Health Canada Santé Canada

Guide to validation of terminal sterilization process of drugs (GUI-0074)

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Process validation: Irradiation sterilization for pharmaceuticals (GUI-0009)
Process validation: Moist heat sterilization for pharmaceuticals (GUI-0010)

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Purpose

This guide is for fabricators of sterile drugs. It provides guidance on how to establish the scientific effectiveness of terminal sterilization processes.

This guidance will help you understand and comply with Part C, Division 2 of the Food and Drug Regulations (regulations), which is about good manufacturing practices (GMP). This guide mainly refers to the requirements for:

- manufacturing control (sections C.02.011 to C.02.012)
- quality control department (sections C.02.013 to C.02.015)
- sterile products (section C.02.029)

This guide should be read along with the current editions of the following guidance documents:

- Good manufacturing practices guide for drug products (GUI-0001)
- Annex 1 to the Good manufacturing practices guide – Manufacture of sterile drugs (GUI-0119)
- Guide to validation – drugs and supporting activities (GUI-0029)

Scope

This guidance will help you validate the terminal sterilization of drugs, including pharmaceutical, radiopharmaceutical, biological and veterinary drugs. The terminal sterilization of drugs refers to sterilizing drugs that are in their final container.

The principles set out in this document can be extended to the sterilization of raw materials, bulk materials, in-process drugs and packaging materials.

For definitions of terms used in this guide, refer to the Glossary.

Introduction

These guidelines explain the requirements for validating the terminal sterilization of drugs. Health Canada developed the guidelines in consultation with stakeholders.

The guidelines are written to align with International Organization for Standardization (ISO) standards.

Note: This document replaces the following sterilization guides:

- Process validation: Gaseous sterilization for pharmaceuticals (GUI-0007)
- Process validation: Irradiation sterilization for pharmaceuticals (GUI-0009)
- Process validation: Moist heat sterilization for pharmaceuticals (GUI- 0010)

Consult the following documents for further information:

- Guide to validation - drugs and supporting activities (GUI-0029)
    - general guidance for qualifying and validating manufacturing processes, facilities, equipment, utilities and analytical methods within the drug lifecycle
- Guide to good manufacturing practice for medicinal products annexes, Annex 15: Qualification and validation (PE 009-17 (annexes)), by the Pharmaceutical Inspection Co-operation Scheme (PIC/S)
    - general qualification and validation guidance
- Annex 1 to the Good manufacturing practices guide – Manufacture of sterile drugs (GUI-0119)
    - guidance on manufacturing of sterile products and validating blow/fill/seal technology and aseptic processing
- Annex 11 to the Good manufacturing practices guide: Computerized systems (GUI-0050)
    - GMP requirements for computerized systems

Note about guidance documents in general

Guidance documents like this one help industry and health care professionals understand how to comply with regulations. They also provide guidance to Health Canada staff, so that the regulations are enforced fairly, consistently and effectively across Canada.

Health Canada inspects establishments to assess their compliance with the Food and Drugs Act (act) and associated regulations. Our inspectors will use this document as a guide to assess your compliance with GMP requirements for validating terminal sterilization processes.

These guidelines are not the only way to interpret GMP regulations and do not cover every possible case. Other ways of complying with GMP regulations will be considered with proper scientific justification. Also, as new technologies emerge, different approaches may be called for.

Guidance documents are administrative and do not have the force of law. Because of this, they allow for a flexible approach. Use this guide to help you develop specific approaches to meet your unique needs.

Principles

Note the following:

Sterilization:

- a suitably designed, validated and controlled process that inactivates or removes viable microorganisms in a product until sterility is obtained (European Medicines Agency)

- validated process used to render product free from viable microorganisms (ISO)

In a sterilization process, the nature of microbial inactivation is exponential and thus the survival of a microorganism on an individual item can be expressed in terms of probability. While this probability can be reduced to a very low number, it can never be reduced to zero.

Terminal sterilization:

- the application of a lethal sterilizing agent to finished product within a sealed container to achieve a predetermined sterility assurance level (SAL) of 10^{-6} or better
    - in other words, the theoretical probability of there being a single viable microorganism present on or in a sterilized unit is equal to or less than 1×10^{-6} (1 in a million) (PIC/S)
- process whereby product is sterilized within its sterile barrier system (ISO)

Terminal sterilization is the preferred method when fabricating sterile products. It provides better assurance of sterility than sterilization during product manufacturing.

For a given sterilization approach, the probability of microorganisms surviving is determined by the:

- number and resistance of microorganisms
- environment in which the organisms exist during treatment

It's important to monitor and assess the resistance as well as the number of organisms to assure that the terminal sterilization parameters continue to provide the required maximal sterility assurance level (SAL).

ISO/TS 19930 describes the elements of a quality management system. These elements are applied to enable the appropriate selection of a SAL for terminally sterilized, single-use health care product that is unable to withstand processing to achieve maximally a SAL of 10^{-6}.

This document assumes that the reader is familiar with the applications, limitations and effects of the following methods of terminal sterilization discussed in this guide:

- moist heat
- ionizing radiation
- ethylene oxide (EO) gaseous sterilization

Other technologies such as dry heat and alternative gaseous technologies are not in the scope of this guidance document

1. Lifecycle approach

The lifecycle approach applies to the validation of terminal sterilization processes. This approach is outlined in Guide to validation: Drugs and supporting activities (GUI-0029).

The validation lifecycle comprises the following 3 phases:

- phase 1, process design
- phase 2, process performance qualification
- phase 3, ongoing process verification

Validation is not a single study. It represents the cumulative knowledge gained during product development and manufacture. Process validation should incorporate a lifecycle approach, including:

- product and process development
- qualification of the commercial manufacturing process
- maintenance of the process in a state of control during routine commercial production

Make sure that an effective quality risk management system is integrated into all areas of the product lifecycle. The goal should be to minimize microbial contamination and ensure the quality of the sterile drugs manufactured.

2. Phase 1, process design

A key concern during this stage is to ensure the sterilization process and potential sources of variability are adequately understood and controlled. This page outlines general considerations that apply to all terminal sterilization methods.

General considerations

When developing a sterilization process, you should aim to control the pre-sterilization bioburden to an appropriate level.

The level of microbial quality must be critically evaluated first in order for the terminal sterilization process to be properly applied. It's thus important to understand the microbial quality of all the materials, such as:

- raw materials
- bulk materials
- packaging materials
- process components, such as:
    - in-process drugs and finished products

Reducing the microbial bioburden of these materials will generate a more effective terminal sterilization process.

1. You should:

a. establish definition for the product to be sterilized (in terms of physical, chemical, pharmacological properties, packaging, loading configuration and microbiological quality) before validation
    - conduct studies to determine bioburden in the materials to be sterilized
    - for products that promote the growth of microorganisms, include in the studies the impact of process hold times as well as partial or interrupted sterilization cycles on the bioburden

b. establish a process definition, which involves setting the maximum and minimum sterilizing conditions for the sterilization process of a defined product
    - conduct studies to determine bioburden of the materials to be sterilized.
    - for products that promote the growth of microorganisms, evaluate the impact of hold times as well as partial or interrupted sterilization process on the bioburden

c. determine the required sterility assurance level (SAL)

d. evaluate the compatibility of the sterilization process with the material to be sterilized
    - ensure that the primary and secondary packaging can tolerate sterilization process parameters, while maintaining product/material and package/container integrity for the expected life of the product/material
    - for test protocols, consider the maximum tolerances for repeat exposures that the product can withstand

e. follow effective and validated premises and equipment cleaning and sanitation procedures to reduce the potential for contamination
    - put controls in place and routinely monitor and document bioburden to ensure the microbiological quality of the product/material that's to be sterilized is controlled and does not compromise the effectiveness of the sterilization process

Note: Use risk assessment(s) to determine the amount of work at the development/prequalification stage. Fully assess and understand the impact of the sterilization process on the drug, including its stability.

Sterilization process development

There are 2 approaches to developing sterilization process parameters:

1. Overkill method: Use when the product/material can withstand prolonged exposure to the sterilization process without adversely affecting the quality of the product/material over the product's life.
- Sterilization is performed for longer than required to kill the bioburden present on or in the material being sterilized.
- A moist heat or EO (ethylene oxide) sterilization process designed with the overkill approach is a process that is sufficient to provide at least a 12 log reduction of microorganisms with a minimum specified D-value.
- For moist heat, the D-value must be a minimum of 1 minute at 121°C.

2. Product-specific or combined BI bioburden microbial approach: Use for products that may be impacted by the sterilization process.
- For moist heat and ethylene oxide (EO) sterilization, the process for the terminal sterilization is validated to achieve the destruction of pre-sterilization bioburden to a level of 10^0, with a minimum safety factor of an additional six-log reduction ($1x10^{-6}$).
- The probability that any 1unit is contaminated is no more than 1 in a million (considered an acceptable level of sterility assurance).
    - The probability of survival is determined using a semi-logarithmic microbial death curve, where a plot of the log of the number of survivors versus time at fixed exposure conditions yields a straight line. The linear portion of the curve is extrapolated to project process

requirements (exposure times or dose) for various survivorship levels below 10^0 (including 10^{-6} to support sterility assurance requirements).
    - The minimum required process lethality used in the probability of survival approach is determined by the:
        - number of microorganisms (bioburden) found in a given product
        - required sterility assurance level (SAL)
        - resistance of the microorganisms to the sterilization method

F_o and D-value

F_0 is the amount of time in minutes (equivalent to time at 121°C) to which a unit has been exposed during a sterilization process. One method of calculating the F_0 is to integrate the time the unit is exposed to heat in terms of equivalent time at 121°C.

D-value is the time (in minutes) required to reduce a microbial population by 90% (1 log value) under specified test conditions (such as fixed temperature, single species, specified medium). When heat labile products will not withstand excessive heat treatment, D-value studies of product isolates can determine the minimum lethality factor (F_0) that will provide an acceptable assurance of sterilization.

The minimum F_0 value required by a process can be related to the D-value of the bioburden by the following equation:

$$D_{121} \times (\log A - \log B)$$

where:

- D_{121} is equal to the time required at 121°C to reduce the population of the most heat-resistant organisms in the unit by 90%
- "A" is the microbial count per container
- "B" is the maximum acceptable probability of survival (1×10^{-6} for pharmaceutical dosage forms)

Lab studies that determine the number and resistance of microorganisms for a product (bioburden) serve to calculate the minimum F_0 value required for sterilization.

A more conservative approach would be to use the D-value of a highly heat-resistant spore-forming organism for the bioburden of the product.

3. Phase 2, process performance qualification

Ensure performance qualification (PQ) shows that the process can be reproduced. PQ should include consecutive successful runs (where specified acceptance criteria are met throughout the load for the duration of the proposed routine process specification). Determine the number of required runs using a quality risk management approach.

Loads used for PQ should represent products routinely sterilized, including the most challenging routine loads.

Equipment

1. Ensure that:

   a. the range, resolution, accuracy, reproducibility and response time of all controlling, monitoring and recording equipment can demonstrate that defined process conditions are met

   b. any failure in control function does not lead to a failure in recording the process parameters, making an ineffective process appear effective (fail-safe feature)

Note: Control instruments should be independent of monitoring instruments and recording charts.

   c. the standards you use for calibration follow an appropriate standard
      - document and keep records of equipment calibration

   d. measuring equipment is adequately calibrated and qualified
      - includes all measuring equipment used in analytical methods and the measurement of process parameters for operating the sterilization process

Note: Before you do a validation study, you must make sure the equipment is appropriately qualified for its intended use. More guidance on equipment qualification is available in Guide to validation: Drugs and supporting activities (GUI-0029).

Sterilization indicators

Clearly label each basket, tray or other carrier and indicate whether it has been processed. You may use physical/chemical indicators or a validated electronic product track and trace systems to distinguish between processed and unprocessed goods. These devices indicate exposure to certain sterilization conditions by a visible change, but do not indicate that the load is sterile.

1. You must:

   a. use calibrated sterilization indicators or dosimeters in validation studies and requalification, where applicable

      i. confirm the supplier's certificate indicates that performance criteria have been met before using the sterilization indicator in validation studies
      ii. ensure sterilization indicators are appropriately stored and used before they expire
      iii. ensure detailed written test procedures and records of test results are available

   b. ensure that data demonstrating adequate pre-determined response to both time and exposure for physical and chemical indicators is available
   c. test biological indicators for viability and quantification of the challenge organism for indicators obtained commercially
      - test biological indicators prepared in-house for D-value, z-value (moist heat only) and survival/kill time

   d. ensure a certificate of testing for each lot is available for commercial biological indicators (indicating the population, expiration, D-value and z-value (moist heat only) of the lot)
      - the quantification is acceptable if a biological indicator count provided by the manufacturer has been qualified and periodically confirmed, as per written procedures

   e. when qualifying commercial or in-house biological indicators, ensure that you choose the media (such as pH, electrolytes, carbohydrates) and sample carriers (such as suspension in ampoules, paper strips, inoculated products and inoculation on solid carriers) based on the BI supplier's recommendations
      - ensure they're consistent with the materials used to validate the terminal sterilization process

Note: Sterilization indicators should not be used in radiation sterilization processes or for qualifications, with the exception of dosimeters. Do not use them as a substitute for a validated quality process that tracks and releases product based on proper parametric or dosimetric measurements.

Microbial performance qualification (MPQ)

Biological challenge reduction studies for moist heat and ethylene oxide sterilization

Biological challenge reduction studies demonstrate that the sterilization processes will effectively reduce microbial levels to required sterility assurance levels. These studies are required for :

- Phase 1
  - to establish a process and assure it is reliable and effective
- Phase 2
  - to demonstrate the terminal sterilization process can consistently meet requirements

1. You should:

   a. consider the product/material bioburden profile over multiple lots of product/material fabricated at different times of the year when choosing the level of biological challenge for the study
      - consider the type and resistance of the surviving microorganism recovered (will allow you to capture possible seasonal changes)

   b. implement a worst-case bioburden challenge using an appropriate organism described in Table 1 or another BI organism that demonstrates a greater D-value than the product bioburden
      - in all other cases, use the microorganism with the highest D-value occurring in the natural population (determined by sampling the environment) and provide a scientific justification for your choice

   c. assess the sterilization process by introducing a known quantity of challenge microorganisms (for example, BI or product bioburden) with established D-values and by assessing the level of reduction over time
      - confirm the sterilization process will deliver a probability of survival of less than 1 in 10^6 in all cases.

Note: The D-value of the chosen organism must be assessed along with the material to be sterilized and its formulation. This is because resistance of the microorganism can change with changes to parameters such as pH.

For more information, consult the section on the F_0 and D-value.

Table 1: Organisms for biological challenges

Sterilization method	Recommended organism
Moist heat	*Geobacillus stearothermophilus*
Ethylene oxide	*Bacillus atrophaeus*

Note: The use of prions (infectious proteins) is not currently recommended to validate moist heat sterilization cycles. The detection and quantification of prions, which is based on animal models, is complex. Also, these proteins may be resistant to moist heat sterilization. They could present a danger if they are accidentally spread in a manufacturing facility.

2. You should:

a. run positive controls for each biological indicator tested with every load to verify the viability of the challenge organism and ensure that viable microorganisms can be detected by the recovery method
b. define the placement of biological challenges
    i. should be located as close as possible to worst-case locations and next to any sensors (if run alone with distribution studies/penetration studies, refer to Process validation, sterilization by moist heat)
    ii. should be in containers wherever possible or within process challenge devices (PCDs) to reflect the desired processing conditions

c. determine the number of cycles for each load configuration under evaluation based on a documented risk assessment as well as knowledge of the process and operations
    - bracketing strategies may apply to intermediate loads

d. conduct robustness studies by changing 1 or more process variables (such as temperature, humidity) and comparing them to the set points used in routine sterilization (below or at minimum levels specified for routine control)

e. document and keep records of the biological challenge reduction studies, including:
    i. the placement of the biological challenge
    ii. organism type and name
    iii. D-value
    iv. challenge level
    v. lot number
    vi. placement
    vii. growth result

Sterilization process interruptions

1. You may need to interrupt the sterilization process for mechanical, safety or operational reasons. For affected products/materials capable of sustaining microbial growth, define the impact of any such interruptions and the maximum length of time allowed for an interruption.

2. Proper procedures must be in place to direct the operator to the appropriate person to contact if the sterilization process is interrupted or delayed at any point. Investigate any process interruptions.

3. Evaluate the potential impact of the process interruption on sterilization cycle efficacy and product/packaging functionality. Ensure data is available to support a decision to resume a sterilization process that has been interrupted.

4. Process validation, sterilization by moist heat

Moist heat sterilization is widely used for aqueous-based products. It's not used in instances where it results in product/material or packaging degradation. You must fully evaluate and document any degradation cases.

Product/material definition

1. You should describe the:

   a. material and the packaging system to be sterilized (for example, size(s), fill volume or primary packaging)
   b. process challenge device (PCD)

Note: When process parameters are defined using a bioburden-based method, you must include an estimation of bioburden.

Sterilizing agent specifications

1. Your specification for a moist heat sterilization process must include, at a minimum:

   a. requirements for purity and quality of steam (saturated steam processes only)
   b. requirements for dryness, superheat, saturation and non-condensable gases (saturated steam processes only)
   c. contaminants (including from additives), which should not be at a level to cause contamination of product or equipment

Sterilization process definition

1. Specify the sterilization process you use. This should include descriptions of the following:

   a. autoclave(s) used for production sterilization, including manufacturer and model
   b. operating cycle and/or graphic presentation
   c. monitoring device, its location and interpretation of results (if used to verify delivery of a specified sterilization process)
   d. holding time and minimum and maximum temperatures (and their locations) measured during this time in an empty sterilizer chamber

The process definition should also include:

   e. the minimum cycle lethality achieved throughout the sterilization load
   f. process parameters and their tolerances

- use both pressure and temperature to monitor the process
- measure physical process parameters to confirm reproducibility

g. the location of reference measuring point
h. the minimum and maximum pressure in sterilizing chamber
i. falling and rising pressure gradient and tolerances
j. quality and purity of water/steam
k. the maximum quantity of each contaminant present in any liquid, gas, steam admitted to sterilizer chamber for product configurations that are unsealed or where there's potential contact with the product formulation or product fluid path
l. requirements for conditioning the product before sterilization, where applicable
m. load configuration
n. restrictions on size and mass of the load
o. reference loads to be used to evaluate the effectiveness of the sterilization process
p. if used, the location and acceptance criteria for biological indicators (BIs) and chemical indicators (CIs) (such as heat penetration and temperature distribution probes)

Note: Wrap your dry porous hard goods item to be sterilized (other than products in sealed containers) in a material that allows air to be removed and steam to penetrate. The material should also prevent re-contamination after sterilization.

Note: All parts of the load should be in contact with the sterilizing agent at the required temperature for the required time. All loaded items should be dry when they're removed from the sterilizer. Visually inspect to confirm load dryness (where possible). May also use gravimetric analysis as a part of the sterilization process qualification and/or acceptance.

Equipment qualification

1. Your moist heat equipment specification should include, at a minimum:

a. a description of materials of construction
b. a description of control, monitoring and recording devices
c. a description and validation status of software used to control/monitor the process
d. the location, space and environment where the equipment is to be installed
e. for saturated steam sterilization processes, the purity and quality of steam (especially any requirements for dryness, superheat, saturation and non-condensable gases)
f. a description of any other gas or water used in the process and means by which they are delivered to the chamber

Examples of instruments that need calibration:

- timers

- thermocouples
- water level indicators
- flow meters for water/steam
- temperature recorders and sensors
- conductivity monitors for cooling water
- pressure sensors for jacket and chamber pressure
- thermometers, including reference thermometers used for calibration of thermocouples and those used for chamber temperature monitoring

Note: The position of the temperature probes used to control and/or record should be determined during the heat distribution and penetration studies. Where applicable, check these against a second independent temperature probe, located at the same position.

Temperature distribution studies

Temperature distribution studies help determine temperature variation throughout the sterilization chamber. Supported by a risk assessment, you may include an evaluation of both the empty chamber and the loaded chamber in these studies.

Note: The extent of the temperature distribution studies should be appropriately justified and based on a risk management approach.

1. Perform:

    a. temperature distribution studies according to written procedures
        i. use temperature-measuring sensors or probes that have been calibrated before and after use
    b. empty chamber temperature distribution runs during equipment qualification
        i. determine the number of runs based on quality risk management principles
        ii. studies should demonstrate that the temperature uniformity throughout the empty chamber is within the temperature variation limits established in the validation protocol

Also:

    c. specify the requirements for temperature uniformity based on the type of sterilizer and specific processing parameters
    d. use multiple temperature probes in each test run
        i. use simultaneous data recording to capture a reading of each individual probe at specified time intervals
        ii. this will allow you to determine the slowest and fastest heating zones in the chamber
        iii. document the location of each probe
        iv. place probes to show temperature distribution throughout the sterilizer chamber

e. collate the data from similar condition runs as appropriate into a temperature profile for the chamber
f. perform loaded chamber temperature distribution studies
    i. use maximum and minimum chamber load configurations to represent various material configurations
    ii. place multiple temperature probes throughout the chamber, but not inside the units of the load (this will determine the effect of any defined loading pattern on the temperature distribution within the chamber)
    iii. perform sterilization cycle test runs using different container sizes
    iv. use the sterilization parameters specified for the normal production process
    v. document the position of each temperature probe in each test run
    vi. determine and document the slowest heating point(s) or cold spot(s) in each run
    vii. repeat runs to establish whether, for a given load configuration, the location of the cold spot(s) is fixed or variable
        - determine the number of required runs using a quality risk management approach
    viii. develop and document a temperature distribution profile for each load configuration
g. evaluate each test run performed
    i. certify completed studies before beginning temperature penetration studies

Note: You must demonstrate that all runs of a sterilization cycle consistently meet the specified criteria for acceptable temperature uniformity.

Heat penetration studies

Heat penetration studies verify that the required temperature or heat history has been reached throughout the load when subjected to moist heat sterilization. These studies are conducted to ensure that the coolest unit within a pre-defined loading pattern (including minimum and maximum loads) will consistently be exposed to sufficient heat lethality (minimum F_0 value).

1. You should:

a. perform heat penetration studies according to detailed written procedures
    i. use temperature-sensing probes that are calibrated before and after use
    ii. ensure simultaneous data recording is available to capture a reading of each individual temperature probe within specified time intervals
    iii. this will allow you to determine the slowest and fastest heating units in the chamber
b. allow for variables such as container size, design, material, viscosity of solution and fill volume in your validation protocol

i. fill the container to maximum fill volume with the slowest-to-heat solution for the specified cycle

c. consider initial container temperature-mapping studies (depending on the container size)
d. conduct heat penetration studies with the maximum and minimum loading configurations for each sterilization cycle
   i. use sterilization parameters that do not exceed normal production cycles
e. monitor heat delivered to the load, including the slowest to heat items, if these are present
   i. use this data to evaluate the achievement of the minimum lethality (F_0 value) requirements
f. perform replicate runs to verify that the desired minimum process F_0 value can be achieved consistently throughout the load
   i. determine the number of required runs using a quality risk management approach
   ii. the process is considered acceptable once such consistency in the achievement of minimum lethality has been adequately established

Note: For concepts on moist heat sterilization, consult:

- ISO 17665 Sterilization of health care products — Moist heat — Part 1: Requirements for the development, validation and routine control of a sterilization process for medical devices

Biological challenge reduction studies

Perform biological challenge reduction studies, when applicable (described in Phase 2, process performance qualification).

Note: You may run the biological challenge along with distribution studies and/or penetration studies.

5. Process validation, sterilization by ionizing radiation

Introduction

Radiation sterilization is used mainly to sterilize heat-sensitive materials and products. However, many materials, drugs and packaging materials are also radiation-sensitive. This method is allowed only when the absence of harmful effects on the material/product has been confirmed prior to use.

Radiation processing (in the context of this guide) means exposing a material/product to ionizing radiation in a controlled way. This ensures that a pre-determined radiation dose is delivered to the material/product.

This section of this guide covers radiation processes employing:

- gamma radiation generated by the radionuclide ^{60}Co (Cobalt- 60) or ^{137}Cs (Cesium-137)
- a beam from an electron generator
- a beam from an X-ray generator

Product/material definition and qualification

1. A product/material qualification program demonstrates the effects of ionizing irradiation on the product/material. The most important outcome of product qualification is to determine the product's maximum acceptable dose $D_{max,acc}$.

2. Your product/material qualification must test the product/material using the D_{maxT} considered to be worst case for product functionality. The worst-case product/material qualification dose may not always be the highest dose (for example, complex cross-linking effects).

Note: Before you can determine the D_{maxT} for a product/material, you must find out if any product/material or their components have received radiation treatment before. Radiation effects are cumulative, so any prior radiation treatment will affect the interpretation of dose-effect experiments.

The absorbed radiation dose is affected by variations in density and the configuration of the products/materials and packages. It depends on the product/material loading pattern and the physical parameters of the irradiator (such as the uniformity of the ionizing radiation field produced by the source).

3. A third factor is the D_{minP}. The ratio of the D_{maxP} to the D_{minP} is known as the D_{max}/D_{min} ratio or dose uniformity ratio (DUR). This ratio determines if the required dose range can be successfully delivered to the product as configured.

Sterilizing agent specifications

There are significant differences between the 3 ionizing radiation technologies that affect process validation:

- Gamma radiation delivers a specified dose relatively slowly.
- Both electron beam generators and X-rays deliver the same dose much more quickly.

As a result, you must validate each source of radiation separately for a product/material.

Before you adopt an alternate radiation source, you must evaluate validation requirements based on the potential product/material effects (and any microbiological effects).

1. At a minimum, you must:

   a. define the type of radiation to be used in sterilization
   b. specify the energy level of the electron beam for electron bean generators and X-rays
   c. assess the potential for induced radioactivity in product/material (for electrons with energy greater than 10 MeV or X-rays with energy greater than 5 MeV)

Sterilization process definition

1. To establish the maximum acceptable (D_{maxT}) dose, the:

   a. product/material must represent what will be routinely fabricated
   b. source of radiation must be able to precisely deliver the required doses

Sterilization dose setting/dose substantiation

There are 3 basic methods used to establish a minimum radiation sterilization dose:

1. Method VDmax dose substantiation:

- verifies that the radiation resistance of the product/material bioburden is less than a microbial population of maximal resistance consistent with attainment of a 10^{-6} SAL at a selected sterilization dose of either 15, 17.5, 20, 22.5, 25, 27.5, 30, 32.5 or 35 kGy

2. Dose-setting method 1:

- depends upon experimental verification that the radiation resistance of the product/material bioburden is less than or equal to the resistance of a microbial population having the standard distribution of resistances (SDR)

- the SDR specifies microorganism resistance in terms of D10 values and the probability of occurrence in the total population
- using computational methods, for increasing levels of average bioburden having the SDR, the doses required to achieve SAL of 10^{-2}, 10^{-3}, 10^{-4}, 10^{-5} and 10^{-6} is calculated

3. Dose-setting method 2:

- uses the radiation resistance of the naturally occurring product/material bioburden
- sterility tests are conducted on samples that have been exposed to a series of incremental doses to estimate the dose at which 1 in 100 is expected to be non-sterile (SAL of 10^{-2})
- the microorganisms surviving exposure to such a dose should have a more homogeneous D10 value than the initial bioburden
- from the incremental dose experiment, an estimate made of this D10 value is used to extrapolate SAL values less than 10^{-2} to determine the sterilization dose

Note: Dose-setting methods use the bioburden on the product and the resistance of that bioburden to tailor a specific radiation treatment for a specific product.

For guidance on bioburden calculations, consult:

- ISO 11137-2: Sterilization of health care products – Radiation – Part 2: Establishing the sterilization dose

For guidance on sterilization using radiation, consult:

- ISO 11137-1: Sterilization of health care products – Radiation – Part 1: Requirements for development, validation and routine control of a sterilization process for medical devices
- ISO/TS 11137-4: Sterilization of health care products — Radiation — Part 4: Guidance on process control
- ISO/TS 13004: Sterilization of health care products — Radiation — Substantiation of selected sterilization dose: Method $VDmax^{SD}$
- ISO 11137-2: Sterilization of health care products – Radiation – Part 2: Establishing the sterilization dose
- ISO 11137-3: Sterilization of health care products — Radiation — Part 3: Guidance on dosimetric aspects

Equipment qualification

1. Your irradiator specification should include, at a minimum:

   a. a description of the irradiator, its characteristics and method of operation
   b. a description and validation status of software used to control/monitor the process

c. location, space and environment where the irradiator is to be installed within the premises
d. a description of the conveyor system including its operation, construction and range of speed
e. the dimensions, materials and nature of construction of the irradiation container(s)
f. for gamma irradiators, the type of radionuclide and the geometry of the gamma source
g. for X-ray irradiators, the dimension, materials and nature of construction of the X-ray converter
h. for electron beam and X-ray irradiators, the characteristics of the beam (electron energy, scan width and uniformity)

Instruments that need calibration for electron beam, X-ray and gamma radiation processing technologies include:

- timers
- recorders
- dosimeters
- calorimeters
- thickness gauges
- spectrophotometers

Dose distribution studies

Dose distribution studies are performed to determine the D_{max} and D_{min} positions in a process load in relation to the radiation source.

1. You should:

a. perform dose studies according to written procedures, using properly placed and calibrated dosimeters
b. document the location of each dosimeter
    - dosimeters to be placed to capture minimum and maximum doses
    - if using a reference monitoring position, place the dosimeter at the monitoring position as well
c. use dosimeters that can measure the dose over the desired range
d. collate the data from all runs into a dose-map profile for each type of irradiation container, product conveyor path and irradiation source
e. conduct dose distribution studies for each product/material-loading configuration and size
    - also place products into processing categories/density families, where the dose distribution studies would be performed for the processing category/density family, if applicable
f. evaluate each test run performed and certify the completed studies

Note: The studies should prove that the dose uniformity requirements as outlined in your process specification are consistently achieved. To conclude your process is validated, operational consistency of the dose uniformity must be demonstrated.

Loading patterns

1. The way the product/material is presented to the radiation source is critical to achieving the specified D_{max}/D_{min} ratio, doses and desired SAL (sterility assurance level). How the product/material will be presented to the source, including detailed loading diagrams (if applicable), should be outlined in the processing specification.

2. Validation studies must confirm that the:

- product in the D_{min} position will receive a dose that meets or exceeds D_{minP}
- product in the D_{max} position will receive a dose not exceeding D_{maxP} during routine processing

If reference monitoring is used, then the dosimeter must be placed in the monitoring position that was determined from the dose distribution studies.

Temperature control

1. For temperature-sensitive products/materials, the following information should form part of your process validation documentation:

a. the allowed temperature range of the product when it arrives at the irradiation facility
b. the time available for irradiation before the product temperature rises to the maximum tolerated level

Note: You may need to cool the product during the irradiation process. Products can be irradiated on wet or dry ice (if the product will tolerate the temperature). You must specify how this is to be done.

Special dose distribution studies may be required, as a dosimeter response depends on the temperature. Cooling the sterilization load during dose mapping will alter the response of the dosimeters. You should also use surrogate material during the dose mapping.

6. Process validation, sterilization by ethylene oxide

Introduction

Ethylene oxide (EO) is mainly used to sterilize items that are sensitive to moist heat or radiation. EO is a toxic, flammable and explosive substance, listed in a schedule 1 of the Canadian Environmental Protection Act.

For guidelines on EO emission, consult:

- Guidelines for the reduction of ethylene oxide releases from sterilization applications

Factors that influence EO sterilization include:

- bioburden
- temperature
- package density
- relative humidity
- EO gas concentration
- pre-cycle conditioning
- packaging/material type
    - includes insulation characteristics of materials
- product/package loading patterns
- exposure, gassing and evacuation times

Product/material definition

1. You should design the:

a. product/material, packaging and loading pattern to allow air to be removed and heat, humidity and EO to penetrate to the most difficult-to-sterilize locations
b. product to allow EO to be removed at the end of the process
c. product/material and package to allow EO, heat and humidity to penetrate

For example, you should avoid:

- using non-permeable materials/configurations
- attaching labels with large surface areas to breathable materials
- using plastic or foam inserts/supports
- applying moisture-resistant coatings
- using pressure-relief valves, stopcocks, manifolds or occluded spaces
    - includes closed containers (such as vials, ampules) that restrict or prevent EO penetration
- applying bleaching agents containing free chlorine, which react with EO, ethylene chlorohydrin (ECH) or ethylene glycol (EG))

d. you should also consider the tolerance of the product/material for the required temperatures

Note: EO must not affect product/material integrity (for example, by causing cracking, phase separation and bio-compatibility).

Sterilizing agent specifications

1. You should:

a. use a defined sterilizing agent (pure EO or a gas mixture) to validate
b. specify the storage conditions and shelf life for the sterilizing agent
c. define ethylene oxide (EO) residues:
   i. determine rates of dissipation of the major EO residues after being subjected to the EO sterilization cycle
   ii. specify the maximum allowable levels of EO residues on drugs (limits must be based on safety studies and published international safety standards)
   iii. validate analytical methods for determining EO and ECH

Note: You may use EO as a pure gas (100%) or in a mixture of gases (such as carbon dioxide or nitrogen).

EO sterilization parameters

1. Monitor the following parameters:

a. dwell time
b. temperatures
c. vacuum/pressure levels
d. air/nitrogen washes humidity
e. steam and gas concentration (if applicable)
f. transfer time from preconditioning room to sterilizer

2. Consider the following when designing your EO sterilization cycles:

a. product/material preparation
b. delivery of the sterilization parameters
c. removal of the residual sterilizing agents

3. Include at least the following in your EO sterilization specification:

a. a definition of the preconditioning, exposure and aeration phases of the sterilization cycle
b. a description of process parameters and their tolerances
   - include cycle variables: humidity, temperature, EO concentration, pressure and time

c. a description of means used to monitor, control and record the process variables and how entire sterilization process is conducted
d. a description of controlled conditions to achieve specified temperature and humidity for pre-treating the product/material within the load

Note:

- Residues of ethylene oxide (EO) and its reaction products may be hazardous. Aeration process helps to desorb them.
- Temperature, dwell time, forced air circulation, load characteristics and product/material and packaging materials affect aeration efficiency.
- Aeration may be performed within the sterilizer or in a separate area or both.

Also note:

- Relative humidity:
  - Maintaining an appropriate humidity in the sterilization chamber increases the effectiveness of EO sterilization by increasing EO penetration through bacterial cell walls.
  - A relative humidity of about 35% is beneficial for EO sterilization. Increased humidity can cause condensation on the product, chamber walls and optical EO sensors. Relative humidity of less than 30% results in less effective EO sterilization.
- Temperature:
  - EO cycle effectiveness improves as the temperature increases. The temperature in the chamber must be high enough to prevent the EO from liquefying.
- Gas concentration:
  - At higher EO levels, the sterilization process is more effective and requires a shorter dwell time.
- Diffusion:
  - The higher the diffusion rate of EO from the chamber to the product in the load, the shorter the required dwell time. Diffusion is improved by creating a vacuum in the chamber before it's charged with EO.
- Time:
  - An increase in gas concentration and temperature may shorten the time needed to achieve sterilization.

Humidity used to precondition and condition the product/material should be generated by steam.

Design of EO sterilization cycles

You should define the process to support the validity of process parameters and their tolerances (as defined in your sterilization process specification).

There are 3 basic approaches for validating an EO sterilization cycle:

1. Overkill ½ cycle:

The cycle is developed by performing 3 consecutive studies resulting in total inactivation of the biological indicators to confirm the minimum exposure time. The specified exposure time for the sterilization process should be at least double this minimum time. A fractional cycle of short duration from which BI survivors can be recovered should also be run to demonstrate the recovery technique for BIs exposed to EO gas is adequate.

Overkill cycle calculation:

The cycle is developed by performing time-graded exposures to EO or population-graded BIs exposed to EO, with all other parameters staying the same. The sublethal exposures are then used to calculate the cycle to ensure a 12 log reduction. Following that, routine bioburden monitoring should be performed.

2. Biological indicator (BI)/bioburden cycle:

The cycle is used when the bioburden of the product/material before EO treatment is fairly consistent over time and less resistant than the biological indicator. This sterilization process involves using a microbial challenge population lower than 10^6 (but not less than 10^3). *Bacillus atrophaeus* is commonly used for EO sterilization because of its high resistance. The BI should be distributed throughout the product load and in the same orientation. Placement should include spots that present the greatest challenge to the sterilization cycle.

Note: When developing the EO sterilization cycle and validation studies, you should test biological indicators as soon as possible after exposure to the sterilization cycle. Microbial inactivation continues after the sterilization cycle has been completed due to the presence of EO residues.

3. Absolute bioburden cycle:

This cycle is used when the product bioburden resistance to the EO process is very high (product's bioburden is more resistant than the BI). This can be caused by a number of factors, such as the configuration of the product/material, the quantity or location of the microorganisms, or the bioburden's intrinsic resistance.

The cycle can also be used when the bioburden is very low in resistance and relatively consistent, allowing an optimized sterilization cycle. The absolute bioburden method requires extensive controls of the manufacturing environment in addition to routine product bioburden monitoring and resistance studies.

Cycle development includes:

- exposing representative samples to incremental exposures
- testing the exposed samples for recovery of survivors

- performing counts

Representative product is used in EO cycle development studies. An inactivation curve is established for the product bioburden to project the exposure time required to achieve the desired SAL.

For additional guidance on EO sterilization, consult:

- ISO 11135: Sterilization of health care products – Ethylene oxide – Requirements for the development, validation and routine control of a sterilization process for medical devices

Equipment qualification

1. Your specification for EO equipment should include equipment from 3 phases of the sterilization process:

- preconditioning
- sterilization
- aeration

2. For your EO equipment specification, include, at a minimum:

a. a description of the equipment
b. the composition of the sterilizing agent and how it will be delivered to the chamber
c. a description of other gases used in the process and how they will be delivered to the chamber
d. the purity and quality of steam and/or compressed gases
e. a description of instruments used to monitor, control and record the sterilization process
    - include the characteristics and locations of sensors
f. the safety features for personnel and environmental protection
g. a description and validation status of software used to control/monitor the process
h. a description of the materials used to make the equipment
i. the location, space and environment where the equipment is being installed

Examples of instruments that need calibration:

- timers
- balances
- recorders
- gas analyzers
- thermocouples
- pressure and humidity sensors

7. Phase 3, ongoing process verification

Routine release

1. You should:

   a. approve sterilization records as part of the batch-release procedure (should be available for each sterilization run)
   b. ensure that the records are reviewed and approved by the appropriate personnel and by the quality department

For more information on reprocessing and reworking, consult:

- Good manufacturing practices guide for drug products (GUI-0001)

For guidance on parametric release, consult:

- Guidance on parametric release - Pharmaceutical Inspection Co-operation Scheme (PIC/S)

Monitoring results

1. You should:

   a. monitor the sterilization process and its parameters routinely to ensure the specified process conditions are met
      - document these results in the processing records
   b. include maintenance of equipment in your routine control
   c. perform maintenance in conjunction with calibration

Note: Include in the validation protocol the requirement for and adherence to effective, routine process-monitoring procedures.

You should also:

   d. document biological challenges for moist heat and ethylene oxide sterilization performed in routine process monitoring procedures
      - include the location, number, type and lot number of the challenge in the records, along with the actual test results (if applicable)
   e. obtain samples from each batch (bioburden-based approach) or periodically (overkill approach) of a drug for ongoing bioburden testing and data collection
      - use the data to determine the limits of species and number of organisms so you can document and control for seasonal/operational variations
   f. document deviations from defined processing conditions
      - investigate and assess the impact on the product and on process objectives

- consider previously processed loads if your requalification indicates the process can no longer achieve the required SAL

g. perform root cause analysis of procedural, process or equipment failure so that the risk to product is correctly understood and suitable corrective and preventative actions (CAPA) are implemented

Note: Sterilization has not been achieved if there is a growth of any biological challenge organisms after moist heat and EO sterilization, including documented change control evaluation runs. If this occurs, you must evaluate the process parameters. If you cannot find a processing error, you must consider the sterilization process unacceptable.

Periodic review and revalidation

1. You should:

a. review the process and change control history at scheduled intervals, at least once a year to ensure nothing has changed inadvertently and to determine the extent of requalification that may be necessary
   - physical and microbial requalification of a sterilization process must take place at least once a year, in accordance with specified acceptance criteria and documented procedures

b. perform periodic review/requalification according to a written procedure
   - should list information/systems to be reviewed and activities that should be performed

c. make sure the appropriate personnel and the quality department review and approve the records of requalification

Change management system

An effective change management system involves evaluating, approving, implementing and documenting sterilization systems or product changes. Include documentation of any testing required to ensure the qualified state of control.

1. You should:

a. use change control procedures to pre-authorize changes to equipment, sterilization system, sterilization or process parameters, load configuration and/or product, material and packaging components

b. define the product/material before introducing a new or altered product, package or loading pattern
   - for example, evaluate changes to primary or secondary packaging, in package or case configuration, case composition
   - these changes may have an impact on sterilization and will require additional studies

c. undertake microbial performance qualification (MPQ) when there are changes to equipment, process parameters or bioburden (based on seasonal variation or routine monitoring)
d. for moist heat sterilization, consider temperature distribution, heat penetration and/or microbiological challenge studies for modifications made to the sterilizer chamber, changes to product carrier/tray design, sterilization medium supply/distribution system or sterilizer operation/control mode
e. revalidate when significant modifications or changes are made

Note: You may not need to revalidate the modified sterilization process if you can demonstrate the product/material, packaging, load configuration, equipment or process equivalence. The process is considered equivalent if it runs within the defined, validated process limits.

You must conduct a technical review that compares the modification candidate with the product/material, packaging, load configuration, equipment or process used to validate the existing sterilization process. You must then document the outcome of this review and include the rationale for any decisions made as a result.

Glossary

Acronyms

BI: biological indicator
CAPA: corrective and preventative action
CEPA: *Canadian Environmental Protection Act, 1999*
CI: chemical indicator
DUR: dose uniformity ratio
ECH: ethylene chlorohydrin
EG: ethylene glycol
EO: ethylene oxide
GMP: good manufacturing practices
ISO: International Organization for Standardization
MPQ: microbiological performance qualification
PCD: process challenge device
PIC/S: Pharmaceutical Inspection Co-operation Scheme
PQ: performance qualification
SAL: sterility assurance level
SDR: standard distribution of resistances

Definitions

The following definitions explain how terms are used in this document. If there's a conflict with a definition in the *Food and Drugs Act* (FDA) or *Food and Drug Regulations* (FDR), the definition in the act or regulations prevails. These definitions supplement those provided in the glossary in the Good manufacturing practices guide for drug products (GUI-0001) .

Note: The source of a definition is provided in parentheses at the end of a definition.

Aeration: Part of the sterilization process during which ethylene oxide and/or its reaction products desorb from the product/material until predetermined levels are reached. (ISO 11135:2014)

Bioburden: The total number of viable microorganisms:

- on or in a packaging material, raw materials, starting materials, intermediates or finish product or
- in the manufacturing environment before sterilization

Biological drug: A drug that is listed in Schedule D to the act that is in dosage form or a drug that is an active ingredient that can be used in the preparation of a drug listed in that Schedule. (C.04.001, FDR)

Biological indicator (BI): A characterized preparation consisting of a number of microorganisms (bacterial spores) of known resistance to the sterilization method to monitor adequacy of sterilization.

Blow-Fill-Seal (BFS): A technology in which containers are formed from a thermoplastic granulate, filled with product and then sealed in a continuous, integrated, automatic operation. The 2 most common types of BFS machines are shuttle type (with Parison cut) and rotary type (Closed Parison). (PIC/S Annex 1)

Bracketing strategy/approach: The design of a stability schedule where only samples on the extremes of certain design factors (such as strength, package size) are tested at all time points as in a full design. The design assumes that the stability of any intermediate levels is represented by the stability of the extremes tested. For a range of strengths to be tested, bracketing applies if the strengths are identical or closely related in composition.

Examples:

- a tablet range made with different compression weights of a similar basic granulation
- a capsule range made by filling different plug fill weights of the same basic composition into different sized capsule shells

Bracketing can be applied to different container sizes or to different fills in the same container closure system. (ICH Q1A)

Bulk drug: A drug in dosage form that's not in its final packaging, usually in quantities larger than the largest commercially available package size.

Calibration: Set of operations that establish, under specified conditions, the relationship between:

- values of a quantity indicated by a measuring instrument or measuring system or values represented by a material measure or a reference material
- corresponding values realized by standards

(ISO 11135:2014)

Chemical indicator (non-biological indicator): Test system that reveals change in 1 or more pre-defined process variables based on a chemical or physical change resulting from exposure to a process. (ISO 11135:2014)

Change control: A written procedure that describes the action to be taken if a change is proposed:

- to facilities, materials, equipment and/or processes used to fabricate, package and test drugs or
- that may affect the operation of the quality or support system

Change management: A systematic approach to proposing, evaluating, approving, implementing and reviewing changes. (ICH Q10)

Conditioning: Treatment of product within the sterilization cycle, but before ethylene oxide admission to attain a predetermined temperature and relative humidity throughout the load.

Corrective action: Action to eliminate the cause of non-conformity and to prevent recurrence. Note 1: There can be more than 1 cause for a non-conformity. Note 2: Corrective action is taken to prevent recurrence whereas preventive action is taken to prevent occurrence. (ISO 9000:2015)

D–value: The decimal reduction time/dose or time required to reduce a microbial population by 90% (1 log value) under specified test conditions.

D_{121}: D-value of a microorganism at an exposure temperature of 121°C. (Sterilization by Moist Heat)

D_{maxP}: The maximum process dose allowed. This dose depends on the product or is determined on a case-by-case basis. It is set below the $D_{max}T$, to prevent damage to the product, but is high enough to achieve a processing dose range (D_{max}/D_{min} ratio). (Sterilization by Irradiation)

D_{maxT}: The maximum dose tolerated by the product before product degradents increase to significant levels. (Sterilization by Irradiation)

D_{minP}: The minimum process dose required to achieve the required sterility assurance level (SAL). This dose is determined by the dose-setting validation. (Sterilization by Irradiation)

Dose uniformity ratio: The ratio of the maximum dose divided by the minimum dose. (Sterilization by Irradiation)

Dosimeter: Device with a reproducible, measurable response to radiation, which can be used to measure the absorbed dose in a given system. (ISO 11137-1:2006)

Drug: Includes any substance or mixture of substances manufactured, sold or represented for use in:

- diagnosing, treating, mitigating or preventing a disease, disorder or abnormal physical state, or its symptoms, in human beings or animals
- restoring, correcting or modifying organic functions in human beings or animals or
- disinfecting premises in which food is manufactured, prepared or kept

(Section 2, FDA)

In Division 1A and Division 2 of the FDR, "drug" does not include:

- a dilute drug premix
- a medicated feed as defined in subsection 2(1) of the *Feeds Regulations, 1983*
- an active ingredient that is for veterinary use and that is not an active pharmaceutical ingredient
- an active pharmaceutical ingredient that is for veterinary use and that isn't required to be sold pursuant to a prescription and that is also a natural health product as defined in subsection 1(1) of the *Natural Health Products Regulations*
- a drug that is used only in an experimental study in accordance with a certificate issued under section C.08.015

(C.01A.001(2), FDR)

Dwell time: The period that items are subjected to a given processing condition.

Fabricate: To prepare and preserve a drug for the purpose of sale.

(C.01A.001, FDR)

F_0: The amount of time in minutes, equivalent to time at 121.1°C, to which a unit has been exposed during a sterilization cycle. The calculation of F_0 is based on a microorganism's D-value and the corresponding z-value (Sterilization by Moist Heat).

Gamma rays: Electromagnetic radiation (photons) originating in atomic nuclei and accompanying many nuclear reactions (such as fission, radioactive decay, neutron capture). Gamma rays are physically identical to X-rays of high energy. The only essential difference is that X-rays do not originate in the nucleus.

In-process drug: Any material or mixture of materials that must undergo further processing to become a drug in dosage form.

Ionizing radiation: Electromagnetic radiation (consisting of photons) or particulate radiation (consisting of electrons, neutrons, protons) capable of producing charged particles through interactions with matter.

Irradiation container: Holder in which product is transported through the irradiator. Note 1 to entry: The holder can be a carrier, cart, tray, product carton, pallet or other container. (ISO 11139:2018)

kGy: Gray (Gy) is the international unit for measuring the radiation dose delivered. 1 kGy=100,000 rads or 0.1 MRad (old terminology).

Label: Includes any legend, word or mark attached to, included in, belonging to or accompanying any food, drug, cosmetic, device or package. (Section 2, FDA) Means to put a drug in its immediate container or to affix the inner or outer label to the drug. (C.01A.001, FDR)

Lifecycle: All phases in the life of a product from the initial development through marketing until the product is discontinued. (ICH Q8)

Material: A general term for raw materials (starting materials, reagents, solvents), process aids, intermediates, finished products and packaging and labelling materials.

Maximum acceptable dose: Dose given in the process specification as the highest dose that can be applied to a specified product without compromising safety, quality or performance. (ISO 11139:2018)

Maximum load: The maximum quantity or mass of items permitted in a sterilizer load.

Microbiological performance qualification (MPQ): Method used to assess the rate of microbiological inactivation for a given process.

Microorganism: A cellular or non-cellular microbiological entity that can replicate or transfer genetic material and cannot be detected by the naked human eye. Microorganisms include bacteria, fungi, viruses and parasites, and may be pathogenic or non-pathogenic in nature. (Canadian Biosafety Standard, second edition)

Minimum load: The minimum quantity or mass of items permitted in a validated sterilization load.

Moist heat: Steam, steam-air mixtures and superheated water used for sterilization.

Non-condensable gases: Air and other gases that will not condense to liquid state, thereby not releasing latent heat under the conditions of sterilization.

Overkill: Sterilization process that demonstrated as delivering at least a 12 spore log reduction to a biological indicator that has a resistance equal to or greater than the product bioburden. (ISO 11135:2014)

Packaging material: Includes a label. (C.02.002, FDR)

Parametric release: A sterility release system based on effective control, monitoring, documentation and batch records review of validated sterilization process. This is in lieu of release procedures based on end-product sterility testing.

Performance qualification (PQ): Documented verification that the equipment and ancillary systems, as connected together, can perform effectively and reproducibly based on the approved process method and specifications. (ICH Q7)

Pharmaceutical: A drug other than a drug listed in Schedule C or D to the act. (C.01A.001, FDA)

Preconditioning: Treating the product before the sterilization cycle to attain a predetermined temperature and relative humidity throughout the load.

Preventive action: Action to eliminate the cause of a potential nonconformity or other potential undesirable situation. Note 1 to entry: There can be more than 1 cause for a potential nonconformity. Note 2 to entry: Preventive action is taken to prevent occurrence, while corrective action is taken to prevent recurrence. (ISO 9000:2015)

Process challenge device (PCD): Item designed to constitute a defined resistance to a sterilization process and used to assess performance of the process. (ISO 11135:2014)

Process parameter: Specific value for a process variable. (ISO 11135:2014)

Process validation: The documented evidence that the process, operated within established parameters, can perform effectively and reproducibly to produce a product that meets its predetermined specifications and quality attributes. (adapted from ICH Q7)

Product: A term used to refer to either raw materials, packaging components or the final pharmaceutical. The context will clarify which material is being referred to.

Qualification: Action of proving and documenting that equipment or ancillary systems are properly installed, work correctly and lead to the expected results. Qualification is part of validation, but the individual qualification steps do not constitute process validation. (ICH Q7)

Quality risk management: A systematic process for assessing, controlling, communicating and reviewing risks to the quality of the medicinal product. Can be applied both proactively and retrospectively. (ICH Q9)

Raw material: Any substance other than packaging material or an in-process drug that is used in drug manufacture. Includes substances that appear in the master formula but not in the drug, such as solvents and processing aids.

Requalification: Repetition of part of validation to confirm a specified process continues to be acceptable. (ISO 11135:2014)

Revalidation: Required when there’s a change in any of the critical process parameters, formulation, primary packaging components, raw material fabricators, major equipment or premises. Failure to meet product and process specifications in sequential batches would also require process revalidation.

Risk: The combination of the probability of occurrence of harm and the severity of that harm. (ICH Q9)

Risk assessment: A systematic process for organizing information to support a risk decision to be made within a risk management process. Consists of identifying the hazards and analyzing and evaluating risks associated with exposure to those hazards. (ICH Q9)

Saturated steam (also referred to as dry saturated steam): Steam that is:

- at a temperature and pressure that corresponds to the vaporization curve of water
- in a state of equilibrium between being a liquid and a gas, with no entrained liquid water

Specification: A detailed description of a drug, the raw material used in a drug or the packaging material for a drug. Includes a:

- statement of all properties and qualities of the drug, raw material or packaging material that are relevant to manufacturing, packaging and using the drug, including the identity, potency and purity of the drug, raw material or packaging material
- detailed description of the methods used to test and examine the drug, raw material or packaging material
- statement of tolerances for the properties and qualities of the drug, raw material or packaging material

(C.02.002, FDR)

State of control: A condition in which the set of controls consistently provides assurance of acceptable process performance and product quality. (ICH Q10)

Sterile: Free from viable microorganisms. (ISO 11135:2014)

Sterility assurance level (SAL): Expected probability of a surviving microorganism on each individual product after being exposed to a valid sterilization process.

Sterilization: A suitably designed, validated and controlled process that inactivates or removes viable microorganisms in a product until sterility is obtained. (EMA guideline on sterilizing the medicinal product, active substance, excipient and primary container)

Sterilization cycle: A sequence of defined operating parameters (such as time, temperature and pressure) and conditions for rendering an item sterile. (Does not apply to Sterilization by Irradiation).

Sterilizing agent: Physical or chemical entity, or combination of entities, that have sufficient microbicidal activity to achieve sterility under defined conditions. (ISO 11135:2014)

Sterilization indicators: Devices used to monitor the presence or attainment of 1 or more of the parameters required for a satisfactory sterilization process or used in a specific test of sterilization equipment.

Survivor curve: Graphical representation of the inactivation of a population of microorganisms with increasing exposure to a microbicidal agent under stated conditions. (ISO 11135:2014)

Temperature distribution: Temperature measurement of the heating medium across the chamber load zone.

Terminal sterilization: The application of a lethal sterilizing agent or conditions to a product in its final container to achieve a predetermined sterility assurance level (SAL) of 10^{-6} or better (for example, the theoretical probability of there being a single viable microorganism present on or in a sterilized unit is equal to or less than 1×10^{-6} (1 in a million)). (PIC/S, Annex 1)

Validation: A documented program that provides a high degree of assurance that a specific process, method or system will consistently produce a result meeting pre-determined acceptance criteria. (ICH Q7)

Validation protocol: A written plan of actions stating how process validation will be conducted. It will:

- specify who will conduct the various tasks
- define testing parameters, sampling plans, testing methods and specifications
- specify product characteristics and equipment to be used

The validation protocol must specify the:

- minimum number of batches to be used for validation studies
- acceptance criteria
- who will sign, approve or disapprove the conclusions derived from such a scientific study

Worst-case: A set of conditions encompassing upper and lower processing limits and circumstances, including those within standard operating procedures that pose the greatest chance of process or product failure (compared to ideal conditions). Such conditions do not necessarily induce product or process failure.

Z-value: The temperature change required to effect a 1 log reduction in the D-value.

X-ray: Ionizing electromagnetic radiation of extranuclear origin.

References

- *Food and Drugs Act*
- *Canadian Environmental Protection Act, 1999*
- *Food and Drug Regulations*
- Good manufacturing practices guide for drug products (GUI-0001)
- Guide to validation - Drugs and supporting activities (GUI-0029)
- Annex 1 to the Good manufacturing practices guide – Manufacture of sterile drugs (GUI-0119)
- Guidance on parametric release - Pharmaceutical Inspection Co-Operation Scheme (PIC/S)
- Annex 11 to the good manufacturing practices guide: Computerized systems: GUI-0050
- Guidelines for the reduction of ethylene oxide releases from sterilization applications
- Canadian Biosafety Standard, second edition
- Guideline on the sterilisation of the medicinal product, active substance, excipient and primary container (EMA)
- Guide to good manufacturing practice for medicinal products annexes, Annex 15: Qualification and validation (PIC/S)
- Guide to good manufacturing practice for medicinal products annexes, Annex 1: Manufacture of sterile products (PIC/S)
- ISO 11137-1: Sterilization of health care products – Radiation – Part 1: Requirements for development, validation and routine control of a sterilization process for medical devices (current version)
- ISO 11137-2: Sterilization of health care products – Radiation – Part 2: Establishing the sterilization dose (current version)
- ISO 11137-3: Sterilization of health care products – Radiation – Part 3: Guidance on dosimetric aspects
- ISO 11137-4: Sterilization of health care products - radiation - Part 4: Guidance on process control (current version)
- ISO 11135: Sterilization of health care products – Ethylene oxide – Requirements for the development, validation and routine control of a sterilization process for medical devices (current version)
- ISO TS 13004: Sterilization of health care products — Radiation — Substantiation of selected sterilization dose: Method VDmax ^{SD} (current version)
- ISO 11139: Sterilization of health care products — Vocabulary of terms used in sterilization and related equipment and process standards (current version)
- ISO 17665-1: Sterilization of health care products - Moist heat - Part 1: Requirements for the development, validation and routine control of a sterilization process for medical devices (current version)
- PDA Technical Report No. 1: Validation of moist heat sterilization processes: Cycle design, development, qualification and ongoing control (revised 2007, Supplement Vol. 61, No. S-1)
- ICH Quality guidelines