New Figure 1

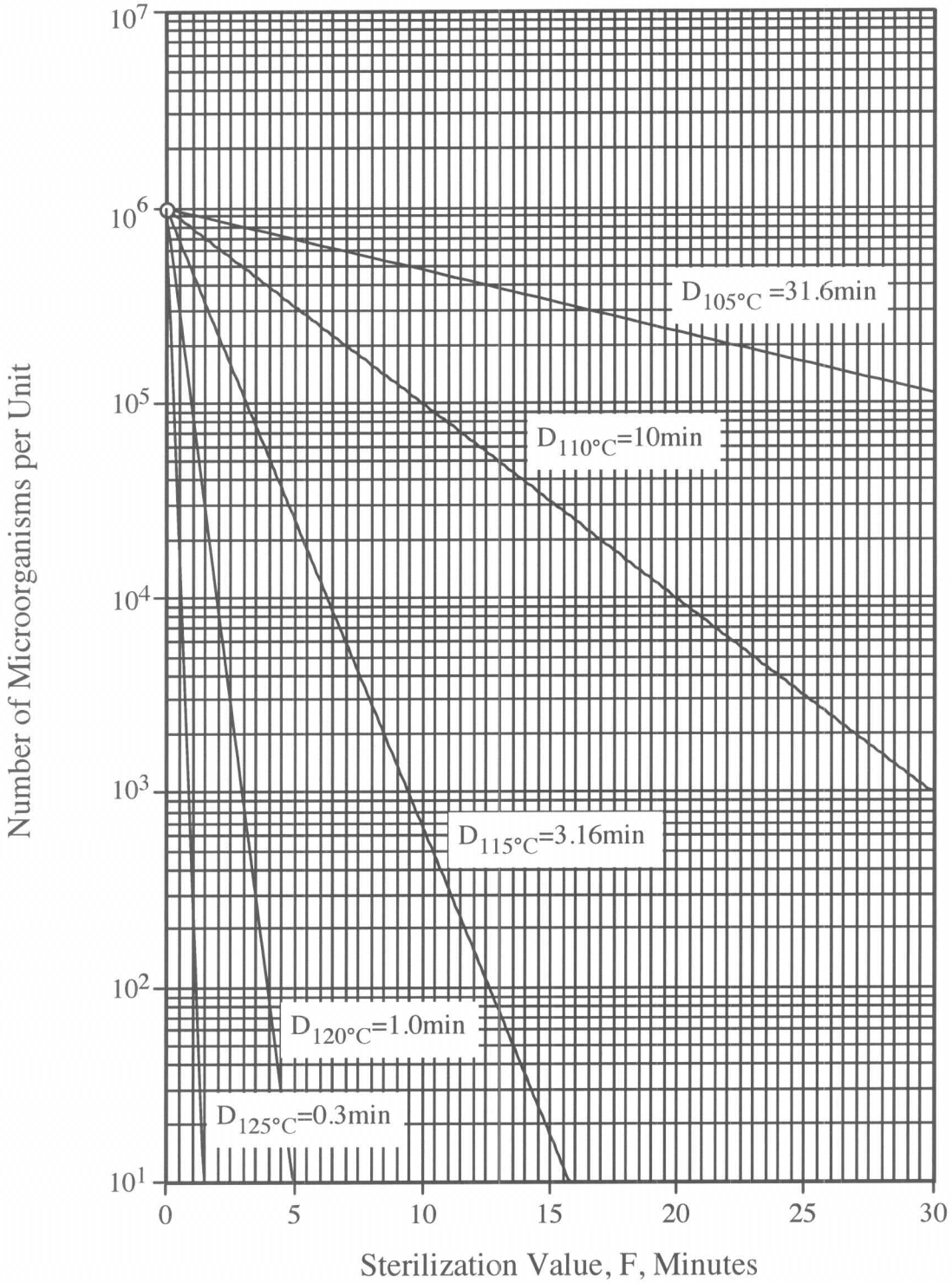

Figure 9.2: Results (D-Values) of Thermal Destruction Tests of a Single Spore Inoculum at Five Temperatures

4E. Lethal Rate Tables

4E1. Lethal Rate Table - Celsius Scale

	z Value				
°C	8	9	10	11	12
100	0.002	0.005	0.008	0.012	0.018
101	0.003	0.006	0.010	0.015	0.022
102	0.004	0.008	0.013	0.019	0.026
103	0.006	0.010	0.016	0.023	0.032
104	0.007	0.013	0.020	0.028	0.038
105	0.010	0.017	0.025	0.035	0.046
106	0.013	0.022	0.032	0.043	0.056
107	0.018	0.028	0.040	0.053	0.068
108	0.024	0.036	0.050	0.066	0.083
109	0.032	0.046	0.063	0.081	0.100
110	0.042	0.060	0.079	0.100	0.121
111	0.056	0.077	0.100	0.123	0.147
112	0.075	0.100	0.126	0.152	0.178
113	0.100	0.129	0.158	0.187	0.215
114	0.133	0.167	0.200	0.231	0.261
115	0.178	0.215	0.251	0.285	0.316
116	0.237	0.278	0.316	0.351	0.383
117	0.316	0.359	0.398	0.433	0.464
118	0.422	0.464	0.501	0.534	0.562
119	0.562	0.599	0.631	0.658	0.681
120	0.750	0.774	0.794	0.811	0.825
121	1.000	1.000	1.000	1.000	1.000
122	1.334	1.292	1.259	1.233	1.212
123	1.778	1.668	1.585	1.520	1.468
124	2.371	2.154	1.995	1.874	1.778
125	3.162	2.783	2.512	2.310	2.154
126	4.217	3.594	3.162	2.848	2.610
127	5.623	4.642	3.981	3.511	3.162
128	7.499	5.995	5.012	4.329	3.831
129	10.000	7.743	6.310	5.337	4.642
130	13.335	10.000	7.943	6.579	5.623
131	17.783	12.915	10.000	8.111	6.813
132	23.714	16.681	12.589	10.000	8.254
133	31.623	21.544	15.849	12.328	10.000
134	42.170	27.826	19.953	15.199	12.115
135	56.234	35.938	25.119	18.738	14.678
136	74.989	46.416	31.623	23.101	17.783
137	100.000	59.948	39.811	28.480	21.544
138	133.352	77.426	50.119	35.112	26.102
139	177.828	100.000	63.096	43.288	31.623
140	237.137	129.155	79.433	53.367	38.312

A pressure transducer with membrane has to be calibrated in situ to ensure that the calibration is performed under normal working conditions. Therefore, a separate pressure transfer standard, traceable to a national pressure standard, should be connected to the autoclave and a two-point comparison made between the standard and the pressure transducer. The transducer zero and span should be adjusted based on the comparison.

18.4 Time Measurement

The use of quartz clock provides a high accuracy. An accuracy of 0.1% is adequate.

18.5 Utilized software

Software used to control and/or monitor the sterilization process shall be prepared in accordance with a quality system that provides documented evidence that the software meets its design intention. The principles to be followed on the design, engineering and validation of software are discussed in documents such as the Guide to Automated Manufacturing Practice 3 (GAMP 3) and the FDA Regulation 21 CFR Part 11, which describes requirements for electronic signatures and electronic records. NOTE: Attention is drawn to ISO 9000-3.

19. Glossary

Accumulated F_0 - The equivalent sterilization time relative to a processing temperature of 121°C and z-value of 10°C imparted by the sterilization process. This should be measured during the cycle dwell phase or over the entire process from come-up through cool down.

Air Detector - An instrument fitted to a steam sterilizer that detects the presence of air in the chamber using a specially designed and calibrated temperature or pressure sensor.

Aseptic - In the pharmaceutical industry it generally refers to areas and practices where the intent is to be sterile, but for practical reasons that degree of microbial control is not achievable.

Aseptic Processing - A process where materials and components which have been previously sterilized individually are assembled in an aseptic environment.

BIER Vessel - Biological Indicator Evaluator Resistometers are miniaturized versions of production size sterilizers. These vessels are designed to have minimal come-up and come-down times and are generally referred to as square wave units from the shape of the graphic image of the cycle. Their primary usage is in the laboratory determination of D- and z-values. A very small sterilizer capable of providing a square wave sterilization profile for the selected sterilization temperature with minimal (NMT 10 seconds) come-up and come-down times.

Bioburden - The number of viable microorganisms per unit before sterilization.

Bioburden/Biological Indicator Sterilization - A process which provides a probability of survival of less than 1 in 10^6 for the bioburden as demonstrated using a resistant biological indicator with a known D-value. The biological indicator may not be fully inactivated during the sterilization cycle. It requires information on the number and heat resistance of the bioburden and requires ongoing monitoring or control over the bioburden.

Biological Indicator - A preparation of microorganisms of known concentration and resistance, which can be expected to follow a predictable death rate when exposed to a known physical or chemical condition, which are placed directly on or in items to be sterilized, or more frequently placed on inert carrier materials and which serve as a challenge to the efficacy of a sterilization process.

Bioburden Sterilization - A process which provides a probability of survival of less than 1 in 10^6 for the most resistant bioburden expected in the load. It requires information on the number and heat resistance of the bioburden and requires ongoing monitoring or control over the bioburden.

Calibration - Demonstration that a measuring device produces results within specified limits over its operating range.

Chain Speed/Rotation Speed - The speed at which the chain moves the containers through a continuous sterilizer.

Chamber Come-up Time - Elapsed time from the initiation of the cycle to the beginning of the dwell or exposure phase of the sterilization cycle.

Chamber Pressure - The ambient pressure within the chamber at any point in the sterilization cycle.

Chamber Temperature - The ambient temperature within the chamber, which is generally defined as a range.

Change Control - A formalized program by which qualified representatives review proposed and actual changes to products, procedures, processes, equipment or software to determine their potential impact on the safety, identity, purity and quality of the product.

Come-Up Time – See Equilibration Time

Commissioning - In the U.S., this refers to the activities immediately following completion of the installation, i.e., calibration, procedure development, mechanical shakedown. In the UK, this term refers to the later steps of more formalized equipment qualification of the sterilizer.

Control F_0 - The lethality value to be achieved during a sterilization process and from which the cycle dwell time can be controlled.

Cooling Water Flow Rate - The flow rate of the water introduced during and/or after the dwell cycle in a water spray autoclave.

Cooling Water Microbial Count - The number of organisms present in a defined quantity of the cooling water.

Cooling Water Temperature - The inlet temperature of the cooling water. Generally measured just prior to chamber entry.

Cooling Fan RPM - Rotational speed of the cooling fan.

D-Value (Decimal Reduction) - D-value is defined as the time in minutes required for a one-log or 90% reduction of a specific microbial population under specified lethal conditions.

Denaturation - The irreversible precipitation of proteins. It causes a fundamental change in the protein, destroying any physiological activity.

Drain Temperature - The temperature in the chamber drain that is often used to control the initiation and completion of various phases of the sterilization cycle. The drain temperature should be the coldest point in the entire system, due to the continual presence of condensate.

Dwell Time - See exposure time

Equilibration Time (Come-up Time) - The time required for the items in the sterilizer to reach the setpoint temperature.

Equipment Qualification (EQ) - Documented verification that all key aspects of the installation adhere to appropriate codes, approved design intentions, manufacturer's recommendations and conformance to specifications. Documentation that the operating performance of a piece of equipment conforms to specifications (equipment manufacturer and/or equipment user). Usually performed in the absence of production materials or components throughout the anticipated operating ranges. Frequently called commissioning in the United Kingdom.

Exposure Time - Sometimes referred to as dwell time, this is the time at which the autoclave is held at the desired operating temperature. Depending upon the control scheme it may be fixed (when used to time the cycle), or variable (when F_0 control is employed).

F-Value (Lethal Rate) - When both the D- and z-values have been determined for a microbial population, they can be used to estimate the lethality for a given sterilization process. When these values are 121°C and a z-value of 10°C the process lethality can be defined as the F_0 value.

F_0-value - Equivalent sterilization time related to the temperature of 121°C and a z-value of 10°C.

Installation/Operational Qualification (I/OQ) - see equipment qualification

Lethal Rate - The rate of microbial destruction at a given temperature expressed in terms of the reference temperature and z-value.

Load Come-up Time - The time for the slowest to heat item in the load to reach or exceed the sterilizer set point temperature.

Load Cool-down Time - The time for the slowest to cool item in the load to reach the desired cooling temperature.

Load Probe Temperature - The temperature measured using by a penetration probe inside a load item. There are generally multiple load probes used during a validation study.

Overkill Sterilization - A cycle which provides a minimum 12-log reduction of a resistant biological indicator with a known D-value of not less than 1 minute. This approach assures substantially greater than a 12-log reduction of the bioburden and therefore only minimal information on the bioburden is required.

Parametric Release - Defined as a sterility release procedure based upon effective control, monitoring and documentation of a validated sterilization process cycle in lieu of release based upon end-product sterility testing (21 CFR 211.167a). All parameters within the procedure must be met before the lot is released.

Pasteurization - The process of destroying most disease producing microorganisms and limiting fermentation of milk, beer and other liquids by partial or complete sterilization.

Performance Qualification (PQ) - Documentation that the process or product conforms to expectations as determined through independent parameter measurement and/or intensive sampling or challenge. Usually performed with actual production materials or components.

Porous Loads

Pre-commisioning - Activities surrounding the preparation of the autoclave for formal equipment qualification. Generally performed by representatives of the autoclave manufacturer. Also termed equipment start-up or shakedown.

Probability of a Non-Sterile Unit (PNSU) - The number which expresses the probability of finding a non-sterile unit in a known number of sterilized units. For sterilization processes in the healthcare industry a maximum acceptable probability of one non-sterile unit in a million units is usual. This term is synonymous with Probability of Survival.

Re-validation - Repetition of the qualification effort or a selected portion of it.

Sanitization - A process which reduces the number of microorganisms to a safe level.

Spore - A dormant form of a microorganism that is more resistant to adverse conditions.

Sterile - An item is deemed to be sterile when it is free of viable life forms.
NOTE: In practice, no such absolute statement regarding the absence of microorganisms can be proven (see sterilization).

Sterility - The state of being sterile. Both sterility and sterile are absolute terms in that an item cannot have a degree of sterility nor be partially sterile.

Sterility Assurance Level (SAL) - An estimate of the effectiveness of a sterilization process generally developed through detailed knowledge of the process itself and the microorganisms likely to be present as established in product and process specific efforts. It is generally expressed as a probability in the form of $1x10^{-n}$. A negative exponent is typically used.

Sterility Test - Test performed to determine if viable microorganisms are present.

Sterilization - An act or process, either physical or chemical, which destroys or eliminates all forms of life. In this context, it is in reference to microorganisms.
NOTE: In a sterilization process, the nature of microbiological death or reduction is described by an exponential function. Therefore, the number of microorganisms which survive a sterilization process can be expressed in terms of probability. While the probability may be reduced to a very low number, it can never be reduced to zero.

Sterilization Model - A term used to describe one of the three principal sterilization approaches: overkill, bioburden/biological indicator or bioburden. It refers to the design of cycle requirements (e.g., F_0) necessary to achieve a minimum SAL of 10^{-6}.

Terminal Sterilization - Sterilization of finished pharmaceuticals in which a formulation is processed to provide a minimum probability of a non-sterile unit of $1x10^{-6}$. The majority of these materials in their final packaging will have some heat induced degradation as a result of the sterilization cycle and the minimization of that input is frequently a major concern in the development and validation of the sterilization process.

Thermochemical Indicator - A thermochemical indicator is a device, which responds to sterilization process parameters in some measurable fashion.

Thermochemical Integrator - A thermochemical integrator is a device that reacts in response to one or more critical sterilization parameters and yields a quantifiable value that correlates to microbial lethality (e.g., F_0) or predictable inactivation of microbial spore populations.

Tyndallization - (Also known as fractional sterilization) - A process of discontinuous heating in which an item is pulsed with brief periods of sterilization followed by ambient conditions.

Validation - Validation is a defined strategy of inter-related practices and procedures which in combination with routine production methods and quality control techniques provides documented assurance that a system is performing repetitively as intended and/or that a product conforms to its pre-determined specifications.

Validation Plan - A document used to define the overall approach to the execution of a validation project. The level of detail varies with the breadth of the plan.

Validation Protocol - Experimental designs intended for use in confirmation of procedures, processes, products or systems.

Validation Report - Documents which provide the results of experiments conducted according to predefined protocols.

Validation Procedure - A standard operating procedure which define repetitive activities commonly utilized in validation: e.g., calibration, sampling plans, test methods, etc.

Worst Case - A set of conditions encompassing processing limits and circumstances which pose the greatest chance of process or product failure when compared to ideal conditions. Such conditions do not necessarily induce product or process failure.

Z-Value (Temperature Coefficient) - The Z-value is defined as the number of degrees of temperature required for a one-log cycle or a 90% change in the D-value. Experimental values for moist heat processing of bacterial spores vary from approximately 8-12°C, but a Z-value of 10°C is widely assumed for moist heat.

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[1] USP 25/NF 20, USPC, Inc., Rockville, MD, 2002, <1211>, p. 2250.
[2] European Pharmacopoeia, 4th ed., Council of Europe, Strasbourg, 2002, Chapter 2.6.1.
[3] PDA Technical Report No. 8, Parametric Release of Parenteral Solutions Sterilized by Moist Heat Sterilization, 1987.
[4] PDA Technical Report No. 30, Parametric Release of Pharmaceuticals Terminally Sterilized by Moist Heat, 1999.
[5] European Pharmacopoeia, 3rd ed., Council of Europe, Strasbourg, 1997, Chapter 5.1.4.
[6] Note for Guidance on Parametric Release, Committee for Proprietary Medicinal Products, Document CPMP/QWP/3015/2001.
[7] Annex 17 to the EU Guide Good Manufacturing Practice. European Commission Document ENTR/6270/00, 2001
[8] Guidance on Parametric Release. Pharmaceutical Inspection Convention / Co-operation Scheme, 2001.