1 Purpose

To provide guidelines for the validation of sterilization processes used in the manufacturing activities for drug products or active Pharmaceutical ingredients (API) and also to outline recommendations on how to achieve compliance.

2 Scope and Applicability

This Guideline is applicable to all manufacturing Operations, sites, functions and departments undertaking work, or providing support services, required to meet Good Manufacturing Practice (GMP) or, in the absence of a GMP standard, International Organization for Standardization (ISO) standards.

This Guideline is applicable for sterilization processes used to produce sterile drug products, components, equipment and other ancillary items required to be sterile for use in the drug manufacturing process.

3 Definitions

3.1 D value

The time in minutes at a specific temperature required to reduce a surviving microbial population by 90%, i.e. a one-logarithm reduction.

3.2 F0

The time required at any given temperature between 100°C -140°C that is equivalent to the sterilization effect of steam at 121.1°C (250°F). Assumes a Z value of 10°C.

3.3 Z value

The number of degrees Celsius required to change the D value by a factor of ten.

3.4 Sterile

State being free from viable microorganisms. In practice no such absolute regarding the absence of microorganisms can be proven.

3.5 Sterilization

Validated process used to render a product free of all forms of viable microorganisms. In a sterilization process, the nature of microbial death is described by an exponential function. Therefore, the presence of microorganisms on any individual item/container 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.

3.6 Overkill cycle

A sterilization cycle that provides a 12-log reduction of a resistant Biological Indicator (BI) with a known D value of not less than 1 minute. A typical cycle would provide a minimum

The BIs must be placed throughout the load, adjacent to the temperature probes, and include locations that are expected to be slow to heat (such as inside tubing, within filters, etc).

5.1.2 Tests to be performed during the validation of a fluids cycle

5.1.2.1 Empty Chamber Temperature Distribution

This study must be performed to demonstrate that uniform heating is occurring throughout the chamber. Temperature measuring probes, e.g. thermocouples, must be located in free space throughout the chamber. One probe is located next to the controlling temperature sensor.

Empty Chamber Temperature Distribution studies should be able to meet an acceptance criteria for the temperature to be within + 1°C of the mean chamber temperature after one minute of the exposure stage. This is particularly important where the sterilizer is being used for terminal sterilization of drug products.

The difference between the control probe, recording chart probe and independent sensor (usually a thermocouple) during the exposure stage should not exceed +1.0°C.

5.1.2.2 Loaded Chamber Temperature Distribution

This study must be performed to demonstrate that the proposed loading patterns do not significantly change the chamber temperature distribution within the chamber. Typically thermocouples are distributed throughout the chamber (not in contact with load items) as for the Empty Chamber Temperature

Distribution study and cycles are run using both the maximum and minimum loads.

Loaded Chamber Temperature Distribution studies should meet an acceptance criteria for the temperature to be within + 1°C of the mean loaded chamber temperature after one minute of the exposure stage.

The difference between the control probe, recording chart probe and independent sensor during the exposure stage should not exceed + 1.0°C.

5.1.2.3 Heat Penetration Studies – Terminal Sterilization of Drug Products and Fluid Loads

The heat penetration studies for the terminal sterilization of drug products in sealed containers must include an assessment of any cold spot(s) within an individual container (container mapping) as well as in containers within each load (product load mapping). These studies are usually part of cycle development. Smaller containers may not have a discernible container cold spot.

In larger containers, fill volume can have an appreciable influence on the location of the container cold spot. Care must be taken to ensure that the placement of thermocouples does not enhance heating of the product during both container and product load mapping. Small volume parenteral drug product loads may not have

Blowers/Fans - for proper air balance and the differential pressure between the tunnel and the room environment
Room pressure differentials

5.4.2.1 Empty Tunnel Temperature Distribution

Temperature probes (thermocouples) are distributed across the width of the tunnel and a temperature profile is produced across the conveyor and along the tunnel during operation. A reasonably uniform temperature profile is expected. A probe needs to be located next to the controlling sensor. Note the come-up time to temperature and cool-down times, as these should be consistent in an empty tunnel.

5.4.2.2 Loaded Chamber Heat Penetration

In dry heat tunnel applications heat penetration studies must be performed. Thermocouples must be placed in contact with vials distributed across the tunnel. The temperature of the vial is usually lower than the air temperature.

Test should be performed with all vial sizes. Endotoxin spiked vials should be located adjacent to the penetration thermocouples. Heat penetration studies, conducted as part of the initial validation, must be repeated several times (e.g. three times) to demonstrate consistency. Consider the loading arrangement of the tunnel i.e. at the start, middle and end of a run.

The temperature profile for a specific load should show good reproducibility.

5.4.3 Demonstrating Biological Lethality

The use of BIs to demonstrate biological lethality must be included in the validation approach.

For dry heat sterilization the indicator of choice is Bacillus atrophaeusspores. However, dry heat is also used to depyrogenate. In this case endotoxin (E. coli) is used to validate the depyrogenation activity. If endotoxin is used then Bacillus atrophaeusspore strips are not required as endotoxin is more heat resistant than Bacillus atrophaeus. These biological studies can be performed at the same time as the loaded chamber temperature mapping. If this is done the carriers should be located as close as possible to the thermocouples.

5.4.4 Washing Process for Depyrogenation

In some cases, the depyrogenation of items that cannot be dry heat sterilised (e.g. rubber stoppers) is carried out in a washing/rinsing process. It must be demonstrated that a 3-log reduction in the endotoxin concentration on spiked stoppers can be achieved.

Recovery studies on the spiked stoppers must be performed. The stoppers must be subsequently sterilized using a validated steam sterilization cycle.

5.5 Radiation Sterilization

