13. Sterility Assurance for Terminally Sterilized Pharmaceutical Products

As indicated in the "Terminal Sterilization and Sterilization Indicators", the pharmaceuticals to which terminal sterilization can be applied, generally must be sterilized so that a sterility assurance level of $10^{-6}$ or less is obtained. The sterility assurance level of $10^{-6}$ or less can be proven by using a sterilization process validation based on physical and microbiological methods, but cannot be proven by sterility tests of the sterilized products. This chapter deals with the necessary requirements for the appropriate management of the important control points of the sterilization process for the parametric release of products, without performing sterility tests on products which have been subjected to terminal sterilization (in the case of radiation sterilization, called dosimetric release). Parametric release is a method that can be applied in cases where the sterilization system is clearly defined, important control points are clearly specified, and the sterilization system process can be validated by microbiological methods using appropriate biological indicators.

1. Definitions

The definitions of the terminology used in this chapter are provided below.

1.1 Terminal sterilization

A process whereby a product is sterilized in its final container or packaging, and which permits the measurement and evaluation of quantifiable microbial lethality.

1.2 Validation

A documented procedure for obtaining, recording and interpreting the results needed to show that a process will consistently yield a product complying with predetermined specifications.

1.3 Periodic re-validation

Validation that is regularly performed to reconfirm that a process is consistently yielding a product complying with predetermined specifications. It should confirm that variables and the acceptable ranges are permissible to yield a product consistently of the required quality.

1.4 Facility/equipment qualification

This is to provide evidence that the manufacturing facilities/equipment, measuring equipment, and manufacturing environment control facilities, etc. have been properly selected, correctly installed, and are operated in conformity with the specifications at the time of installation and during operation.

1.5 Operation qualification

This is to provide evidence to confirm physically, chemically and microbiologically that equipment, operated in accordance with its operational instructions, operates as specified and affords a product meeting the specifications.

1.6 Support system for sterilization process

This refers to the facility/equipment that is associated with the sterilization devices, such as the pre-conditioning and aeration for ethylene oxide sterilization, the steam supply equipment for moist heat sterilization, and the loading devices for radiation sterilization.
1.7 Quality system
The procedures, resources and organizational structure of a manufacturer (responsibilities, authorities and relationships between these) required to implement quality management.

1.8 Change control system
A system designed to evaluate all of the changes that may affect the quality of the pharmaceutical product, in order to ensure that the process is continuously controlled.

1.9 $F_0$ value
Assume a value of 10°C for the Z value defined as the number of degrees of temperature required for a 10-fold change in the D value. The $F_0$ value indicates the time (minutes) required to give the equivalent lethality at $T_b$ of the sterilization heat obtained by integrating the lethality rate ($L$) over an entire heating cycle.

$$ L = \log^{-1} \left( \frac{T_b - T_0}{T_b} \right) = 10^{\frac{b - b}{z}} $$

$T_0 = $ Temperature inside the chamber or inside the product to be sterilized

$T_b = $ Reference temperature (121°C)

$$ F_0 = \int_{t_0}^{t_f} L dt $$

$t_f - t_0 = $ Processing time (minutes)

1.10 Control device
A general term for the devices and measurement equipment, including the equipment for controlling, measuring and recording the physical parameters that can be measured (temperature, humidity, pressure, time, radiation dose, etc.).

1.11 Parametric release
A release procedure based on an evaluation of the production records and critical parameters of the sterilization process (temperature, humidity, pressure, time, radiation dose, etc.) based on the results of validation, in lieu of release based on testing results of the final product.

2. Sterilization Validation
2.1 Subject of the Implementation
A manufacturer of sterile pharmaceuticals (hereafter, “manufacturer”) must establish a quality system, implement product sterilization validation for the categories below as a general rule, and continuously control the sterilization process based on the results of the sterilization validation.

a. Sterilization process
b. Sterilization process support system

2.2 Documenting Sterilization Validation Procedure
2.2.1 The manufacturer must prepare a “Sterilization Validation Procedure” defining the items listed below regarding the procedures for managing the sterilization process.

a. Details related to the range of duties of the persons responsible for the validation, as well as the extent of their authority

b. Details related to the implementation period for the sterilization validation
c. Details related to the creation, modification, and approval of the sterilization validation plan documents
d. Details related to the reporting, evaluation, and approval of the sterilization validation implementation results

e. Details related to the storage of documentation concerning the sterilization validation
f. Other required matters

2.2.2 The sterilization validation procedure must list the names of the enactors, the date of enactment, and when there are revisions, must also list the revisers, date of revisions, revised sections and reasons for the revisions.

2.2.3 The manufacturer must properly store and maintain the sterilization validation procedure after clarifying the procedures related to alterations and deletions of the contents of the sterilization validation procedure.

2.3 Persons Responsible for the Validation
The manufacturer must assign persons to be responsible for the sterilization validation. The responsible parties must perform each of the duties listed below according to the sterilization validation procedure.

2.3.1 For products that are to be produced according to the sterilization validation procedure, a written sterilization validation implementation plan must be prepared. The implementation plan will specify the following points based on a consideration of the implementation details of the sterilization validation.

a. Subject pharmaceutical name (product name)
b. Purpose of the applicable sterilization validation
c. Expected results
d. Verification methods (including inspection results and evaluation methods)
e. Period of verification implementation
f. Names of persons performing the sterilization validation (persons-in-charge)
g. Names of the persons who created the plan, creation date, and in the event of revisions, the names of the revisers, date of the revisions, revised sections, and reasons for revision.
h. Technical requirements for the applicable sterilization validation

2.3.2 Other required matters for the implementation of the applicable sterilization validation

2.3.3 The following sterilization validation is implemented according to the plan defining the items above.

a. When the manufacturing license and additional (modification) licenses for product production are obtained, implementation items for the sterilization validation to be executed

1. Product qualification
2. Facility/equipment qualification
   1) Installation qualification
   2) Operation qualification
3. Performance qualification
   1) Physical performance qualification
   2) Microbiological performance qualification
b. Sterilization validation to be executed until it is time to renew the manufacturing license

1. Re-validation when there are changes
2. Periodic re-validation (The items implemented, etc. must be determined based on a consideration of relevant factors such as the sterilization method.)

2.3.4 Evaluate the results of the sterilization validation and verify that sterility is assured.

2.3.5 Make a written report of the results of the sterilization validation to the manufacturer’s authorized person.

2.3.6 Perform the day-to-day management of the sterilization process.
3. Microorganism Control Program
When parametric release is adopted, it is important to control the bioburden in the raw materials of the product, the containers and stoppers, and in the product before sterilization. The bioburden is measured with a previously specified method and frequency, and when required, surveys of the characteristics of the isolated microorganisms are made to investigate their resistance to the applicable sterilization method. Refer to the “Microbiological Evaluation of Process Areas for Sterile Pharmaceutical Products” regarding the method for evaluating the environmental microorganisms in the processing areas of pharmaceutical products.

4. Sterilization Indicators
Biological indicators (BI), chemical indicators (CI), and dosimeters are among the means used to monitor a sterilization process and as indices of sterility (refer to Terminal Sterilization and Sterilization Indicators). When using sterilization indicators it is important to consider environmental and human safety, and to take all necessary precautions. The BI used for sterilization validation and daily process control must be defined in the specification, and recorded in writing. When BI are used for daily process control it must be verified that the loading pattern on the form, product, or simulated product has a resistance equal to or greater than that used for the microbiological performance qualification.

5. Establishment of a Change Control System
Changes which have a large effect on the sterile quality, such as changes in sterilization equipment, loading pattern, and sterilization conditions, correspond to changes of the parametric release conditions for the relevant pharmaceutical product. A change control system must be defined in the sterilization validation procedure; and when there are changes in the causes of variation that have been previously specified, there must be an investigation of the causes of variation and of acceptable conditions to verify that the pharmaceutical product is guaranteed always to conform to the quality standards. Furthermore, before modifications are made to a sterilization process that has been validated, it is mandatory to obtain approval for the implementation of the modifications in question from the appropriate authorized person.

6. Release Procedure
A release procedure must be created to clarify the conditions required for shipment based on parametric release of terminally sterilized products. The following points must be evaluated and recorded when a product is released.
Depending on the sterilization method, some of these items may be omitted or modified.
   a) Batch record
   b) Microorganism evaluation data of production environment
   c) Bioburden data for the raw materials and product before sterilization
   d) Data related to the sterilization indicators
   e) Data on the maintenance management of the sterilization process and sterilization process support systems
   f) Data on the management of sterilization parameters
   g) Data on the calibrations of measurement equipment
   h) Re-validation data
   i) Other

7. Critical Control Points
The important control points for each sterilization method are presented.

7.1 Moist heat sterilization
Moist heat sterilization is a method for killing microorganisms in which saturated water vapor is generated or introduced into a sterilization chamber at the appropriate temperature and pressure, and the chamber is then heated for a certain period of time. It is roughly classified into saturated vapor sterilization, in which the target microorganisms are directly exposed to the saturated vapor, and unsaturated vapor sterilization, in which the fluid inside a container, such as an ampule, is subjected to moist heat energy or highfrequency energy from the outside.

7.1.1 Important control points
A process control procedure must be created, specifying the process parameters that affect the sterile quality of the pharmaceutical product, and the permissible range of variation for each parameter. The important control points for the moist heat sterilization are indicated below.
   a) Heating history (usually indicated by F0 value)
   b) Temperature
   c) Pressure
   d) Time
   e) Product loading format/loading density
   f) Other necessary matters

7.1.2 Utilities
The utilities and control devices required for moist heat sterilization determine the quality and precision.
   a) Quality of the vapor used
   b) Quality of the air introduced into the sterilization chamber to restore pressure, etc.
   c) Quality of the water used for cooling
   d) Precision of the temperature control devices
   e) Precision of the pressure control devices
   f) Precision of the time control devices
   g) Other

7.2 Ethylene oxide gas sterilization
Ethylene oxide gas allows sterilization at low temperatures, so there is typically little injury to the substance being sterilized; however, since the gas is toxic it must be handled with extreme caution. The sterilization process consists of preconditioning, a sterilization cycle, and aeration. The preconditioning is performed before the sterilization cycle to process the product so that temperature and relative humidity in the room or container are within the range in the specifications. The sterilization cycle indicates the stage at which the actual sterilization is performed, and consists of removal of the air, conditioning (when used), injection of the sterilization gas, maintenance of the sterilization conditions, removal of the sterilization gas, and replacement of the air. The aeration is the process of eliminating the residual ethylene oxide gas from the product, either inside the sterilization chamber or in a separate location.

7.2.1 Important control points
The important control points for the ethylene oxide gas sterilization are indicated below.

7.2.1.1 Preconditioning (when performed)
   a) Time, temperature, humidity
   b) Product loading pattern/loading density
   c) Sterilization loading temperature and/or humidity
   d) Time from the end of preconditioning until the start of the sterilization
14. Tablet Friability Test

The Tablet Friability Test is a method to determine the