VALIDATION OF STERILIZATION EQUIPMENTS

Aseptic Area Validations

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Suat Kumser
Pfizer İlaçları Ltd. Şti.
e-mail: suat.kumser@pfizer.com

Turkish Pharmaceutical & Chemical Industry Research and Development Foundation

Content:

- Definition of Sterilization and Depyrogenation
- Microbiological aspects of Sterilization and Depyrogenation, Lethality calculation,
- D Value, F_H & F_0 Values
- Z Value and use of microbiological indicators.

Content:

- Dry Heat Ovens
- Dry Heat Sterilization Tunnels
- Steam Sterilizator (Autoclaves)

1. Design Qualification
2. Installation Qualification
3. Operational Qualification
4. Performance Qualification

4.1. Thermodynamical aspects of Sterilization

3.2. Temperature Distribution and Heat Penetration studies.

Definitions:

- 1. Sterilization:

  Validated process used to render a product free of living microorganisms including bacterial endospores.
- 2. Depyrogenation:

  Removal or inactivation of bacterial endotoxin.

Sterilization Only:

- The cycle is designed to assure that the probability of survival of the native microflora is no greater than one cell in one million units of the commodity.

  (10^{-6} probability of nonsterility)
- Dry Heat Sterilization, Theoretical requirement: 170 ^{0}C, 32 min.
- Steam Sterilization Theoretical requirement: 121 ^{0}C, 15 min.

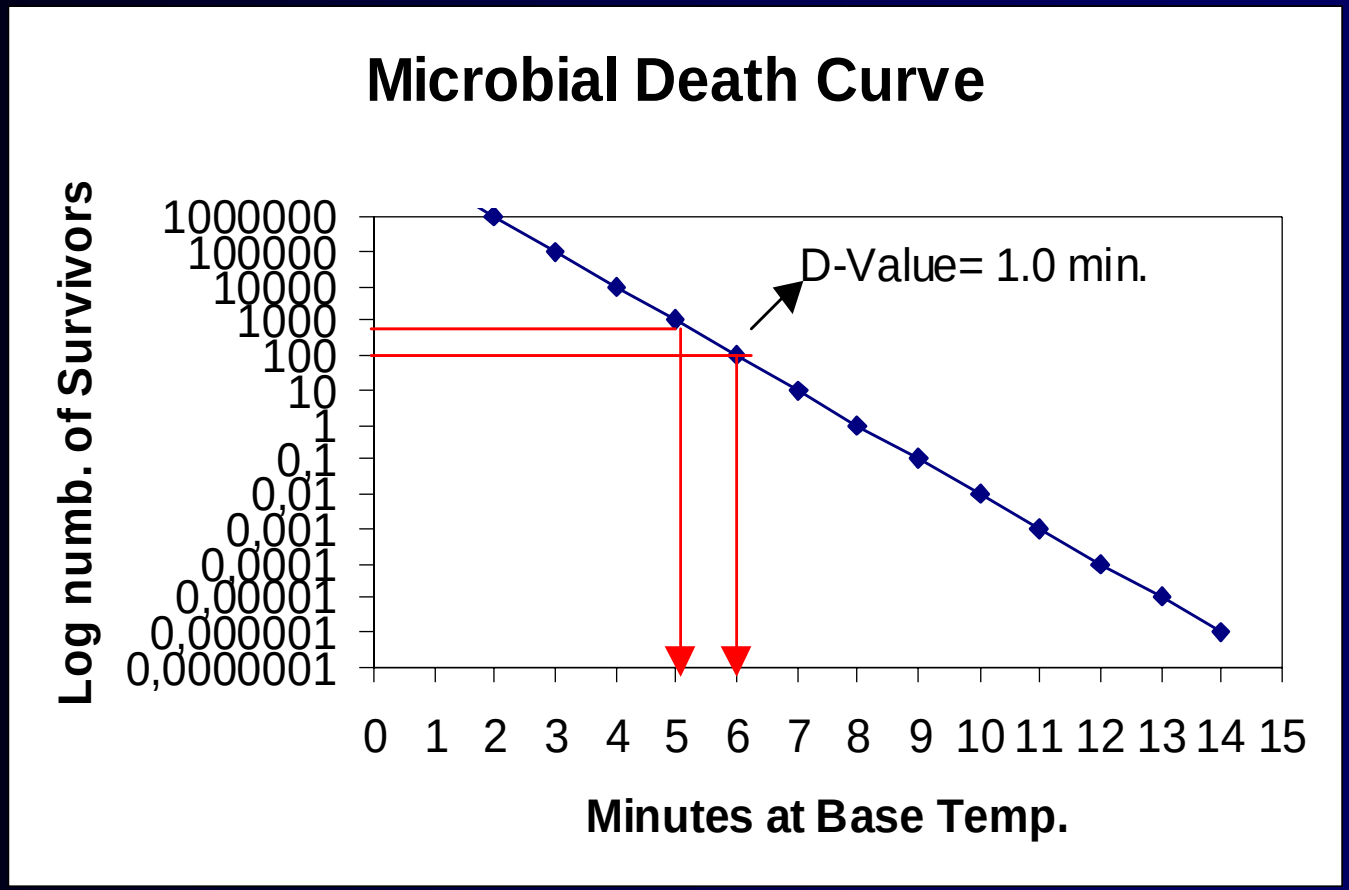
Sterilization - Overkill

- The overkill approach provides assurance of sterilization well in excess of the 10^{-6} probability of non-sterility. For example an F_H provided by an overkill cycle may produce a 12 log reduction of a biological indicator that exhibits a high resistance to dry heat.

Sterilization & Depyrogenation

- Applies to the cycles where the purpose is both sterilization and depyrogenation. Whenever depyrogenation is a desired end point, relatively high temperatures and/or extended heating times are necessary. Thus, microbial lethality delivered by these cycles provides a margin of safety far in excess of a 10^{6} probability of nonsterility.
- Dry Heat Depyrogenation Theoretical requirement: 250 ^{0}C-30 min.

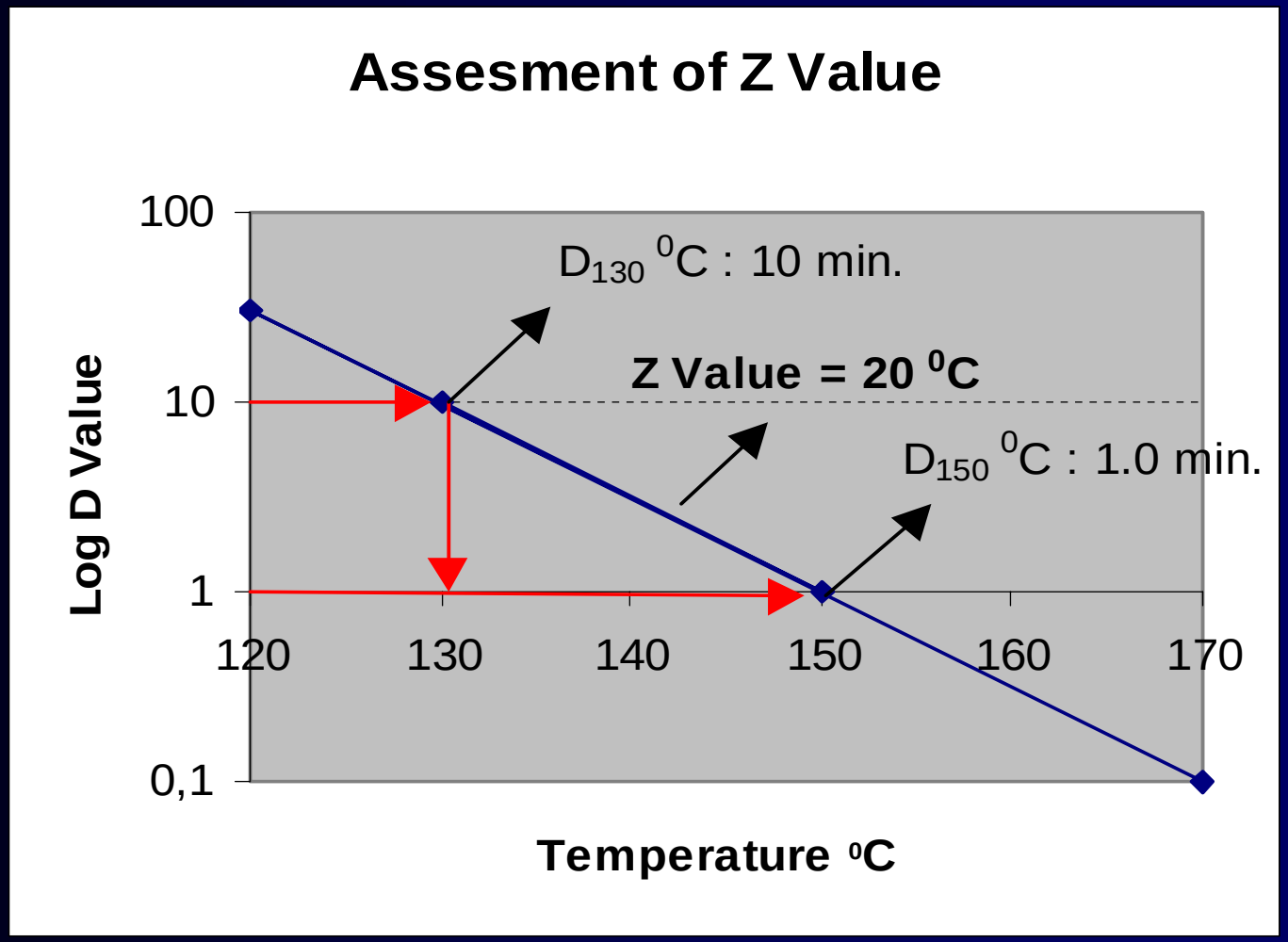
D - Value : Time required for one log (or 90%) reduction of microorganism population at base temperature.



Determination of Z - Value:

- Determine the D- value of an organism at min. three different temperatures.
- Construct a Thermal Death Curve by plotting the logarithm of the D Value versus temperature.

Z-Value: Death Rate Constant



Z-Value:

- In general, for Dry Heat sterilization, Z Value may be assumed as 20 ^{0}C. And for Steam Sterilization as 10 ^{0}C.

- However, it will be appropriate to verify for the biological indicators when they are used to measure the integrated lethality of a dry heat or steam sterilization cycle.

LETHALITY RATE:

Also defined as :

- F_H For Dry Heat Sterilization
- F_o For Steam Sterilization
- The equivalent sterilization time spent at the base temperature.
- T_b : 170 ^oC (For Dry Heat Sterilization)
- T_b : 121 ^oC (For Steam Sterilization)

LETHALITY CALCULATION "Patashnik Method"

Lethality Rate : $\mathbf{10}^{(T-Tb)/Z}$

$F_H = \Delta t \times$ Lethality Rate

Δt : Cycle time

T : Actual Cycle temperature

T_b : Base Temperature

Z : Microbial Death Rate Constant

LETHALITY CALCULATION

Example:

Determination of F_H of a 3 min. dry heat sterilization cycle at 175 ^{0}C

t = 3 min

T = 175 ^{0}C

Tb = 170 ^{0}C

z = 20 ^{0}C

$F_H = 4 \times 10^{(175-170)/20}$

$F_H = 5.31$

Sterilization at 175 ^{0}C for 3 min. is equivalent to 5.31 min. at 170 ^{0}C .

Lethality in Dry Heat Sterilization

Time (min)	Temperature (^{0}C)	Lethality Rate min. at 170 ^{0}C
5	105	0,0006
10	110	0,0010
15	120	0,0032
20	135	0,0178
25	150	0,1000
30	165	0,5623
35	170	1,0000
40	172	1,2589
45	174	1,5849
50	174	1,5849
55	174	1,5849
60	175	1,7782
65	165	0,5623
70	150	0,1000
75	140	0,0316
80	130	0,0100
85	110	0,0010
90	105	0,0006

– Σ of Lethal Rates : 10.1912

– $F_H = \Delta t \times \Sigma$ of Lethal Rates

– Δt = 5 min.

– $F_H = 5 \times 10.192$

– F_H = 50.961 min. at 170 ^{0}C .

PART-1

DRY HEAT STERILIZATION AND DEPYROGENATION VALIDATION

DRY HEAT STERILIZATION & DEPYROGENATION

- Dry heat is often the agent of choice for sterilizing items which will tolerate high temperatures. Dry heat sterilization processes are generally less complicated than steam processes, although higher temperature and/or longer exposure times are required because microbial lethality associated dry heat is much lower than that for saturated steam at the same temperature.

Thermodynamical Aspects of Heating Process:

1. Convection Heating Process:

- The heat transfer through a medium by motion of it 's parts. Natural convection is a result of differences in density caused by temperature gradients in the fluid mass.
- Forced convection heating is effected by the action of a mechanical device.

Thermodynamical Aspects of Heating Process:

2. Conduction Heating Process:

- Conduction is accomplished ether by a molecular interaction from higher energy level to a lower energy level or by free electrons.
- Thus, the ability of solids to conduct heat varies directly with the free electron concentration. Pure metals are best conductors and non-metals are the poorest.

Thermodynamical Aspects of Heating Process:

3. Radiant Heating Process:

- Radiant heating is the process which energy flows from high temperature body to a lower temperature.
- The geometry of both source and the exposure section of the unit will affect the uniformity of the radiation density in a unit.

Dry Heat Sterilization Equipment Validation

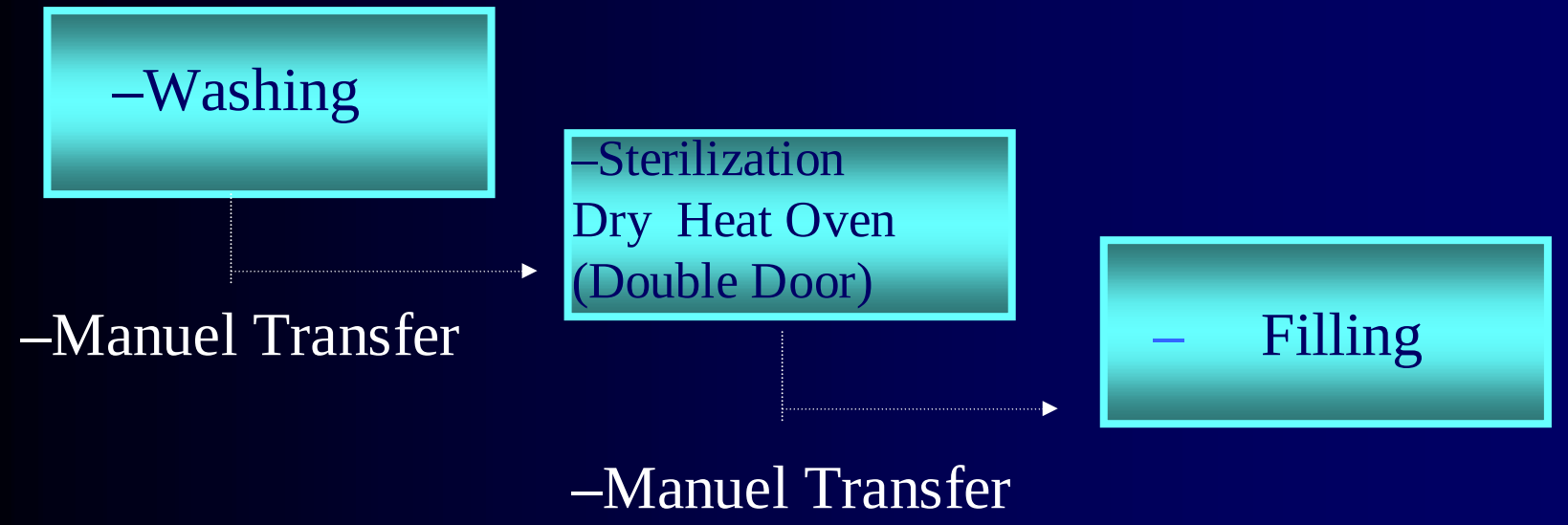
- **Batch Sterilizers**

  Dry Heat Ovens
- **Continuous Sterilizers**

  Sterilization Tunnel
- The basics of the Batch and Continuous sterilizers are mainly the same. Since the continuous (Tunnel) sterilizer validation is more complicated, the topics will concentrate on the Convection continuous process qualification.

Batch & Continuous Processing

–1. BATCH PROCESSING:



–1. CONTINUOUS PROCESSING:

Dry Heat Sterilization Validation

1. Design Qualification:

- Facility layout, decision of batch or continuous process.
- Utility requirements and specifications.
- Pressure differential requirements.
- Required capacity of the sterilizer.
- Type of materials to be sterilized.
- Any requirements for presterilization.

Dry Heat Sterilization Validation

2. Installation Qualification:

- The equipment should comply with the original purchase specifications.
- Exceptions should be appropriately documented.
- The structural installation like;

  Leveling, insulation, and air flow requirements should meet manufacturer's specifications.

Dry Heat Sterilization Validation

2. Installation Qualification:

- All utility connections such as electrical and HVAC should meet the design specifications.
- Materials of construction of both the sterilizer and the facility should meet the design specifications.

Dry Heat Sterilization Validation

2. Installation Qualification- CALIBRATIONS:

The following pieces of equipment should be calibrated by removing or in situ:

- Temperature sensors and recording devices
- Temperature Controllers (in situ)
- Pressure gauges
- Belt speed controller and recorder
- Cycle set point switches
- Velometers

Dry Heat Sterilization Validation

3. Operational Qualification:

- The actual operational performance of the electro/mechanical components should be verified and documented.
- Electrical Logic: Ensure that each step is in the correct sequence and it's repeatable.
- Cycle Set Point Adjustability: Limit Switch sequencing should be verified.

Dry Heat Sterilization Validation

3. Operational Qualification:

- Overload interlocks: Should not allow excess commodity build up during processing.
- Gasket Integrity: Zone to zone leak rate should be within the limits at all panel gaskets.
- Air Balance Ability: Check that, the baffle/linkage mechanisms can be adjusted for balance.

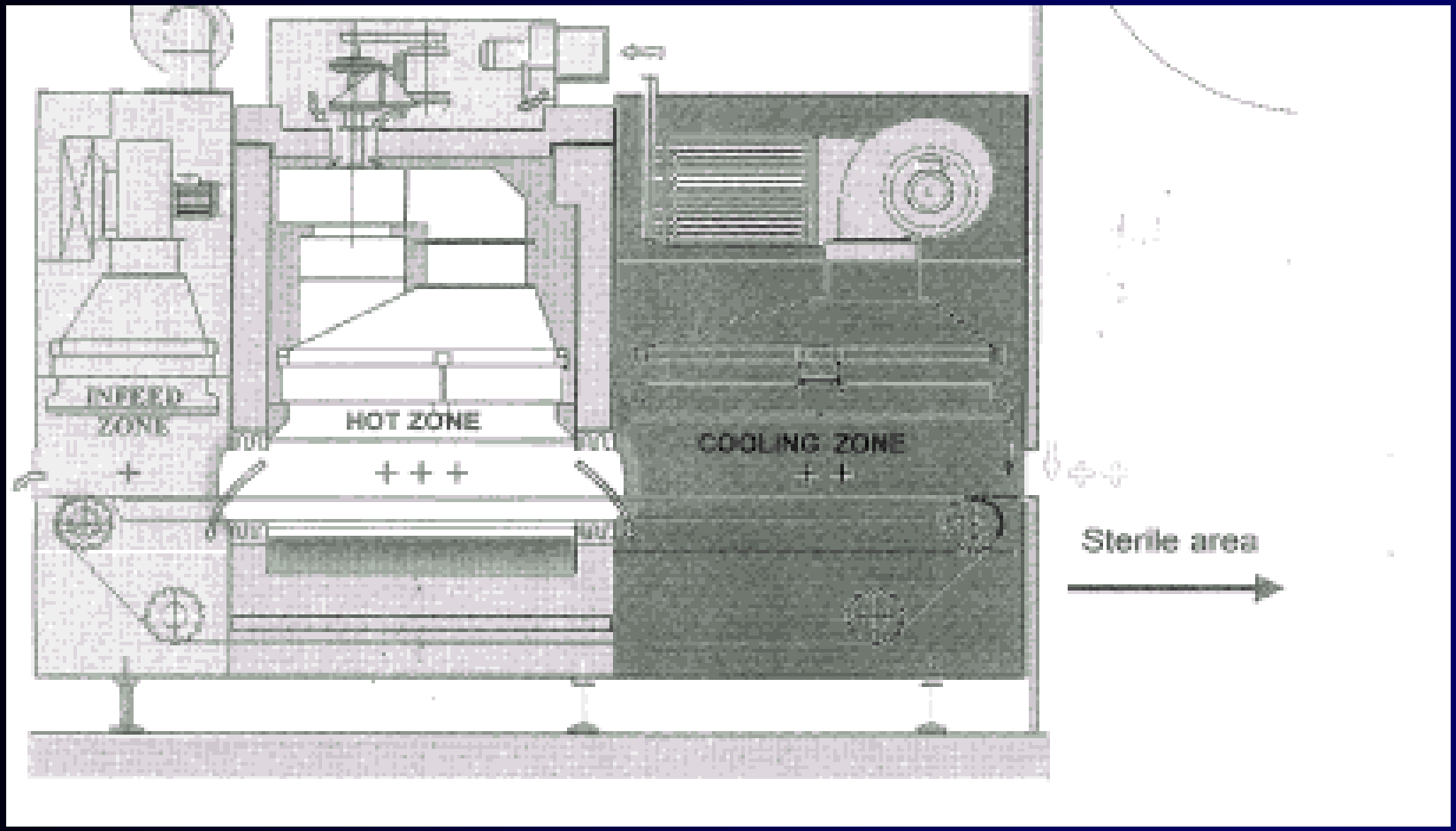
Dry Heat Sterilization Validation

3. Operational Qualification:

- Blower Rotation: Check that the blowers rotated in the specified direction and speed.
- Vibration Analysis: Check the dynamic balancing of the blowers to minimize the vibration in each phase.
- Air Balance: Check that the ΔP is positive with respect to the preparation side of the tunnel.

Tunnel Sterilizer

Pressure Differential



Dry Heat Sterilization Validation

3. Operational Qualification:

- Heater Elements: Check that all the heater elements are properly operating.
- Belt Speed: Check that the belt and belt speed recorder are operable.
- HEPA Filters: Verify the integrity of the filters.

Dry Heat Sterilization Validation

4. Performance Qualification:

- In a conductive dry heat sterilization and depyrogenation process, significant variations may occur depending on the load configuration.
- Initial load temperature, specific heat of the load components, and the load variations should be tested for delta temperature and slowest to heat zone.

Dry Heat Sterilization Validation

4. Performance Qualification:

Temperature Distribution:

- External monitoring and recording instruments shall be calibrated before and after the OQ/PQ studies (3 point calibration, ± 0.5 ^{0}C tolerance).
- Uniformity of the temperature distribution in case of Min&Max. loading should be verified by using Thermocouples with 3 replicates.
- T/C (Thermocouple) placement shall be documented on a diagram.

Dry Heat Sterilization Validation

4. Performance Qualification:

Temperature Distribution:

- Min. 10-12 T/C 's shall be used and they should not be inserted in the load. Data should be recorded during the whole cycle at 1 min. intervals.
- At least one T/C shall be placed adjacent to the equipment temperature controller.
- Location of the "cold spot" should be determined and documented.

Dry Heat Sterilization Validation

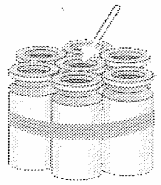
4. Performance Qualification:

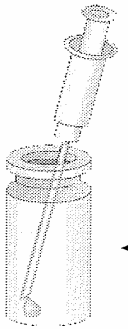
Heat Penetration- Acceptance Criteria:

- Thermocouples should be inserted into the load.
- At least three biological indicators and T/C's shall be placed around the cold spot.
- External T/C readings should comply with manufacturer's specifications (with Max ± 3 ^{0}C difference)
- Biological indicator inactivation results should assure 6-log reduction for Bacillus Subtilis and 3-log reduction for endotoxin. Lethality calculation should verify the Equivalent F_H value for defined cycle.

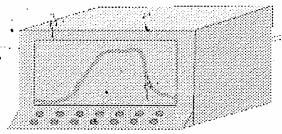
HEAT PENETRATION STUDIES

When introducing the probes inside the central vial - inside a group - we simulate the critical condition

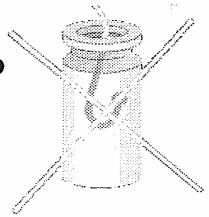


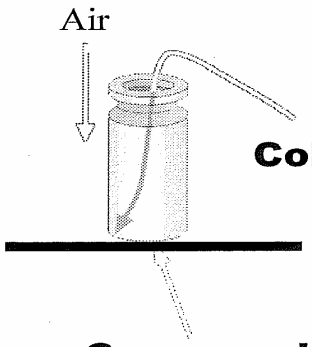


Endotoxins inoculation point

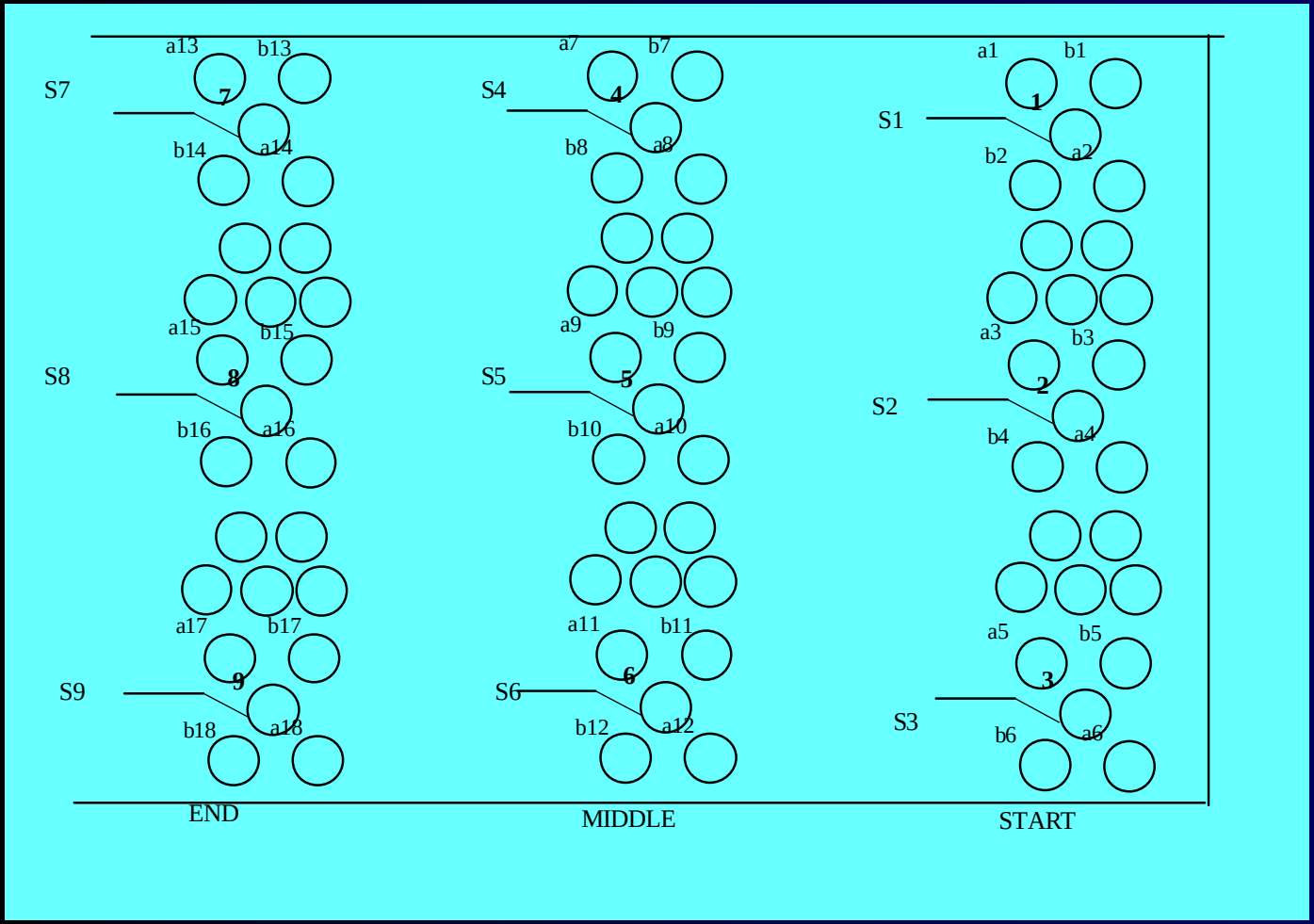


Temperature check-point to have data to be compared with the results of the LAL test





HEAT PENETRATION STUDIES LOAD CONFIGURATION



–S1-S9 : Thermocouples

–a1-a18: Bio-Indicators (Bacillus Subtilis)

–b1-b18: Endotoxin challenged containers.

PART-2

STEAM STERILIZATION VALIDATION

STEAM STERILIZATION

Various types of steam sterilzers are commercially available;

- Saturated Steam
- Water Immersion
- Water Cascade System
- Air-Steam Mixtures
- Gravity Air Displacement (unpacked materials sterilization)
- Vacuum air Displacement (Packed materials)

STEAM STERILIZATION

- Microbiological aspects of Steam Sterilization and Dry Heat Sterilization are basically the same;
- D Value is determined in the same way
- Z Value = 10 ^{0}C
- T_{b} = 121 ^{0}C
- Lethality (F_{0}) can be calculated in the same way.

Lethality in Steam Sterilization

Time (min)	Temperature (^{0}C)	Lethality Rate min. at 121 ^{0}C
5	100	0,0080
6	103	0,0160
7	106	0,0320
8	109	0,0630
9	112	0,1260
10	115	0,2510
11	118	0,5010
12	121	1,0000
13	121	1,0000
14	121	1,0000
15	118	0,5010
16	115	0,2510
17	112	0,1260
18	109	0,0630
19	106	0,0320
20	103	0,0160
21	100	0,0080

Steam Sterilization Validation

1. Design Qualification :

- Facility layout.
- Utility requirements and specifications.
- Required capacity of the sterilizer.
- Type of materials to be sterilized
  (Liquids, wrapped ,hollow or porous materials)
- Requirement for Gravity and/or Prevacuum cycles.

Steam Sterilization Validation

2. Installation Qualification- CALIBRATIONS:

The following pieces of equipment should be calibrated by removing or in situ:

- Pressure Gauges
- Timing Devices
- Temperature Recording Devices
- Verification of safety Systems and Devices (EN 61010 Part 1 and EN 61010 -2041)

Steam Sterilization Validation

3. Operational Qualification:

- The actual operational performance of the electro/mechanical components and utilities should be verified and documented.
- Clean Steam Generator

  (Free from non-condensables EN 285)
- Air Filtration Systems and compressed air
- Power Source
- Heat Exchanger, Cooling Water

Steam Sterilization Validation

4. Performance Qualification:

Temperature Distribution:

- External monitoring and recording instruments shall be calibrated before and after the OQ/PQ studies (3 point calibration, ± 0.5 ^{0}C tolerance).
- Uniformity of the temperature distribution in case of Min&Max. loading should be verified by using Thermocouples with 3 replicates.
- T/C placement shall be documented on a diagram.

Steam Sterilization Validation

4. Performance Qualification:

Temperature Distribution:

- At least one T/C shall be placed located in the steam exhaust line or adjacent to the equipment temperature controller.
- Min. 10-12 T/C 's shall be used and they should not be inserted in the load. Data should be recorded during the whole cycle at 1 min. intervals.
- Location of the "cold spot" should be determined and documented.

Steam Sterilization Validation

4. Performance Qualification:

Heat Penetration- Acceptance Criteria:

- Thermocouples should be inserted into the load.
- At least three biological indicators and T/C's shall be placed around the cold spot.
- External T/C readings should comply with manufacturer's specifications (with Max ± 1 ^{0}C difference)
- Biological indicator (bacillus stearothermophilus) results should ensure the 6-log reduction and Lethality calculation should verify the Equivalent F_0 (15 min. at 121 ^{0}C) value for defined cycle.

Steam Sterilization Validation

4. Performance Qualification:

AIR REMOVAL TEST:

- The ability of the pre-vacuum autoclaves to effectively remove the air and non-condensable gases should be tested. If the air is not effectively removed, air pockets will occur in the chamber and sterilization conditions will not be attained.
- Bowie-Dick or DART Test pack, the uniformity of the colour change on the indicator sheet should be checked. (3.5 min. at 134 ^{0}C)

Steam Sterilization Validation

4. Performance Qualification:

LEAK RATE TEST:

- The presence of air prevents proper penetration of of the load by steam and thus inhibits sterilization.
- Air leaking from outside into the chamber at the end of sterilization cycle will contaminate the load.
- A leak rate equivalent to a rate of change in pressure of 1 mm Hg/min. over a period of 10 min. after stabilization is the maximum permitted rate.

STERILIZATION VALIDATION-GENERAL CHANGE CONTROL AND REVALIDATION

- Any changes to the sterilization equipment and/or related utilities should be evaluated by a Change Control Procedure.

Typical Changes Requiring Revalidation

- Any changes in operating cycle (i.e:temperature , time, belt speed, chamber pressure)
- Change in load configuration.
- Change in sterilized materials.
- Major maintenance work on critical instruments/elements or utilities.

.....The END.....

Thanks For Your Attention,
Any Questions Please?

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