Steam Sterilization and the 2007 Revision of PDA Technical Report 1

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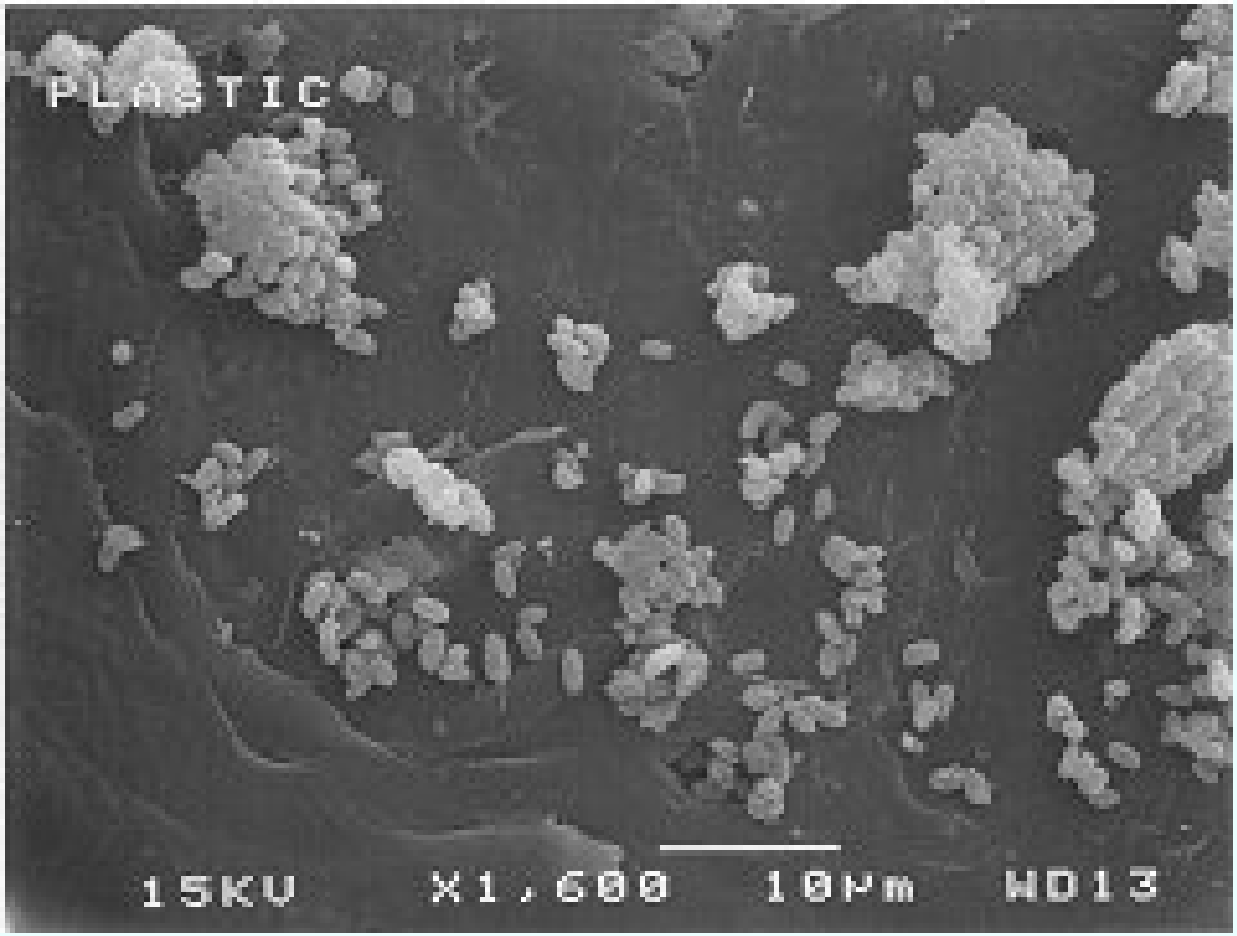
Agenda:

- Introduction
- Sterilization Science
- Sterilization Process Development
- Process Performance Qualification
- Ongoing Process Control
- Trends to Follow; Trends to Avoid

What Is It?



Just Tell Me What I have to Do!

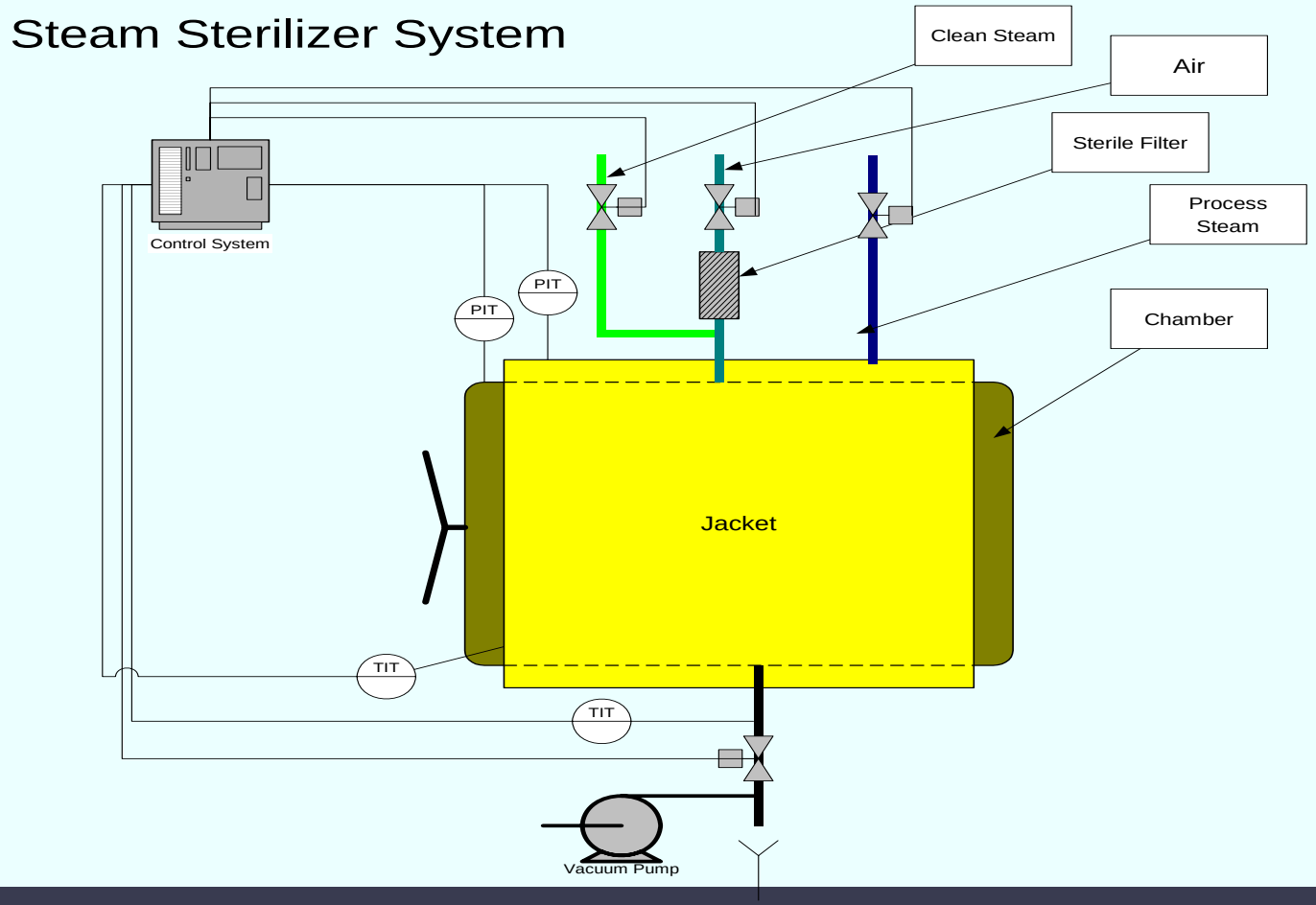
Or

If this is such a well established science why are there so many questions?

Sterilization Science

- **What is an Autoclave?**
- **Used to sterilize products and "goods"**
  - Finished product
  - Medical Devices
  - X-RAY Contrast Media
  - Lab Supplies
  - Manufacturing Equipment
  - "Packaging" Equipment
  - Gowns
- **Come in all shapes and sizes (i.e. walk-in, bench-top, pass through, etc.)**
- **All have:**
  - Chamber
  - "Heat" Supply (Process Steam for jacket or heat exchange, Clean Steam or Steam/Air mixture in chamber)
  - Vacuum Source (as applicable) or Ventilator (fan)
  - Control System

Example Autoclave P&ID



Sterilization Fundamentals:

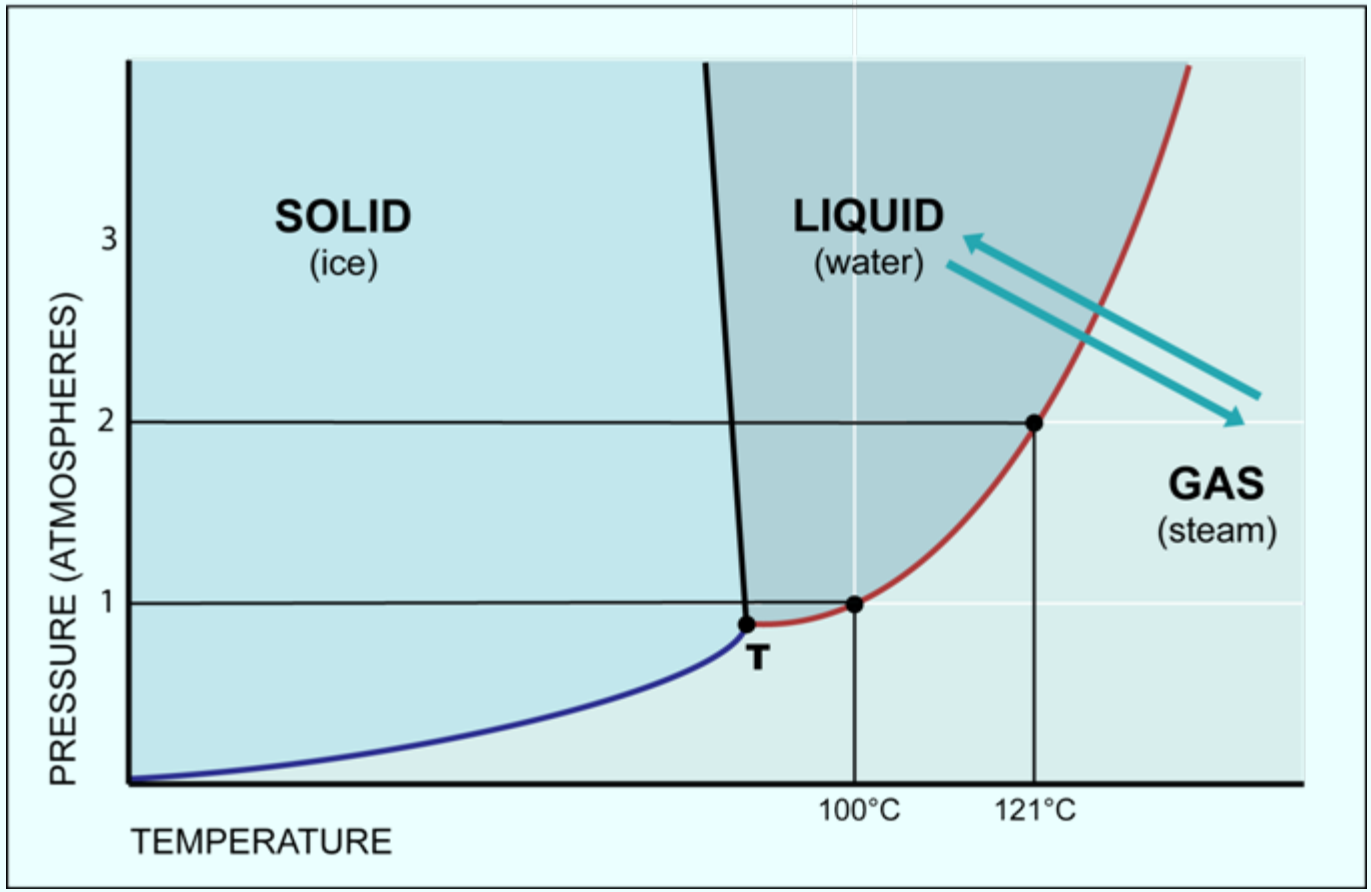
- **What do we mean by Sterilization? (Sterilization versus Sanitization)**
- **Steam as a Sterilization Medium**
- **The importance of Time and Temperature - F_0 (Minutes of Accumulated Lethality)**
- **Logarithmic Model of Reduction**
- **Biological Indicators**

Sterilization versus Sanitization:

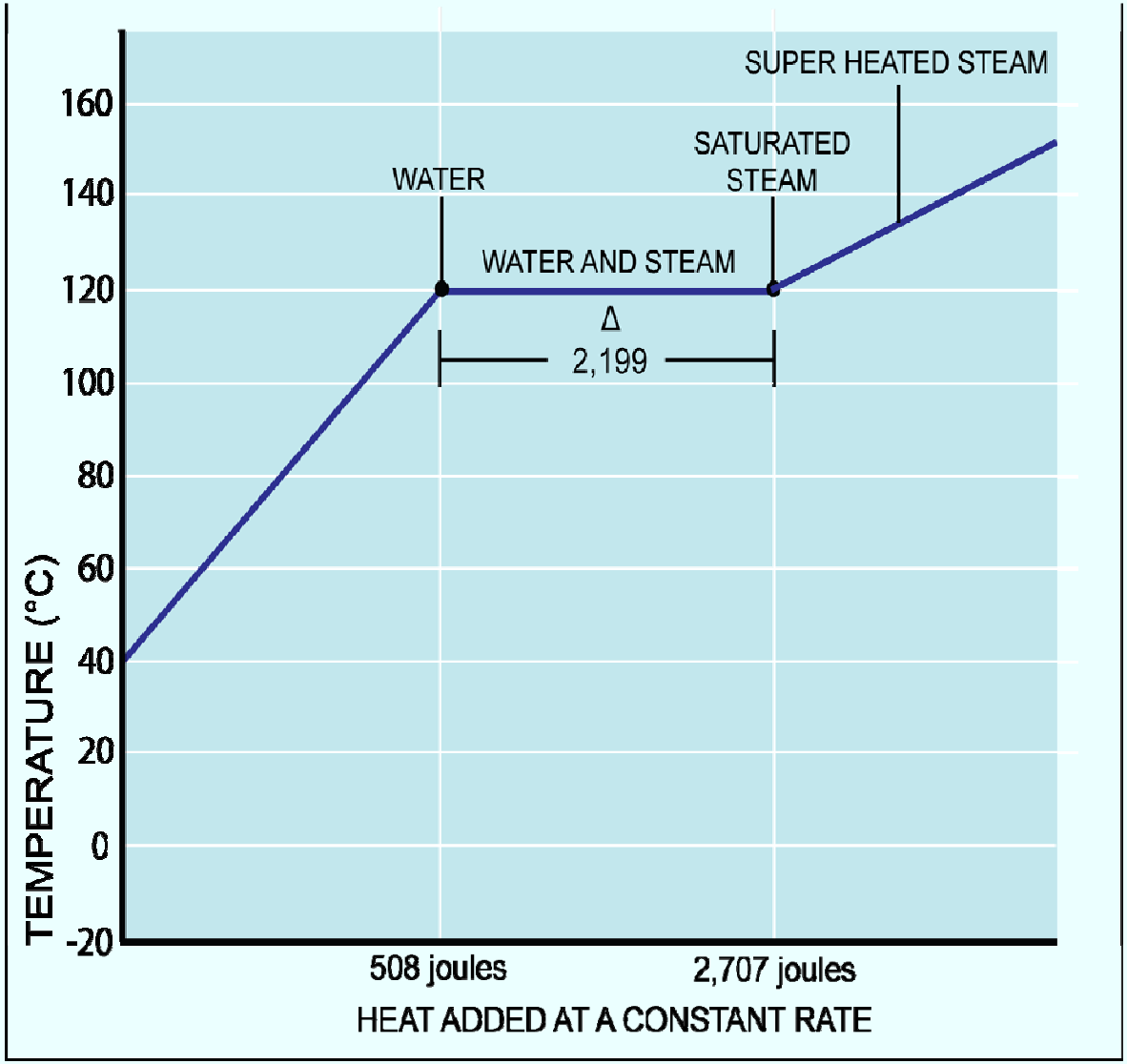
- **Sterilization:**
  - Sterilization – A process used to render a product free of viable organisms with specified probability. – PDA TR1
  - "Sterilization is an absolute term and implies the total destruction of all forms of microbial life in terms of their ability to reproduce" - G. Sykes
  - "Validated Process used to render a product free of all forms of viable microorganisms" - ISO
- **Sanitization:**
  - Process of reducing viable microorganisms to an acceptable level.

Saturated Steam:

- **Saturated steam is important because the physical change in state as the steam condenses provides the maximum amount of heat transfer to the objects being sterilized.**
  - Envision passing your finger over a candle then over a tea kettle.
- **As the steam cools (condenses), the latent heat is released to the surrounding chamber and load.**
  - The condensing of steam results in a significant volume loss which the autoclave steam supply replaces.


SOLID
(ice)
LIQUID
(water)
GAS
(steam)
T
3
2
1
PRESSURE (ATMOSPHERES)
100°C
121°C
TEMPERATURE

--PDA TR 1 2007

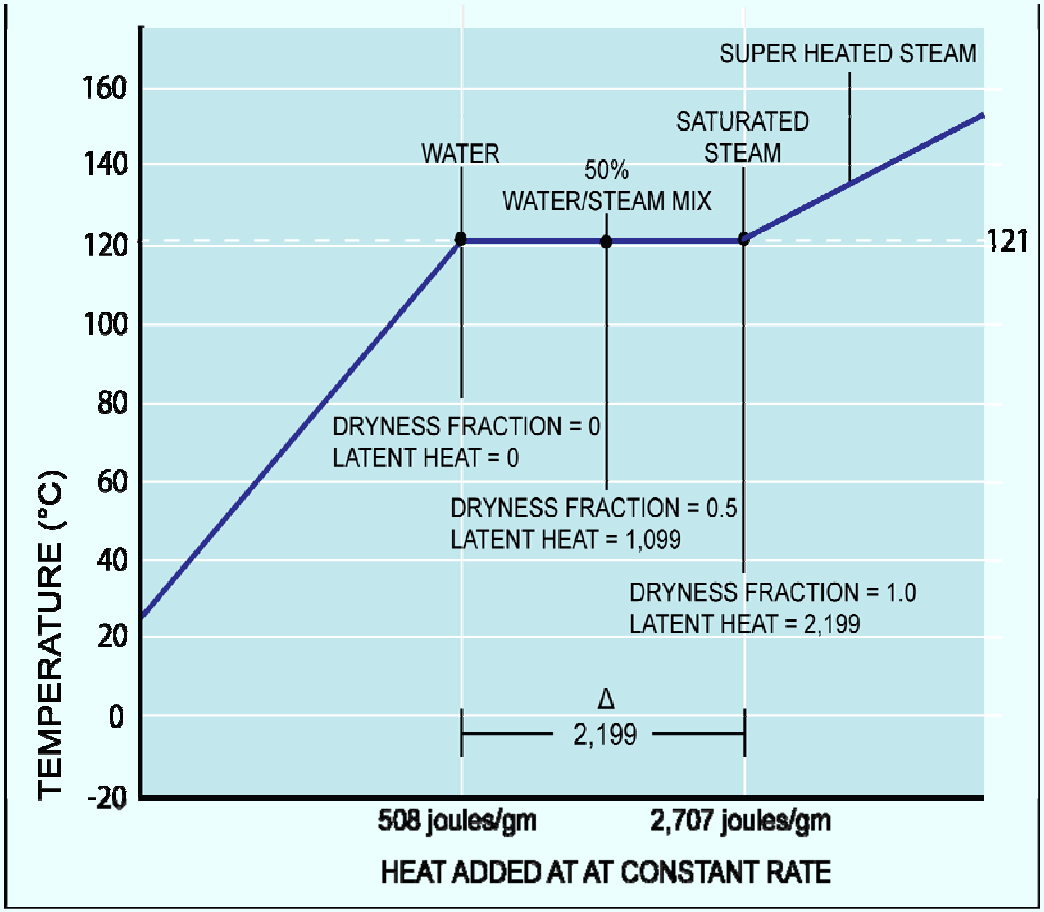

SUPER HEATED STEAM
160
140
120
100
80
60
40
20
0
-20
WATER
SATURATED STEAM
WATER AND STEAM
Δ
2,199
TEMPERATURE (°C)
508 joules
2,707 joules
HEAT ADDED AT A CONSTANT RATE

--PDA TR 1 2007

Categories of Non-Saturated Steam:

- Super Heated Steam:
  - Results in higher temperatures but much less effective heat transfer (BTU/lb-^{o}F) ability approaching dry-heat conditions.
  - As superheated steam cools, it does not condense.
- Non Condensable Gases/ Steam Air Mixtures:
  - Results in lower temperatures at elevated pressures.
  - Steam could contain mixtures of air, nitrogen, CO_2 etc
- Steam Dryness

Steam Dryness



--PDA TR1 2007

When is it desirable to have a controlled steam/air mixture?

- Sterilization of sealed containers with gas within the head space.
  - The injection of air raises the chamber pressure above the saturation pressure of steam, reducing the pressure differential between the headspace and chamber.
- Sterilization of heat labile products where a quick cool-down is desired.

Time and Temperature - F_0 "F sub O":

What is F_0 ?

- A mathematical method of defining the equivalent time at 121.1 °C for a given temperature (in minutes).
- Referred to as "Minutes of Accumulated Lethality"
- Simply stated -
  - Chamber Temp = 121.1°C F_0 = 1.0 minute/exposure minute
  - Chamber Temp = 117.0°C F_0 = 0.4 minute/exposure minute
  - Chamber Temp = 124.0°C F_0 = 2.0 minute/exposure minute

Time and Temperature - F_0 "F sub O": (continued)

How is F_0 Calculated?

- The calculation of F_0 is based on a microorganism's "D"-value and the corresponding "z"-value.
  - The D-value is a measure of the heat resistance of a particular microorganism. The D-value represents the time in minutes that is required to effect a 1-log reduction in the population of a particular microorganism. Most naturally occurring microorganisms have a D-value < 1.0.
  - The z-value is the temperature change required to effect a 1 log reduction in the D-value.

Time and Temperature - F_0 "F sub O": (continued)

Why is F_0 Important?

- F_0 provides a relationship between sterilization temperature and biological "kill".
- F_0 provides a method of determining the Sterility Assurance Level (SAL).
- F_0 can be accumulated. (More of a convenience for SIP processes which may have temperature variations).

Time and Temperature - F_0 "F sub O": (continued)

How is F_0 Used?

- F_0 is used to calculate the log reduction of a spore population having a *theoretical* D-value of X minutes.
  - Examples:
    - Spores with a D-value of 1.0 minute will be reduced by 1 log for each minute of F_0.
    - Spores with a D-value of 2.0 minutes will be reduced by 1 log for every (2) two minutes of F_0.

Biological Indicators (BI's):

What are They?

- A BI "is a characterized preparation of specific microorganisms resistant to a particular sterilization process. It is used to assist in the qualification of the physical operation of sterilization…" - USP 25
- There are three forms of BI's:
  - SPORE STRIPS - (Paper strips inoculated with spores and placed inside a glassine envelope).
  - AMPOULE - (glass vial filled with spore suspension and chemical indicator).
  - SUSPENSION - (solution of spores suspended in Ethanol or Water used for direct surface inoculation).

Biological Indicators (BI's): (Continued)

How are they characterized?

- BI's are characterized by:
  - Species/Strain of microorganism
  - Carrier Form or Type (e.g. Spore Strip)
  - Spore Population (e.g. 1 x 10^6)
  - Heat Resistance or……..
    - D-value

Note that many firms perform an internal verification for each BI lot to verify population and in some cases the D-value.

Biological Indicators (BI's): (Continued)

Why are they Used?

- BI's provide a direct measure of sterilization effectiveness. (e.g. growth / no-growth)
- Available with varying ranges of D-values to provide user with worst-case microorganism.
- "Validate" the use of calculated F_0.

BI's for Steam Sterilization:

There are a number of BI's recommended for use in moist heat sterilization:

- Bacillus Subtilis
- Bacillus smithii (formerly Bacillus coagulans)
- Clostridium Sporogenes
- Geobacillus Stearothermophilus

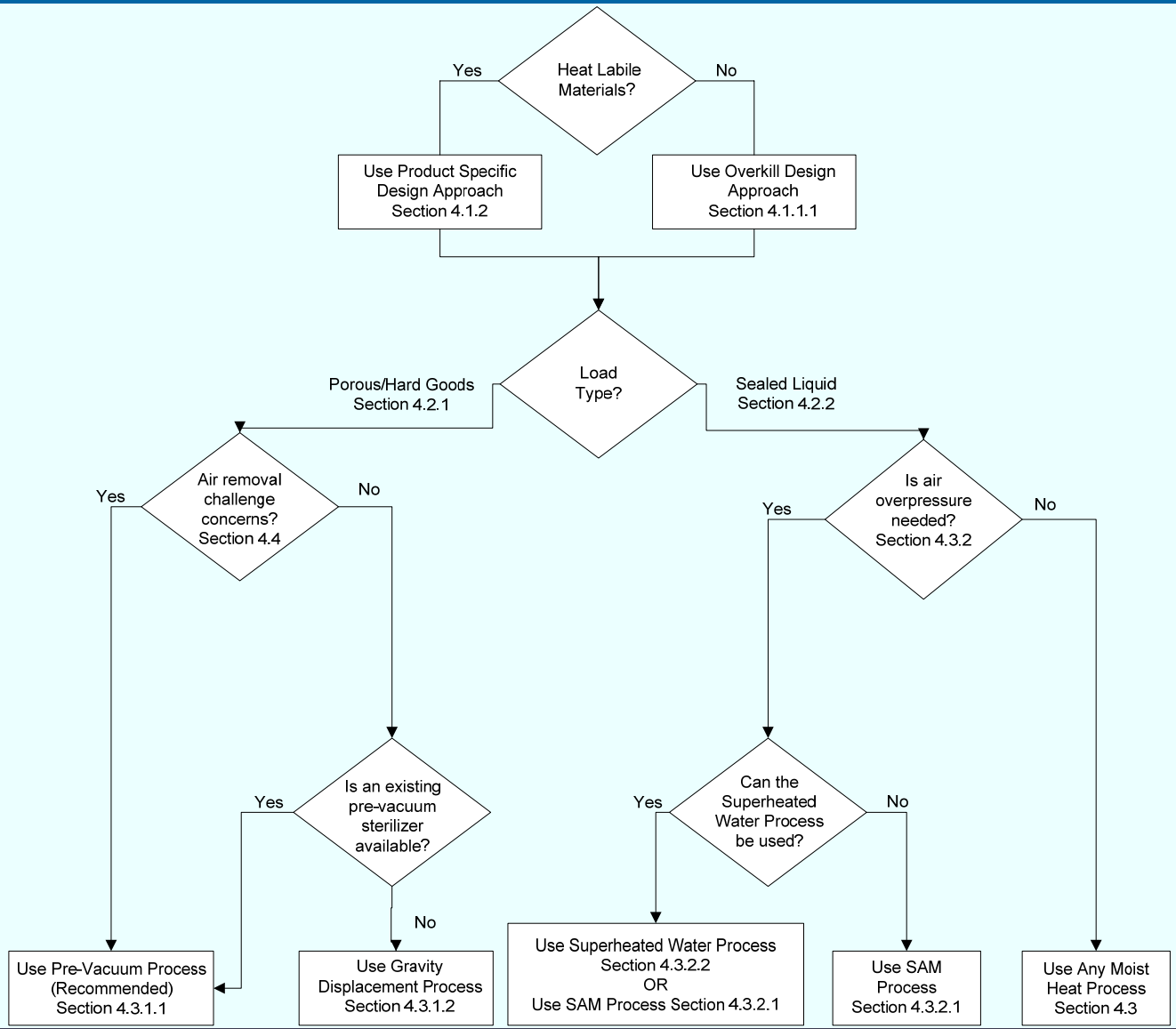
Geobacillus Stearothermophilus is the most common:

- Highly resistant to heat and in most cases is a worst-case organism.
- Wide range of D-values (1.0 to 3.0 minutes).
- Wide range of population available (10^4 to 10^6)
- All Carrier forms available

Sterilization Process Development:

First determine the steam sterilization method based upon product / material type within defined loading pattern.

- Bioburden Approach
  - Used for sterilization of heat labile materials and products.
- Bioburden / Bioindicator Approach
  - Used for materials and products with intermediate heat resistant characteristics
- Overkill Approach
  - Used for materials and products that are heat stable


Heat Labile Materials?
Yes
No
Use Product Specific Design Approach Section 4.1.2
Use Overkill Design Approach Section 4.1.1.1
Load Type?
Porous/Hard Goods Section 4.2.1
Sealed Liquid Section 4.2.2
Air removal challenge concerns? Section 4.4
Yes
No
Is air overpressure needed? Section 4.3.2
Yes
No
Is an existing pre-vacuum sterilizer available?
Yes
No
Can the Superheated Water Process be used?
Yes
No
Use Pre-Vacuum Process (Recommended) Section 4.3.1.1
Use Gravity Displacement Process Section 4.3.1.2
Use Superheated Water Process Section 4.3.2.2 OR Use SAM Process Section 4.3.2.1
Use SAM Process Section 4.3.2.1
Use Any Moist Heat Process Section 4.3

--PDA TR1 2007

Bioburden Approach:

Objective is to provide sufficient heat to provide a minimum of 10^{-6} probability of microbial survival without adversely affecting the product or materials.

- Accomplished by:
  - Determining the number and resistance of naturally occurring microorganisms associated with the product.
    - *PDA Technical Monograph No. 1*
  - Calibrating Biological Indicators in order to challenge the process lethality.
  - Validating equipment and sterilization cycle.

Bioburden / Bioindicator Approach:

Objective is to provide sufficient heat to provide a *calculated* minimum of 10^{-6} probability of microbial survival without adversely affecting the product or materials.

- Accomplished by:
  - Determining the number and resistance of naturally occurring microorganisms associated with the product.
  - Using commercially available Biological Indicators to demonstrate process lethality. (...but accepting positive results…)
  - Validating equipment and sterilization cycle.

Overkill Approach:

Objective is to provide sufficient heat to provide a minimum of 10^{-6} probability of microbial survival regardless of the number and heat resistance of the naturally occurring microorganisms.

- Accomplished by:
  - Designing a sterilizing process that results in a 12-log reduction of microorganisms having a “D”-value of 1 minute.
  - Validating equipment and sterilization cycle.

Comparison of Approaches:

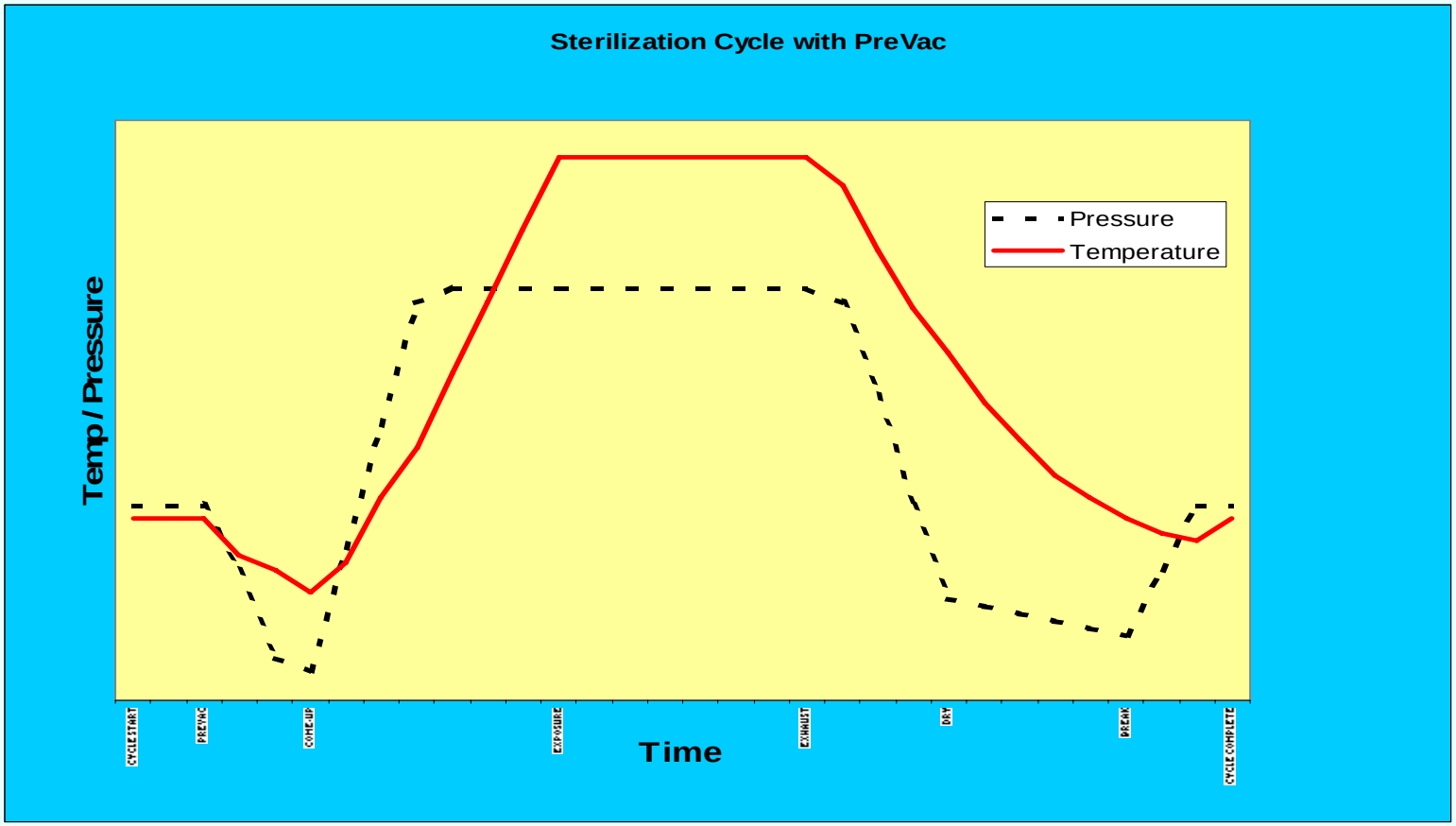
The fundamental difference between each approach is in the amount of upfront work needed to calculate the required Process Lethality (F-Value).

- Bioburden and Combination Approach:
  - Number of naturally occurring microorganisms. (population)
  - Heat Resistance of naturally occurring microorganisms. (D-value)
  - Change in heat resistance w.r.t. temperature changes. (z-value)
- Overkill Approach:
  - F-Value is assumed to be 12 based upon a D-value of 1 minute, resulting in a 12-log reduction.

Anatomy of a Steam Sterilization Cycle:

- **Phase 1: Preconditioning (Air Removal)**
  - Gravity
  - Forced (vacuum)
  - Pulsing (vacuum/steam inject)
- **Phase 2: Come-up**
- **Phase 3: Exposure**
- **Phase 4: Postconditioning (Exhaust / Drying)**

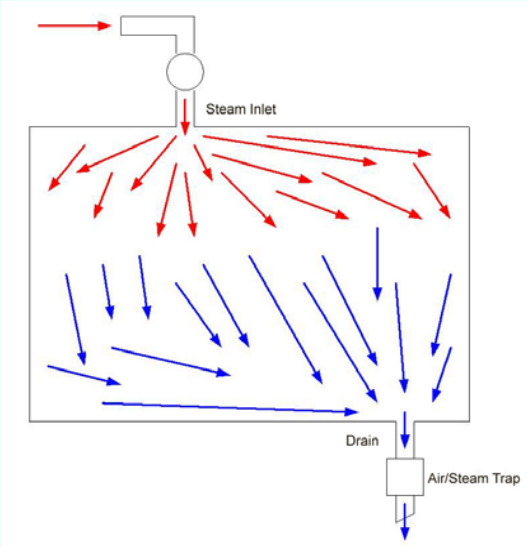
Anatomy of a Steam Sterilization Cycle: (continued)



Phase 1:
Preconditioning - Gravity Air Removal:

For Gravity Air Removal, the basic principle is that the density of air is greater than that of steam. Thus air will "settle" and be evacuated from the chamber as steam is introduced.

- While this typically does not present a problem for studies within empty chambers, it can be very difficult to remove air from items within a loaded chamber such as filters and tubing, resulting in a lack of sterility assurance.



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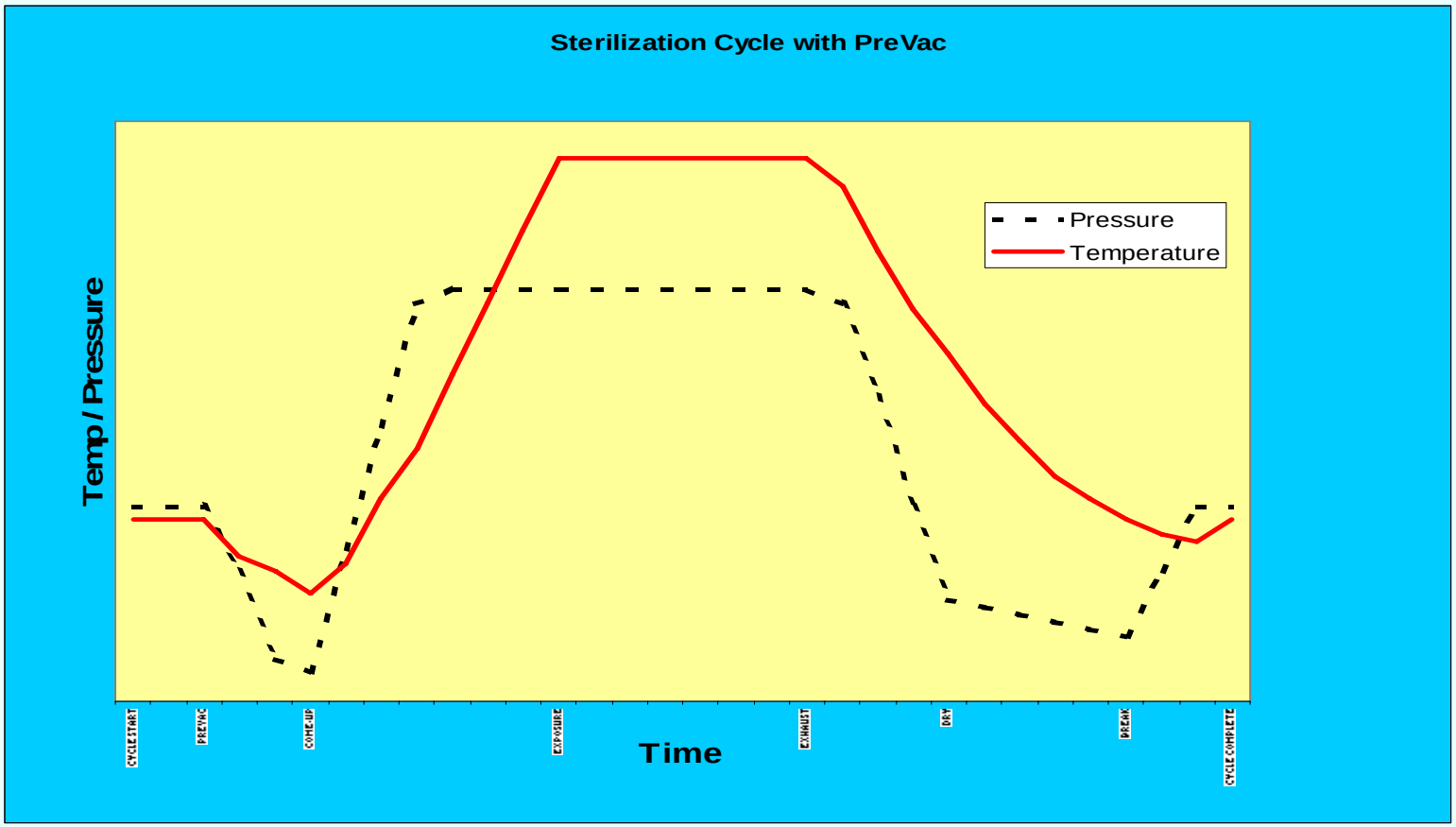
Phase 1:
Preconditioning - Forced Air Removal:

The use of a Prevacuum step ensures the removal of air from the autoclave chamber.

- The prevacuum step is typically executed until a specified vacuum level is reached.
- For many processes, multiple vacuum cycles may be employed to remove air from within various loads.

Phase 1:
Preconditioning - Forced Air Removal: (continued)

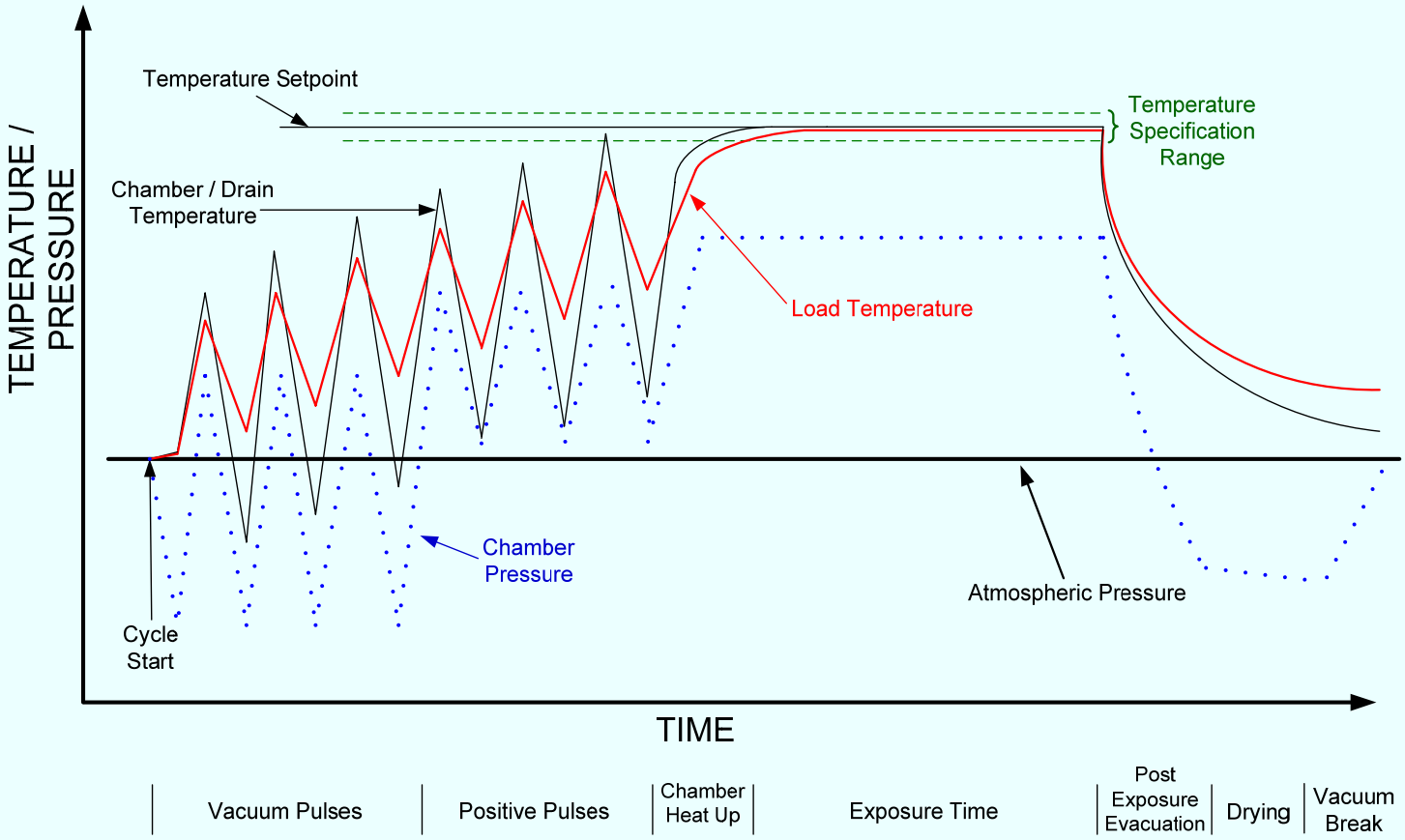


Phase 1:
Preconditioning - Pulsing Air Removal:

The use of intermittent vacuum and steam inject "pulses" allows for the complete removal of air at lower vacuum levels.

- Similar to Forced Air Removal, a vacuum is pulled until a desired vacuum level is reached. This is followed by an injection of steam until the desired chamber pressure is reached. This process is then repeated for a set number of times.

Phase 1: Preconditioning - Pulsing Air Removal: (continued)



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Phase 2: Come-up

Come-up is simply that point within the cycle in which steam injection is taking place in an attempt to raise the chamber temperature to the desired setpoint (typically 121.1 ºC) .

Phase 3: Exposure

Exposure is the term used to indicate that the chamber is at the desired temperature (typically 121.1 ºC) and the control system has begun to record the exposure "time".

- Once the chamber reaches the desired conditions, a "timer" is started to "time" the exposure period.
- The completion of the exposure period is indicated by time, accumulated F_0, or some combination of both.

Phase 4: Postconditioning

The objective of postconditioning is to cool and dry the objects within the chamber and to return the chamber to ambient conditions.

Cycle Development - What's Next?

At this point, we have determined the approach to be followed and the required lethality…..what's next?

- Ensure autoclave has been qualified demonstrating proper installation and operation qualification

Cycle Development: (cont.)

Perform information gathering studies

- Liquids
  - Perform Container Mapping (LVP) to identify temperature gradients within containers
  - Determine effect of liquid on the Bioburden
- Dry Goods - Determine hardest to heat items
  - Items with a lot of mass
  - Items that present a potential barrier to steam penetration
  - Items that are wrapped or packaged
- Define load configuration(s)
  - Condensate Pooling (as applicable)
  - Air Removal (as applicable)
  - Wrapping and orientation of goods
  - Manufacturing flexibility

Cycle Development: (cont.)

- Perform engineering studies to verify appropriate lethality and reproducibility of load.
  - Place TCs throughout load to demonstrate acceptable temperature limits, including min, max , and uniformity are being achieved.
  - Place BIs to demonstrate required lethality is delivered and therefore air is removed from chamber and goods is being achieved.
- Generate / Modify SOPs to reflect:
  - loading configurations (e.g. fixed locations, orientation restrictions)
  - load options
  - Wrapping conditions
  - Orientation of items

Process Performance Qualification:

The key is to first understand that a cycle is designed to deliver a minimum lethality.

Then understand that the concepts presented earlier are used to prove that this lethality is consistently delivered.

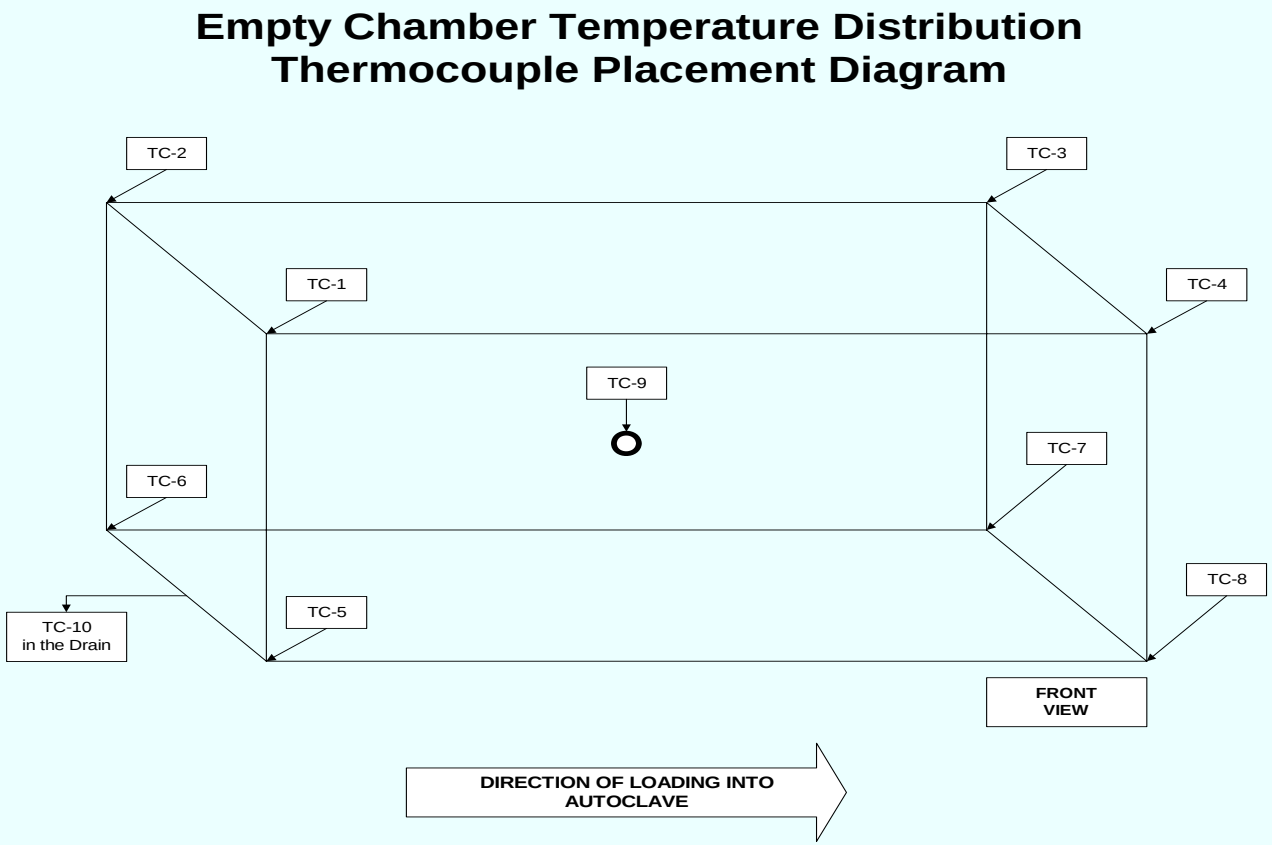
- Accumulated F_0
- Biological Indicators

Empty Chamber Temperature Distribution Test:

Testing Design:

- Calibrated Type T (copper-constantan) thermocouples should be distributed evenly throughout the chamber interior in representative horizontal and vertical planes, including the center and all corners.
- One (1) thermocouple should be placed adjacent to the controlling probe (in drain).
- Thermocouples should be suspended within chamber to avoid direct contact with interior surfaces.
- A minimum of ten (10) thermocouples should be used, including control probe locations.
- For “large” chambers, five (5) thermocouples per 100 cubic feet of volume is recommended.

Empty Chamber Temperature Distribution Test: (continued)



Heat Penetration Test:

The objective of this test is to verify the effectiveness of the sterilization cycle for each load configuration.

- Testing should be conducted in triplicate:
  - Temp. Uniformity throughout the load should be based on realistic requirements for each load. For example, LVP cycles may require tight temp. uniformity while dry goods may not.
  - Demonstrate that each cycle is capable of providing the required lethality.
    - Demonstrate reproducibility for:
      - » Loading
      - » Orientation
      - » Wrapping

Heat Penetration Test: (continued)

- Common Acceptance Criteria:
  - Temperature during exposure phase is greater than 121.1 °C.
  - Average Temperature of each probed location (during exposure phase) does not fluctuate by more than 1 °C.
  - Average Temperature throughout the chamber does not fluctuate by more than 2 °C.
  - For cycles with a sterilization of 115 °C. All temperatures are within 115 °C to 118 °C.
    - » 121 °C 121 °C to 124 °C
    - » 126 °C 126 °C to 129 °C
    - » 134 °C 134 °C to 137 °C

Heat Penetration Test: (continued)

Test design:

- Autoclave should be loaded in accordance with company SOP for a specific load
- Cold spots identified using good engineering practices
  - Items that come in contact with a sterile product
  - Items that present a potential barrier to steam penetration
  - Items with a lot of mass
  - Items that are wrapped or packaged
- One (1) thermocouple next to drain control probe
- Calculate F_0 at each location

Heat Penetration Test: (continued)

Testing should employ the use of Biological Indicators

- For Steam Sterilization and Overkill Approach
  - Bacillus Stearothermophilus
  - "D"-Value = 1.0 to 3.0 minutes
  - Population of 1×10^6

Biological Indicators should be placed at the hardest to heat locations within the load. Mapping studies can be employed to identify these spots.

Ongoing Process Control:

Post Processing Cycle Review:

- **Verify each critical parameter identified in the validation is meet**

Routine Monitoring:

- Air removal test - Bowie-Dick
- Leak Rate Testing
- Air Detector Device

Change Control:

- An effective change control process must be established and used

Periodic Requalification:

- Requalification, Revalidation, Validation Maintenance

Routine Monitoring:

- Daily
  - Bowie-Dick (EU Standard)
- Weekly
  - All Daily Tests
  - Safety Checks (door seal, door safety checks, safety valves/devices)
  - Leak Rate Testing
- Quarterly
  - All Weekly Tests
  - Thermometric Response (Small Load) {Not Common}
- Yearly
  - All Quarterly Tests
  - Steam Quality
  - Requalification

Requalification - Revalidation:

- **Revalidation is conducted at defined frequencies to demonstrate that the autoclave is within a "state-of-control".**
- **Revalidation should be conducted when:**
  - Changes are made to the Autoclave
    - Load Configuration
    - Cycle Parameters
  - Changes are made to the steam supply source that may have an impact on the performance of the autoclave.
  - Annually

Revalidation: (continued)

Revalidation testing should consist of:

- A documentation review:
  - Change Control records
  - Maintenance records
  - SOP revisions
  - Regulatory guidance documents
- Heat Penetration of a defined load configuration
  - Utilize BI's but be aware of original validation testing
    - Initial Validation….. D-value = 1.0
    - Revalidation…….. D-value = 2.0

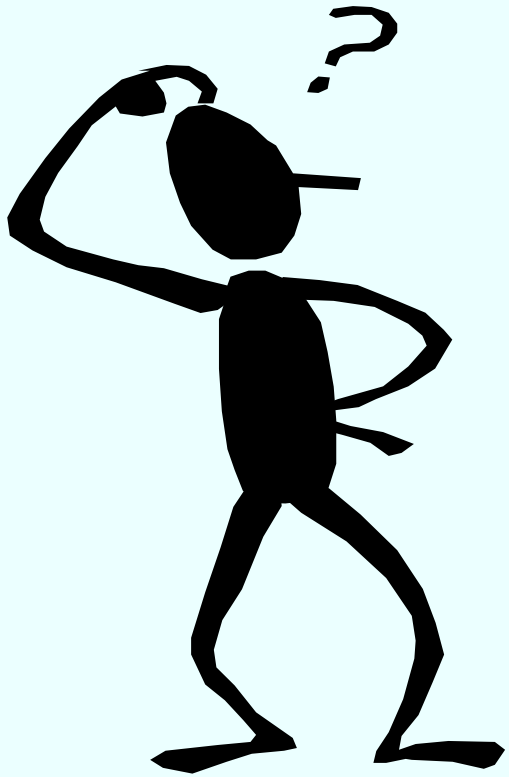
Trends to Follow; Trends to Avoid

- **Tell me about HTM 2010 and this 15 and 30 second equilibration time**
  - "HTM 2010 gives guidance…of the following types of sterilizes in use in the National Health Services:
    - clinical sterilizers
    - laboratory sterilizers" (Preface, p. 3)

Trends to Follow; Trends to Avoid

- **Inoculation of Stoppers directly**
- **Inoculation of The Vial Stopper Seal**
- **Annual Requalification Loads**

Questions?



Course References:

- *The United States Pharmacopeia*, USP 24/NF19, 1999, Rockville, MD, The United States Pharmacopeial Convention
- *Guidance for Validation and Routine Control of Industrial Moist Heat Sterilization*, ANSI/AAMI/ISO 11134 - 1993
- *Validation of Pharmaceutical Processes - Sterile Products*, 1999, New York, Carleton and Agalloco
- *Health Technical Memorandum (HTM) 2010*
- Technical Report No. 1 Revised 2007, Validation of Moist Heat Sterilization Process: Cycle Design, Development, Qualification and Ongoing Control
- AAMI TIR No. 13, *Principles of Industrial Moist Heat Sterilization*, 1997.
- Therapeutic Products Program, Canada, *Moist Heat Sterilization for Pharmaceuticals*, March , 2001.
- ISO 11138-1 (1994), *Sterilization of Health Care Products: Bioindicators: Part 1, General*
- *ISO 11138-3 (1995), Sterilization of Health Care Products: Bioindicators: Part 3, B.I.'s for Moist Heat Sterilization*
- CEN TC 102/WG 5, N270, *Small Steam Sterilizers*.
- *EN 285, Sterilization – Steam- Large Sterilizers*
- *EN 554, Sterilization of Medical Devices- Validation and Routine Control of Sterilization by Moist Heat.*

Europe's Approaches to Moist Heat Sterilization

- **Widespread acceptance of standard 121 °C, 15 min cycle. Little development of alternative cycles.**
- **Greater emphasis on measurement of entrained air in product and load, super heated or dry steam, and non-condensable gases.**
- **B.I. use and inactivation considered an option in some cases. B.I. use considered an added verification.**
- **Acceptance of 121 °C, 15 min cycle without B.I. challenge**
- **Development of alternative cycles is the exception.**
- **When B.I.'s are used, *G. stearothermophilus* is the microorganism of choice.**
- **Heavily influenced by UK hospital practices.**

U.S. Approaches to Moist Heat Sterilization

- **Inactivation of heat resistant microorganisms to assure at least a 10^6 SAL is the focus.**
- **Variable cycle time/temperatures can be used to attain a 10^6 SAL. Variable cycles acceptable.**
- **B.I.'s required in cycle development and validation programs.**
- **Use of different types of heat resistant B.I.'s are acceptable.**
- **Recognized importance of cycle thermal profile data, but emphasis is on the use of microorganisms for validation purposes.**
- **Importance of method validation is recognized.**

Other Moist Heat Sterilization References

- Technical Report No. 1 Revised 2007, Validation of Moist Heat Sterilization Process: Cycle Design, Development, Qualification and Ongoing Control
- AAMI TIR No. 13, *Principles of Industrial Moist Heat Sterilization*, 1997.
- Therapeutic Products Program, Canada, *Moist Heat Sterilization for Pharmaceuticals*, March , 2001.
- ISO 11138-1 (1994), *Sterilization of Health Care Products: Bioindicators: Part 1, General*
- ISO 11134 (1994) *Sterilization of Health Care Products-Requirements for Validation and Routine Control of Industrial Moist Heat Sterilization.*
- *ISO 11138-3 (1995), Sterilization of Health Care Products: Bioindicators: Part 3, B.I.'s for Moist Heat Sterilization*
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