Process validation: Terminal sterilization processes for drugs

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Table of contents

The following table shows the three types of icons used in this document, and the way they are intended to be used.

Important: Key or cautionary information.

Information: Supplementary information like quotes and legal references.

Tip: Things for people to do or understand.

About this document

1. 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* (the Regulations), which is about good manufacturing practices (GMP). This guide mainly refers to Manufacturing Control (sections C.02.011 - C.02.012), Quality Control Department (sections C.02.013 - C.02.015) and Sterile Products (section C.02.029) requirements of the *Food and Drug Regulations*.

This guide should be read in conjunction with the current edition of the *Good manufacturing practices guide for drug products (GUI-0001)*, *Annex 1 to the Good manufacturing practices guide – Manufacture of sterile drugs (GUI-0119)* and *Validation Guidelines for Pharmaceutical Dosage Forms (GUI-0029).*

2. 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 within this document can be extended to the sterilization of raw materials, bulk materials, in process drugs and packaging materials.

Definitions of terms used in this guide can be found in Appendix A.

3. Introduction

These guidelines explain requirements for validating the terminal sterilization of drugs and were developed by Health Canada in consultation with stakeholders. They were written to align with International Organization for Standardization (ISO) standards (see references in Appendix B).

This document replaces Health Canada previous versions of 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)

See *Validation Guidelines for Pharmaceutical Dosage Forms (GUI-0029)* for a general guidance on proper qualification and validation of manufacturing processes, facilities, equipment, utilities and analytical methods within drugs lifecycle.

See Pharmaceutical Inspection Co-operation Scheme (PIC/S) "*Guide To Good Manufacturing Practice For Medicinal Products Annexes", Annex 15: "Qualification And Validation*" *(PE 009-14 (Annexes))* for general qualification and validation guidance.

Please refer to *Annex 1 to the Good manufacturing practices guide – Manufacture of sterile drugs (GUI-0119)* for additional information regarding manufacturing of sterile products and for validation of blow/fill/seal technology and aseptic processing.

Please refer to PIC/S Annex 11: Computerised Systems for GMP requirements as they relate to Computerised Systems.

Guidance documents like this one are meant to help industry and health care professionals understand how to comply with regulations. They also provide guidance to Health Canada staff, so that the rules are enforced in a fair, consistent and effective way across Canada.

Health Canada inspects establishments to assess their compliance with the *Food and Drugs Act* (the Act) and associated regulations. When we conduct an inspection, we will use this document as a guide in judging your compliance with GMP requirements with respect to validation of terminal sterilization processes.

These guidelines are not the only way GMP regulations can be interpreted, and are not intended to 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 flexibility in approach. So use this guide to develop specific approaches that meet your unique needs.

Guidance

4. Principles

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

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 (i.e. the theoretical probability of there being a single viable microorganism present on or in a sterilized unit is equal to or less than 1 x 10^{-6} (one in a million) (PIC/S).

Terminal sterilization is the preferred method when fabricating sterile products because it provides better assurance of sterility.

For a given sterilization approach, the probability of survival of microorganisms is determined by the number and resistance of microorganisms and by the environment in which the organisms exist during treatment. It is important to track the resistance as well as the number of organisms to assure that the terminal sterilization parameters continue to provide the required sterility assurance level (SAL).

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

5. Lifecycle Approach

The lifecycle approach outlined in *Validation Guidelines for Pharmaceutical Dosage Forms (GUI-0029)*) is also applicable to the validation of terminal sterilization processes. The validation lifecycle is comprised of the following three 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

Ensure that an effective quality risk management system is integrated into all areas of the product life cycle with the goals of minimizing microbial contamination and ensuring the quality of sterile drugs manufactured.

6. Phase 1- Process Design

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

General considerations

The goal, when manufacturing sterile drugs, is to control the pre-sterilization bioburden to an appropriate level. It is important that the level of microbial quality be critically evaluated first, in order for the terminal sterilization process to be properly applied. It is important to understand the microbial quality of all the materials (raw materials, bulk materials, packaging materials, process components

e.g. in-process drugs and finished products). Reducing the microbial bioburden of these materials will allow for a more effective terminal sterilization process.

1. Establish definition for the product to be sterilized (in terms of physical, chemical, pharmacological properties, packaging, loading configuration and microbiological quality) before validation.

2. Establish a process definition. The purpose of process definition is to establish the maximum acceptable dose and the sterilization dose for the sterilization process of a defined product. Conduct studies to determine bioburden in the materials to be sterilized. These studies should also include evaluation of the impact of hold times as well as partial or interrupted cycles on the bioburden.

3. Determine the required sterility assurance level (SAL).

4. Evaluate the compatibility of the sterilization process with the material to be sterilized. Ensure that the primary and secondary packaging is able to tolerate cycle parameters, while maintaining product/material and package/container integrity for the expected life of the product/material.

5. Follow effective premises and equipment cleaning as well as sanitation procedures to prevent contamination. You must control and document bioburden to ensure the microbiological quality of the product/material presented for sterilization is controlled and does not compromise the effectiveness of the sterilization process.

Risk assessment(s) should be used to determine the amount of work at the development / prequalification stage. Ensure that the impact of the sterilization process on the drug, including its stability, is fully assessed and understood.

Sterilization cycle development (dose setting methods)

Two basic approaches are used to develop sterilization cycles for terminal sterilization processes:

1. The overkill method is used when the product/material can withstand prolonged exposure to the sterilization process without adversely affecting the quality of the product/material. Using the overkill method, sterilization is performed for longer than is required to kill the bioburden present on or in the material being sterilized. A cycle designed with the overkill approach can be defined as a process that is sufficient to provide at least a 12 log reduction of microorganisms having a minimum D value of 1 minute.

2. The probability of survival approach is used for products that may be impacted by the sterilization process being used. In this approach, 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 one unit is contaminated is therefore no more than one in a million; this is considered to be an acceptable level of sterility assurance.

    a. 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).

    b. The determination of the minimum required process lethality used in the probability of survival approach is based on:

        - the number of microorganisms (bioburden) found in a given product
        - the required sterility assurance level (SAL)
        - the resistance of the microorganisms to the sterilization method

See Appendix C for more information regarding D-value and F_0.

7. Phase 2- Process performance qualification

Ensure performance qualification (PQ) demonstrates reproducibility of the process. It 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 quality risk management approach.

Loads used for performance qualification (PQ) should represent products routinely sterilized including the most challenging routine loads.

Equipment

1. You must ensure that the range, resolution, accuracy, reproducibility and response time of all controlling, monitoring and recording equipment is adequate to demonstrate that defined process conditions are met.

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

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

3. The standards you use for calibration must be traceable to an appropriate standard. You must document and keep records of equipment calibration.

Prior to commencing validation studies, it is necessary that the equipment be appropriately qualified for its intended use. More guidance on equipment qualification is available in *Validation Guidelines for Pharmaceutical Dosage Forms (GUI-0029).*

4. Complete the validation of analytical methods with adequate calibration and qualification of measuring equipment. This includes all measuring equipment used in analytical methods and the measurement of process parameters in the operation of the sterilization cycle.

Sterilization indicators

Clearly label each basket, tray or other carrier and indicate whether or not it has been sterilized. In addition, you can use physical/chemical indicators to distinguish sterile from non-sterile goods. These devices indicate adequacy of the sterilization conditions by a visible change, but do not indicate that the load is sterile.

1. Calibrate sterilization indicators used in validation studies and requalification. Ensure they are appropriately stored and used before their expiry date. Ensure detailed written test procedures and records of test results are available.

2. Test physical and chemical indicators to demonstrate adequate pre-determined response to both time and exposure.

3. Test biological indicators for viability and quantification of the challenge organism as well as for the time and exposure response. This applies to indicators either prepared in-house or obtained commercially.

4. Ensure a certificate of testing for each lot is available for commercial indicators (indicating the D-value of the lot). The quantification is acceptable if the biological indicator count provided by the manufacturer has been qualified and periodically confirmed as per written procedures.

5. When qualifying commercial or in-house biological indicators, ensure the choice of media (pH, electrolytes, carbohydrates, etc.) and sample carriers (suspension in ampoules, paper strips, inoculated products and inoculation on solid carriers) are consistent with the materials used in the validation of the terminal sterilization process.

Microbial performance qualification (MPQ) - biological challenge reduction studies

Biological challenge reduction studies demonstrate that the sterilization processes will effectively reduce microbial levels to required sterility assurance levels. Such studies will be required during both Phase 1 (to establish a process and have confidence in its reliability and effectiveness) and Phase 2 (to ultimately demonstrate that the terminal sterilization process is capable of consistently meeting requirements).

1. Consider the product/material bioburden profile over multiple lots of product/material fabricated during different times of the year when choosing the level of biological challenge for the study, including the type and resistance of the surviving microorganism recovered. This will allow you to capture possible seasonal changes.

2. You may use a worst-case bioburden challenge using an appropriate organism as described in the table below. In all other cases, you should use the microorganism with the highest D-value occurring in the natural population (as determined by sampling the environment). You should have proper scientific justification available to support the use of the chosen organism.

3. Assess the sterilization cycle by introducing a known quantity of specific microorganisms with established D-values and assessing the level of reduction over time. You must confirm that the sterilization process will deliver a probability of survival of less than 1 in 10^6 in all cases.

The D-Value of the chosen organism must be assessed in association with the material to be sterilized and its formulation because resistance of the microorganism can change with changes to parameters such as pH.

See Appendix C for more information regarding D-value.

Table 1: Organisms for biological challenges

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

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

4. Run positive controls for each lot of biological indicator tested with every load to verify the viability of the challenge organism.

5. Define the placement of biological challenges. The challenge should be located as close as possible to worst-case locations and placed adjacent to any sensors (if run along with distribution studies/penetration studies - see section 8 (Process validation: Sterilization by moist heat)). The challenge should be placed in containers wherever possible, or within process challenge devices (PCDs) to reflect the desired processing conditions.

6. 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.

7. Consider conducting robustness studies by changing one or more process variables (e.g. temperature, humidity) and comparing them to the set points used in routine sterilization (below or at minimum levels specified for routine control).

8. Document and keep records of the biological challenge reduction studies, including the placement of the biological challenge, the organism type and name, D-value, challenge level, lot number, placement and growth result.

Cycle interruptions

1. The sterilization process may need to be turned off during the course of a sterilization treatment due to mechanical, safety or operational reasons, interrupting the sterilization process. 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.

Ensure data is available to support the resumption of interrupted cycles when interruptions occur.

2. You must have proper procedures in place to direct the operator to the appropriate person to contact in the event of a cycle interruption or a delay in the commencing/completion of the sterilization cycle. Investigate any cycle interruptions.

8. Process validation: Sterilization by moist heat

Introduction

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

Product/material definition

1. Describe the material and the packaging system to be sterilized (e.g., size(s), fill volume, or primary packaging).

2. Describe the process challenge device (PCD).

When process parameters are defined using a bioburden-based method, estimation of bioburden must be included.

Sterilizing agent characteristics

1. Your specification for a steam sterilization process must include at minimum:

    a. requirements for purity and quality of steam

    b. requirements for dryness, superheat, saturation and non-condensable gases

    c. additives, which should not be at a level to cause contamination of product or equipment

Sterilization process definition

1. You must specify the sterilization process you use, including:

    a. a description of the autoclave(s) to be used for production sterilization, including manufacturer and model

    b. a description of the operating cycle and/or graphic presentation

    c. the minimum cycle lethality achieved throughout the sterilization load

    d. a description of the monitoring device, its location and interpretation of results (if used to verify delivery of a specified sterilization process)

    e. process parameters and their tolerances (you should use both pressure and temperature to monitor the process, and measure physical process parameters to confirm reproducibility)

    f. the location of reference measuring point

    g. the minimum and maximum pressure in sterilizing chamber

    h. falling and rising pressure gradient and tolerances

    i. the maximum quantity of each contaminant present in any liquid, gas, steam admitted to sterilizer chamber

    j. a description of the holding time, and the minimum and maximum temperatures (and their locations) measured during this time in an empty sterilizer chamber

    k. requirements for the conditioning of product before sterilization (where applicable)

    l. load configuration

m. restrictions on size and mass of the load

n. the reference loads to be used to evaluate the effectiveness of the sterilization process

o. the location and acceptance criteria for biological indicators (BIs) and chemical indicators (CIs)

Wrap your dry item to be sterilized (other than products in sealed containers) in a material that allows removal of air and penetration of steam, and prevents re-contamination after sterilization. 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 upon removal from the sterilizer. Load dryness should be confirmed by visual inspection as a part of the sterilization process acceptance.

Equipment qualification

1. Your moist heat equipment specification should include at minimum:
    a. a description of materials of construction
    b. description of control, monitoring and recording devices
    c. the 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. 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 cooling water used in the process, and means by which they are delivered to the chamber

Examples of instruments that need calibration:

- temperature recorders and sensors
- thermocouples
- pressure sensors for jacket and chamber pressure
- timers
- conductivity monitors for cooling water
- flow meters for water/steam
- water level indicators

- thermometers including those for thermocouple reference and chamber monitoring

The position of the temperature probes used for controlling and/or recording should be determined during the heat distribution and penetration studies. Where applicable, these should be checked 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. You must include an evaluation of both the empty chamber and the loaded chamber in these studies.

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

1. Perform temperature distribution studies according to written procedures, using temperature-measuring sensors or probes that have been calibrated before and after use.

2. Specify the requirements for temperature uniformity based on the type of sterilizer and specific processing parameters.

3. Perform empty chamber temperature distribution runs during equipment qualification. This should consist of runs using the maximum and minimum cycle times and temperatures specified for the equipment. The number of runs should be determined based on quality risk management principles. These studies should demonstrate that the temperature uniformity throughout the empty chamber is within the temperature variation limits established in the validation protocol.

4. Use multiple temperature probes in each test run. Use simultaneous data recording to capture a reading of each individual probe at specified time intervals. This will allow you to determine the slowest and fastest heating zones in the chamber. Document the location of each probe. Place probes in a way that adequately shows temperature distribution throughout the sterilizer chamber.

5. Collate the data from all runs into a temperature profile for the chamber.

6. Perform loaded chamber temperature distribution studies. Use maximum and minimum chamber load configurations to represent various material configurations.
    a. 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.
    b. Perform the sterilization cycle test runs using different container sizes. Use the sterilization parameters specified for the normal production process.
    c. Document the position of each temperature probe in each test run.
    d. Determine and document the slowest heating point(s) or cold spot(s) in each run.
    e. Perform 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.
    f. Develop and document a temperature distribution profile for each load configuration.
7. Evaluate each test run performed. Certify completed studies before beginning temperature penetration studies.

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 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. Perform heat penetration studies according to detailed written procedures. Use temperature-sensing probes that are calibrated before and after use. Ensure simultaneous data recording is available to capture a reading of each individual temperature probe within specified time intervals. This will allow you to determine the slowest and fastest heating units in the chamber.

2. Allow for variables such as container size, design, material, viscosity of solution and fill volume in your validation protocol.

The container should be filled up to maximum fill volume with the slowest-to-heat solution for the specified cycle.

3. Consider initial container temperature-mapping studies (depending on the container size).

4. Conduct heat penetration studies with the maximum and minimum loading configurations for each sterilization cycle. Use sterilization parameters that do not exceed normal production cycles.

5. Monitor heat delivered to the slowest heating unit of the load. Use this data to calculate the minimum lethality (F_0 value) of the sterilization process. See Appendix C for more information regarding D-value and F_0 value.

6. Once you have identified the slowest heating units of the load, perform replicate runs to verify that the desired minimum process F_0 value can be achieved consistently throughout the load. Determine the number of required runs using a quality risk management approach. The process is considered acceptable once such consistency in lethality has been adequately established.

Biological challenge reduction studies

Perform biological challenge reduction studies, as described in Section 7 (Phase 2- Process performance qualification).

You may run the biological challenge along with distribution studies/penetration studies.

9. 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 to ensure 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 a 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 tolerated dose (D_{maxT}). The maximum process dose (D_{maxP}) and minimum process dose (D_{minP}) should also be set.

The D_{maxT} is that dose of radiation that causes an unacceptable change in the analytical profile of the material or product packaging.

2. It is important that your initial product/material qualification tests the product/material using widely separated radiation doses. This will allow you to quickly assess the ability of the product/material to withstand radiation and to zero in on the most appropriate radiation dose for further testing.

Before starting to 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 radiation dose is affected by variations in density and configuration of the products/materials and packages, 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. The D_{maxP} for a product/material must not exceed its D_{maxT}. It is usually set below the D_{maxT} to ensure the product/ material is not overexposed.

4. 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. This ratio is the key to successful radiation processing.

Sterilizing agent characteristics

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

Gamma radiation delivers a specified dose relatively slowly (over a period of minutes to hours) to a large volume of product.

Electron beam generators can deliver the same dose in a fraction of a second to a very small volume of product.

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

1. Define the type of radiation to be used in sterilization.

2. Specify the energy level of the electron beam (for electrons or X-rays).

3. Assess the potential for induced radioactivity in product/material (for electrons or X-rays).

Sterilization process definition

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

- The product/material must be representative of what will be routinely fabricated.
- The source of radiation must be capable of precisely delivering required doses.

Sterilization cycle development

There are three basic approaches to set up a dose for a radiation sterilization process:

1. The overkill method has traditionally been used when the product/material can withstand radiation doses in excess of 25 kGy without adverse effects to product/material quality. It is based on worst-case bioburden assumptions.

You must select the irradiator and product/material-loading parameters in a manner that assures that the product/material receives the D_{minP} of 25 kGy while not exceeding the D_{maxT}.

2. The bioburden-based method is only used in cases where the product's/material's bioburden before radiation treatment can be proven to be consistent. The result is a treatment dose that is tailored to the actual need (bioburden), which is less than the very high 25 kGy.

See ISO 11137-2:2013 for guidance related to bioburden calculations.

3. The species-specific bioburden approach relates the radiation dose delivered to the most resistant organism in the bioburden population found in the manufacturing area and on the product/material. This population should be significantly skewed in the direction of radiation-sensitive organisms, especially when dealing with aseptic processing areas. This should result in a much lower dose of radiation being needed to achieve sterilization. For this method to be effective, you must conduct dose distribution studies (see section (Dose distribution studies) below for details) to determine the product loading pattern that achieves the best possible D_{max}/D_{min} ratio.

Detailed guidance on sterilization using radiation can be found in:

- ISO 11137-1:2006 Sterilization of Health Care Products (Radiation – Part 1) – Requirements for development, validation and routine control of a sterilization process for medical devices
- ISO 11137-2:2013 Sterilization of Health Care Products (Radiation – Part 2) –Establishing the sterilization dose
- ISO 11137-3:2017 Sterilization of Health Care Products (Radiation – Part 3) – guidance on dosimetric aspects of development, validation and routine control

Equipment qualification

1. Your irradiator specification should include at 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 the 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)

Examples of instruments that need calibration for electron beam and gamma radiation processing technologies include:

- dosimeters
- spectrophotometers
- thickness gauges

- timers
- recorders

Dose distribution studies

Dose distribution studies are performed in order to determine the D_{max} and D_{min} positions in the irradiator transport mechanism for the product/material in its predetermined loading configuration. They also confirm that the radiation dose delivered to the product/material is within process specifications.

1. Perform dose studies according to written procedures, using properly placed dosimeters that have been calibrated.
2. Document the location of each dosimeter. The placement of dosimeters must ensure that an acceptable distribution is achieved throughout the transport/irradiation system.
3. Use dosimeters that are capable of measuring the dose over the desired range.
4. Collate the data from all runs into a dose-map profile for each type of irradiation container, product conveyor path, and irradiation source.
5. Perform dose distribution studies for each product/material-loading configuration and each product/material size.

The studies you conduct should prove that the dose uniformity requirements as outlined in your process specification, are consistently achieved. You must demonstrate operational consistency of the dose uniformity to conclude your process is validated.

6. Evaluate each test run performed and certify the completed studies.

Loading patterns

1. The way the product/material is configured in or on the transport mechanism that will carry it through the irradiator is critical to achieving the specified D_{max}/D_{min} ratio, doses and desired SAL (sterility assurance level). A detailed map of how the product/material is to be placed in or on the transport mechanism should be part of your process validation documentation.

2. Validation studies must confirm that the product in the D_{min} position will receive a dose meeting or exceeding D_{minP} and that the product in the D_{max} position will receive a dose not exceeding D_{maxP} during routine processing (at the defined irradiator operating parameters and routine monitoring dose acceptance range).

Temperature control

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

1. Document the allowed temperature range of the product when it arrives at the irradiation facility.

2. Document the time available for irradiation before the product temperature rises to the maximum tolerated level.

You may need to provide an opportunity for cooling of the product during the irradiation process. The manner in which this is to be done must be specified.

10. Process validation: Sterilization by ethylene oxide

Introduction

Ethylene oxide (EO) is primarily used to sterilize items that are moisture or heat sensitive and cannot be sterilized by steam sterilization.

Ethylene oxide (EO) is a toxic, flammable and explosive substance, listed in a schedule 1 of the *Canadian Environmental Protection Act (CEPA).* Please consult *Guidelines for the reduction of ethylene oxide releases from sterilization applications* for guidelines on ethylene oxide (EO) emission.

Factors that influence ethylene oxide (EO) sterilization include:

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

Product/material definition

1. Product/material, packaging and loading pattern should be designed to allow the removal of air and the penetration of heat, humidity and EO to the most difficult-to-sterilize locations.

2. Product should be designed to allow removal of EO at the end of the process.

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

3. Product/material and package design should allow ethylene oxide (EO), heat and humidity penetration. For example, you should avoid:
    a. using non-porous materials
    b. attaching labels with large surface areas to breathable materials
    c. using plastic or foam inserts/supports
    d. applying moisture-resistant coatings
    e. using pressure relief valves, stopcocks, manifolds or cotton plugs that restrict EO penetration
    f. applying bleaching agents that contain free chlorine (which react with ethylene oxide (EO), ethylene chlorohydrin (ECH) or ethylene glycol (EG))

4. Product/material tolerance for the required temperatures must be considered.

Sterilizing agent characteristics

1. Carry out validation using a defined sterilizing agent.
2. Specify the storage conditions and shelf life for the sterilizing agent.
3. You may use ethylene oxide (EO) as a pure gas (100%) or in a mixture of gases (such as carbon dioxide or nitrogen).
4. Define ethylene oxide (EO) residues:
    a. Determine rates of dissipation of the major EO residues after being subjected to the EO sterilization cycle.
    b. Specify the maximum allowable levels of EO residues on drugs. These limits must be based on safety studies and on published international safety standards.
    c. Validate analytical methods for the determination of ethylene oxide (EO), ethylene chlorohydrin (ECH) and ethylene glycol (EG) residues.

EO sterilization parameters

1. Monitor the following parameters:
    - vacuum/pressure levels
    - temperatures
    - dwell time
    - steam and gas concentration
    - air washes and air flow
    - humidity
    - transfer time from preconditioning room to sterilizer
2. Consider the following in your ethylene oxide (EO) sterilization cycles design:
    - product/material preparation
    - delivery of the sterilization parameters
    - removal of the residual sterilizing agents
3. Include at least the following in your ethylene oxide (EO) sterilization specification:

a. a definition of the preconditioning, exposure and aeration phases of the sterilization cycle

- 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 all affect the efficiency of aeration.
- Aeration may be performed within the sterilizer or in a separate area or both.

b. a description of process parameters and their tolerances including the following cycle variables: humidity, temperature, EO concentration, pressure and time.

- Relative humidity: Maintaining an appropriate humidity in the sterilization chamber increases the effectiveness of the ethylene oxide (EO) sterilization by increasing EO penetration through cell walls. A relative humidity of about 35% is desirable as it has been shown to be beneficial for effective ethylene oxide (EO) sterilization. Increased humidity can cause the formation of condensation on the product, the chamber walls and optical EO sensors. Products and materials sterilized using cycles with relative humidity of less than 30% are known to have poorer effectiveness of ethylene oxide (EO) sterilization.
- Temperature: Ethylene oxide (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 ethylene oxide (EO) levels, the sterilization process is more effective and requires a shorter dwell time. As the EO gas concentration increases from e.g. 50 to 500 mg/L, the inactivation rate increases.
- Diffusion: The higher the diffusion rate of ethylene oxide (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 is charged with EO.
- Time: An increase in gas concentration and temperature may shorten the time necessary for achieving sterilization.

c. a description of means by which monitoring, controlling and recording of the process variables and of the whole sterilization process is performed.

d. a description of controlled conditions to achieve specified temperature and humidity for the pre-treatment of product/material within the load.

Humidity used for preconditioning and conditioning of product/material should be generated by steam.

Design of ethylene oxide (EO) sterilization cycles

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

There are three basic approaches to set up a dose for an ethylene oxide (EO) sterilization cycle:

1. Overkill cycle: The cycle is developed by performing fractional cycles to establish the survivor curve with biological indicators and product/material samples. The exposure time is then doubled to provide the overkill sterilization process. Thereafter routine bioburden monitoring should be performed.

2. Biological indicator (BI) cycle is only used in cases where the product's/material's bioburden before ethylene oxide (EO) treatment can be proven to be consistent. 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 ethylene oxide (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.

During ethylene oxide (EO) sterilization cycle development and validation studies, test biological indicators as soon as possible after exposure to the sterilization cycle. Microbial inactivation continues after completion of the sterilization cycle due to the presence of EO residues.

3. Absolute bioburden cycle: This cycle is used when the product bioburden resistance to the ethylene oxide (EO) process is very high (product's bioburden is more resistant than the BI), which can be caused by any 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 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, and performing counts. The more resistant organisms are isolated and used in ethylene oxide (EO) cycle development studies, and an inactivation curve is established. The inoculums should consist of the bioburden average plus three standard deviations (3σ).

Additional guidance on ethylene oxide (EO) sterilization can be found in:

ISO 11135:2014 Sterilization of health-care products – Ethylene oxide – requirements for the development, validation and routine control of a sterilization process for medical device

Equipment qualification

Your specification for ethylene oxide (EO) equipment should include equipment from three phases of sterilization process:

- preconditioning,
- sterilization and
- aeration.

1. Your ethylene oxide (EO) equipment specification should include at minimum:
    a. a description of the equipment
    b. the composition of the sterilizing agent and the means by which it is delivered to the chamber
    c. a description of any other gases used in the process, and the means by which they are delivered to the chamber
    d. the purity and quality of steam and/or compressed gases
    e. a description of instrumentation for monitoring, controlling and recording the sterilization process, including sensors characteristics and their locations
    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 materials of construction
    i. the location, space and environment where the equipment is to be installed

Examples of instruments that need calibration:

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

Vapor phase hydrogen peroxide (VHP) is used mainly in surface sterilization (such as in flexible and rigid isolators, pass-throughs, production filling lines, biological safety cabinets and clean rooms). Its use in terminal sterilization of pharmaceutical dosage forms is very limited.

11. Phase 3 – Ongoing process verification

Routine Release

1. Approve sterilization records as part of the batch-release procedure. Sterilization records should be available for each sterilization run.

2. Ensure that the records are reviewed and approved by the appropriate personnel and by the quality department.

For more information related to reprocessing and reworking please consult *Good manufacturing practices guide for drug products (GUI-0001).*

Please refer to *Guidance on Parametric Release - Pharmaceutical Inspection Co-Operation Scheme (PIC/S)* for guidance regarding parametric release.

Monitoring of results

3. Monitor the sterilization process and its parameters routinely to ensure that the specified process conditions are met. Document these results in the processing records.

4. Include maintenance of equipment in your routine control. Perform maintenance in conjunction with calibration.

The requirement for and adherence to effective, routine process-monitoring procedures should be included in the validation protocol.

5. Document biological challenges when 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.

6. Obtain samples from each batch of a drug for ongoing bioburden testing and data collection. Use the data to determine the limits of species and number of organisms in order to adequately document and control for seasonal/operational variations.

7. 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 that the process is no longer capable of achieving the required SAL.

8. Perform root cause analysis of procedural, process or equipment failure in such a way that the risk to product is correctly understood and suitable corrective and preventative actions (CAPA) are implemented.

Growth of any biological challenge organisms following any of the runs, including documented change control evaluation runs, means that sterilization has not been achieved. In such cases, you must evaluate the process parameters. If no processing error can be found, the sterilization process must be considered unacceptable.

Periodic review and revalidation

1. Re-validate the process at scheduled intervals, at least annually to ensure there has not been an undetected change in the product or process. Requalification should be performed using the same operational parameters and acceptance criteria as the original qualification runs.

2. Perform periodic review/requalification according to a written procedure, which should list information/systems to be reviewed and activities that should be performed.

3. Ensure that the records of requalification are reviewed and approved by the appropriate personnel and by the quality department.

Change management system

An effective change management system should evaluate, approve, implement and document sterilization systems or product changes. Include documentation of any testing required to ensure the qualified state of control.

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

2. Perform product/material definition before introducing a new or altered product, package or loading pattern, for example evaluate any changes to primary or secondary packaging, in package or case configuration, case composition, as it may have an impact on the sterilization and will require additional studies.

3. Microbial performance qualification (MPQ) may also be required when there are changes to equipment, process parameters or bioburden (based on seasonal variation or routine monitoring).

4. For moist heat sterilization, consider temperature distribution, heat penetration and /or microbiological challenge studies for changes involving modification of the sterilizer chamber, product carrier/tray design, sterilization medium supply/distribution system or the sterilizer operation/control mode.

5. Carry out re-validation whenever significant modifications or changes are made.

If equivalence of the product/material, packaging, load configuration, equipment or process is demonstrated, re-validation of the sterilization process modification may not be required. The process is considered equivalent if it is running within the defined, validated process limits. A technical review must be performed comparing the modification candidate with the product/material, packaging, load configuration, equipment or process that was used to validate the existing sterilization process. The outcome of the technical review, including the rationale for all decisions reached, must be documented.

Appendix A – Glossary

Acronyms

BI: Biological indicator

CAPA: Corrective and Preventative Action

CEPA: Canadian Environmental Protection Act, 1999

CI: Chemical indicator

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

VHP: Vapor phase hydrogen peroxide

Terms

These definitions explain how terms are used in this document. If there is a conflict with a definition in the *Food and Drugs Act* or *Food and Drug Regulations*, the definition in the Act or Regulations prevails.

The following definitions supplement the definitions provided in the Glossary in the current edition of the *Good manufacturing practices guide for drug products (GUI-0001).*

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)

Asepsis - A state of control attained by using an aseptic work area and performing activities in a manner that precludes microbiological contamination of the exposed sterile product. (PIC/S annex 1)

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 prior to sterilization processing.

Biological drug - As defined in Division 4 of the FDR "drug" means 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)

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 two most common types of BFS machines are the Shuttle type (with Parison cut) and the Rotary type (Closed Parison) types. (PIC/S annex 1)

Bracketing strategy/approach - The design of a stability schedule such that only samples on the extremes of certain design factors (e.g. 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. Where a range of strengths is to be tested, bracketing is applicable if the strengths are identical or very closely related in composition (e.g. for a tablet range made with different compression weights of a similar basic granulation, or 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 is 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, and the corresponding values realized by standards. (ISO 11135:2014)

Chemical indicator (non-biological indicator) - Test system that reveals change in one 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 (a) to facilities, materials, equipment, and/or processes used in the fabrication, packaging, and testing of drugs, or (b) 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 prior to 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. Note1: There can be more than one 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% (one log value) under specified test conditions.

D_{121} - D-value of the BI at an exposure temperature of 121 ˚C. (Sterilization by Moist Heat)

D_{maxP} - The maximum process dose allowed. This dose is product dependent or 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 ensure that the D_{minP} will achieve the desired sterility assurance level SAL. (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. This dose is determined by the configuration of the irradiation facility and the loading pattern/density of the product. (Sterilization by Irradiation)

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

Drug - "Drug" includes any substance or mixture of substances manufactured, sold or represented for use in:

(a) the diagnosis, treatment, mitigation or prevention of a disease, disorder or abnormal (a)physical state, or its symptoms, in human beings or animals,

(b) restoring, correcting or modifying organic functions in human beings or animals, or (b)

(c) disinfection in premises in which food is manufactured, prepared or kept; (c)

(Section 2 of the Food and Drugs Act)

In Division 1A and Division 2 of the Food and Drug Regulations, "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 for veterinary use that is not 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 for the purposes of an experimental study in accordance with a certificate issued under section C.08.015. (See FDRs C.01A.001(2))

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. (See FDRs C.01A.001)

F_0 - The amount of time in minutes, equivalent to time at 121˚C, to which a unit has been exposed during a sterilization cycle. (Sterilization by Moist Heat)

Gamma rays - Electromagnetic radiation (photons) originating in atomic nuclei and accompanying many nuclear reactions (e.g., fission, radioactive decay, and 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, etc.) 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 - The 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 (see Section 2 of the Act). Means to put a drug in its immediate container or to affix the inner or outer label to the drug. (See FDR C.01A.001)

Lifecycle - All phases in the life of a product from the initial development through marketing until the product's discontinuation. (ICH Q8)

Material - A general term used to denote 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, capable of replication or transferring genetic material and that cannot be reasonably 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 (CBS) 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 is demonstrated as delivering at least a 12 spore log reduction to a biological indicator having a resistance equal to or greater than the product bioburden (ISO 11135:2014).

Packaging material - Includes a label. (C.02.002)

Parametric release - A sterility release system based upon effective control, monitoring, documentation, and batch records review of validated sterilization process cycle in lieu of release procedures based upon 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)

Preconditioning - Treatment of product prior to 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 one cause for a potential nonconformity. Note 2 to entry: Preventive action is taken to prevent occurrence whereas 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 meeting 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 actually lead to the expected results. Qualification is part of validation, but the individual qualification steps alone do not constitute process validation. (ICH Q7)

Quality Risk Management - A systematic process for the assessment, control, communication and review of risks to the quality of the medicinal product. It can be applied both proactively and retrospectively (ICH Q9).

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

Requalification - Repetition of part of validation for the purpose of confirming the continued acceptability of a specified process. (ISO 11135:2014)

Re-validation - Required when there is 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 re-validation.

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

Risk assessment - A systematic process of organizing information to support a risk decision to be made within a risk management process. It consists of the identification of the hazards and the analysis and evaluation of the risks associated with exposure to those hazards. (ICH Q9)

Saturated steam - Steam that is at a temperature and pressure that corresponds to the vaporization curve of water. It is in a state of equilibrium between being a liquid and a gas, with no entrained liquid water. [Synonym: dry saturated steam]

Specification - Means a detailed description of a drug, the raw material used in a drug, or the packaging material for a drug and includes:

(a) a statement of all properties and qualities of the drug, raw material or packaging material that are relevant to the manufacture, packaging, and use of the drug, including the identity, potency, and purity of the drug, raw material, or packaging material,

(b) a detailed description of the methods used for testing and examining the drug, raw material, or packaging material, and

(c) a statement of tolerances for the properties and qualities of the drug, raw material, or packaging material. (C.02.002.)

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 exposure 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 the sterilisation of the medicinal product, active substance, excipient and primary container)

Sterilization Cycle - A sequence of defined operating parameters (e.g., time, temperature and pressure) and conditions required to render an item sterile.

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

Sterilization indicators - Devices used to monitor the presence or attainment of one 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 to finished product within a sealed container to achieve a predetermined sterility assurance level (SAL) of 10^{-6} or better (i.e. 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} (one 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 and define testing parameters; sampling plans, testing methods and specifications; will specify product characteristics, and equipment to be used. It must specify the minimum number of batches to be used for validation studies; it must specify the acceptance criteria and who will sign/approve/ 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 (when compared to ideal conditions). Such conditions do not necessarily induce product or process failure.

X-ray - Ionizing electromagnetic radiation of extranuclear origin.

Appendix B – References

Food and Drugs Act
https://laws-lois.justice.gc.ca/eng/acts/F-27/index.html

Canadian Environmental Protection Act, 1999
https://laws-lois.justice.gc.ca/eng/acts/C-15.31/index.html

Food and Drug Regulations
https://laws-lois.justice.gc.ca/eng/regulations/C.R.C.,_c._870/index.html

Good Manufacturing Practices (GMP) Guidelines (GUI-0001)

https://www.canada.ca/en/health-canada/services/drugs-health-products/compliance-enforcement/good-manufacturing-practices/guidance-documents/gmp-guidelines-0001/document.html

Validation Guidelines for Pharmaceutical Dosage Forms (GUI- 0029)
https://www.canada.ca/en/health-canada/services/drugs-health-products/compliance-enforcement/good-manufacturing-practices/validation/validation-guidelines-pharmaceutical-dosage-forms-0029.html

Annex 1 to the Good manufacturing practices guide – Manufacture of sterile drugs - published on February 28, 2018 (GUI-0119)
https://www.canada.ca/en/health-canada/services/drugs-health-products/compliance-enforcement/good-manufacturing-practices/guidance-documents/gmp-guidelines-annex-1-manufacture-sterile-drugs-0119.html

Guideline on the sterilisation of the medicinal product, active substance, excipient and primary container
https://www.ema.europa.eu/en/documents/scientific-guideline/guideline-sterilisation-medicinal-product-active-substance-excipient-primary-container_en.pdf

Guidance on Parametric Release - Pharmaceutical Inspection Co-Operation Scheme (PIC/S)
https://www.canada.ca/en/health-canada/services/drugs-health-products/compliance-enforcement/international/partnerships/guidance-parametric-release-pharmaceutical-inspection-operation-scheme.html

PIC/S Annex 11: Computerised Systems

https://www.canada.ca/en/health-canada/services/drugs-health-products/compliance-enforcement/good-manufacturing-practices/guidance-documents/annex-11-computerized-systems.html

Guidelines for the reduction of ethylene oxide releases from sterilization applications
https://www.canada.ca/en/environment-climate-change/services/canadian-environmental-protection-act-registry/guidelines-objectives-codes-practice/reduction-ethylene-oxide-releases-sterilization.html

PIC/S "Guide To Good Manufacturing Practice For Medicinal Products Annexes", Annex 15 "Qualification And Validation"
https://picscheme.org/en/publications?tri=gmp#zone

PIC/S "Guide To Good Manufacturing Practice For Medicinal Products Annexes", Annex 1 "Manufacture of Sterile Products"
https://picscheme.org/en/publications?tri=gmp#zone

ISO 11137-1:2006 Sterilization of Health Care Products (Radiation – Part 1) – Requirements for development, validation and routine control of a sterilization process for medical devices

ISO 11137-2:2013 Sterilization of Health Care Products (Radiation – Part 2) –Establishing the sterilization dose

ISO 11137-3:2017 Sterilization of Health Care Products (Radiation – Part 3) – guidance on dosimetric aspects of development, validation and routine control

ISO 11135:2014 Sterilization of health-care products – Ethylene oxide – requirements for the development, validation and routine control of a sterilization process for medical devices

PDA Technical Report No. 1 (revised 2007) Supplement Vol. 61, No. S-1 "Validation of Moist Heat Sterilization Processes: Cycle Design, Development, Qualification and Ongoing Control".

Appendix C – D-value and F_0

D-value and F_0

1. 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 cycle. 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.

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

3. 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:

   a. D_{121} is equal to the time required at 121°C to reduce the population of the most heat-resistant organism in the unit by 90%.

   b. "A" is the microbial count per container.

   c. "B" is the maximum acceptable probability of survival (1×10^{-6} for pharmaceutical dosage forms).

4. Lab studies that determine the number and resistance of microorganisms associated with a product (bioburden) serve as the basis for calculating the minimum F_0 value required for sterilization.

5. 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.