasons (Excuses?!?) for Not Adopting Parametric Release

1. PR Program is Too Expensive/Requires a Dedicated Submission—It's easier to just do the Sterility Test!
   …Sterility test suites, media, training, investigations…

2. Lack of Confidence with Sterilization/Don't Understand Requirements/Sterility Assurance Competency
   …PDA course in November…See website for 2019 courses…

Top Reasons (Excuses?!?) for Not Adopting Parametric Release

3. Can't Use the Sterility Test to Support Release if Critical Parameter Not Met

   …remember what we said about sterility tests?

4. Legal Issues Due to Continued Existence of Recognized Compendial Sterility Test

   …QA, Operations, Validation, Regulatory onboard….but Legal?

5. Not Permitted/Recognized in Current Local Regulation

   …they can be convinced…

Parametric Release is Difficult to Achieve

Parametric Release Program

- **Built on the Foundation of a Comprehensive and Mature Quality System**
- **<u>Risk Assessment</u> Conducted to Demonstrate Mitigation of all Risks to Sterility**

Personnel Training
Product Design Control
Equipment and Facility Design/Qualification
Process Development and Validation
Manufacturing Control
Quality Risk Management System
Change Control System

SCIENCE

Survivor Curve Model

Log N_F = -F/D_T + Log N_0

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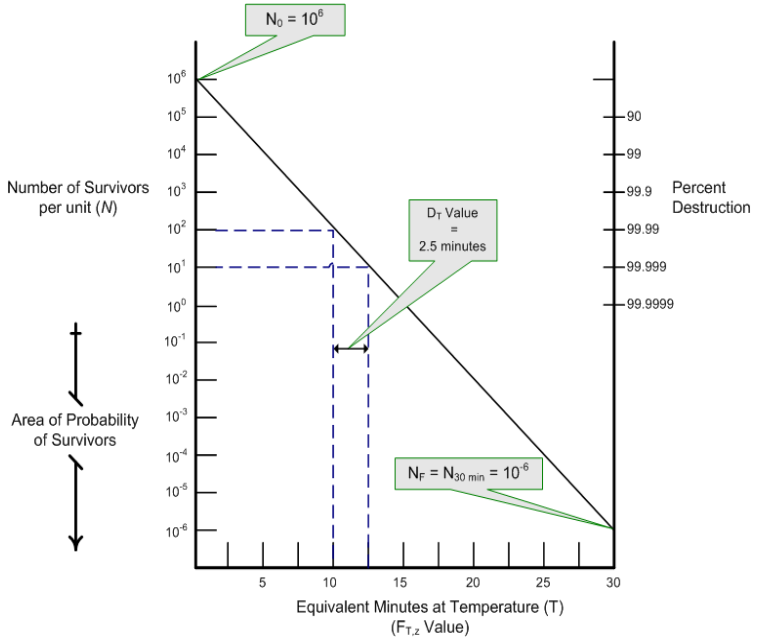


Alternate Load Monitor Case Study

Load Monitor – Required for Parametric Release to meet requirements for a laboratory test per 21 CFR 211.167a and 211.167e

Load Monitor Types

1. **Chemical Indicator/Integrator** – provides visual confirmation that product exposed to sterilization process – cannot be used to confirm sterility
2. **Load Probe** – utilizes penetration temperature from limited number of product units or surrogate of product to calculate Physical Lethality/F_0
3. **Biological Indicator** – placed in limited number of product units to determine biological lethality

Alternate Load Monitor Case Study

PDA Technical Report No. 30 on Parametric Release Section

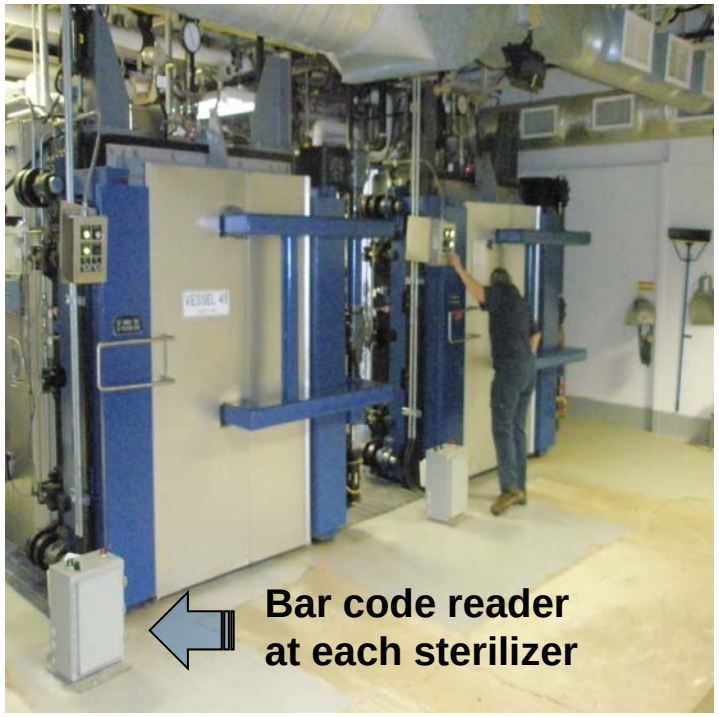
> "A validated, automated product tracking and control system may be used to segregate **sterilized from non-sterilized product**. Additional features for these systems may include human error prevention mechanisms that may prevent the use of non-calibrated sterilizers or non-validated sterilization processes."

Baxter Manufacturing Tracking and Control System (BMTCS)

- Ensures that sterilizer in qualification is current for product to be sterilized
- Ensures current sterilizer calibration
- Ensures current loading pattern
- Ensures critical parameters met for sterilization
- Uses barcode system to ID and control product movement/segregation

Alternate Load Monitor Case Study

Baxter Manufacturing Tracking and Control System



Each truck has a bar code license plate

Sterilizer operator can see product and process status on screen.

I hope that we have helped to resolve any misconceptions you might encounter

Thank You for Your Interest!

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