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Sterilization of health care products — Requirements for validation and routine control — Industrial moist heat sterilization

Stérilisation des produits sanitaires — Prescriptions pour la validation et le contrôle de routine — Stérilisation industrielle par chaleur humide

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Contents

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Foreword

ISO (the International Organization for Standardization) is a worldwide federation of national standards bodies (ISO member bodies). The work of preparing International Standards is normally carried out through ISO technical committees. Each member body interested in a subject for which a technical committee has been established has the right to be represented on that committee. International organizations, governmental and non-governmental, in liaison with ISO, also take part in the work. ISO collaborates closely with the International Electrotechnical Commission (IEC) on all matters of electrotechnical standardization.

Draft International Standards adopted by the technical committees are circulated to the member bodies for voting. Publication as an International Standard requires approval by at least 75 % of the member bodies casting a vote.

International Standard ISO 11134 was prepared by Technical Committee ISO/TC 198, *Sterilization of health care products*.

Annexes A, B and C of this International Standard are for information only.

Introduction

The manufacture of a safe and sterile health care product requires attention to product characteristics and to sterilization methods and controls. This International Standard provides the essential elements of good manufacturing practice for moist heat sterilization of health care products.

A sterile product is one that is free of viable microorganisms. Even items produced under controlled manufacturing conditions may, prior to sterilization, have microorganisms on them. Such products are, by definition, non-sterile. The purpose of sterilization processing is to destroy the microbiological contaminants on these non-sterile products.

The destruction of microorganisms by physical and chemical agents follows an exponential law. Accordingly, one can calculate a finite probability of a surviving microorganism regardless of the magnitude of the delivered sterilization dose or treatment.

The probability of survival is a function of the number and types (species) of microorganisms present on the product, the sterilization process lethality, and, in some instances, the environment in which the organisms exist during treatment.

It follows that the sterility of individual items in a population of products sterilized cannot be guaranteed in the absolute sense. The probability of non-sterility of each individual product unit is derived mathematically. For example, with a probability of 10^{-6}, the likelihood of a non-sterile product unit is less than or equal to one in a million.

Requirements for the quality system for the design, development, production, supply, installation and servicing of health care products are given in the ISO 9000 series of Standards.

The ISO 9000 series of Standards designates certain processes used in the manufacture of health care products as "special" in that the result cannot be fully verified by subsequent inspection or testing of the product. Sterilization is an example of a special process because efficacy cannot be verified by inspection or testing of the product. For this reason, sterilization processes must be validated before use, the process routinely monitored and the equipment maintained.

Sterilization of health care products — Requirements for validation and routine control — Industrial moist heat sterilization

1 Scope

This International Standard specifies requirements for the use of moist heat in sterilization process development, validation of the sterilization process and control of routine sterilization.

It covers all moist heat processes, including saturated steam and air-steam mixtures, and applies to all industrial manufacturers and all others who perform contract moist heat sterilization. Although moist heat sterilization in non-industrial health care facilities is not specifically covered in this International Standard, the principles outlined may be useful to the user of moist heat sterilization in these facilities.

NOTE 1 While the general requirements of this International Standard may apply to the sterilization of pharmaceuticals, other technical or regulatory requirements may also apply.

This International Standard does not cover the quality assurance system which is necessary to control all stages of manufacture, including the sterilization process.

2 Normative references

The following standards contain provisions which, through reference in this text, constitute provisions of this International Standard. At the time of publication, the editions indicated were valid. All standards are subject to revision, and parties to agreements based on this International Standard are encouraged to investigate the possibility of applying the most recent editions of the standards indicated below. Members of IEC and ISO maintain registers of currently valid International Standards.

ISO 9001:1987, *Quality systems — Model for quality assurance in design/development, production, installation and servicing.*

ISO 9002:1987, *Quality systems — Model for quality assurance in production and installation.*

ISO 9003:1987, *Quality systems — Model for quality assurance in final inspection and test.*

ISO 11138-1:—[1], *Sterilization of health care products — Biological indicators — Part 1: General.*

IEC 1010-1:1990, *Safety requirements for electrical equipment for measurement, control, and laboratory use — Part 1: General requirements.*

IEC 1010-2-041, *Safety requirements for electrical equipment for measurement, control, and laboratory use — Part 2-041: Particular requirements for autoclaves using steam for the treatment of medical materials and for laboratory purposes.*

3 Definitions

For the purposes of this International Standard, the following definitions apply.

3.1 air-steam mixture: Uniform mixture of air and saturated steam used for sterilization.

NOTE 2 Air is used to compensate for pressures generated within sealed containers that exceed saturated steam pressures.

3.2 bioburden: Population of viable microorganisms on a raw material, component, a finished product and/or a package.

1) To be published.

3.3 certification: Documented review and approval process carried out as a final step in the validation programme to permit product release.

3.4 D value: Exposure time required under a defined set of conditions to cause a 1-logarithm or 90 % reduction in the population of a particular microorganism.

3.5 electromechanical control: Control system that uses mechanical means (e.g. cams or punch cards) to time and initiate the electrical control signals.

3.6 environmental controls: Controls established in the product manufacturing areas to control bioburden.

NOTE 3 These may include air and fluid filters, surface disinfection, personnel uniforms and administrative procedures.

3.7 F value: Measure of the microbiological inactivation capability of a heat sterilization process.

3.8 F_0 value: F value calculated at 121,1 °C (250 °F) with a z value of 10 K and a D value of 1 min.

3.9 materials of construction: Materials used in the sterilization equipment composition.

3.10 microbiological challenge: Biological indicators, biological-indicator test packs, or inoculated product that contain known populations of microorganisms and can be used in testing sterilization cycles.

3.11 moist heat: Heat that is derived from water, either as a liquid or as steam under pressure.

3.12 moist heat sterilization: Process of using moist heat to produce a sterile product.

3.13 primary packaging: Element of the packaging system that maintains the sterility of the product.

3.14 process lethality: Capability of the sterilization process to destroy microorganisms.

NOTE 4 This may be determined by measurements of microbial death or by establishing and measuring the required physical parameters.

3.15 product carrier system: Mechanism used to hold the product and its packaging for sterilization.

NOTE 5 The carrier system should prevent product damage and allow uniform access by the sterilizing agent.

3.16 commissioning: Obtaining and documenting evidence that equipment has been provided and installed in accordance with its specification and that it functions within predetermined limits when operated in accordance with operational instructions.

3.17 recommissioning: Repetition of part or all of the commissioning test requirements for the purpose of reconfirming process reliability.

3.18 revalidation: Repetition of part or all of the validation test requirements for the purpose of reconfirming process reliability.

3.19 saturated steam: Water vapour at a temperature corresponding to the boiling point of the source liquid.

3.20 simulated product load: Load that is used as an alternative to the actual product load and that represents an equal or greater challenge to the process.

3.21 sterile: State of being free from viable microorganisms.

NOTE 6 In practice no such absolute statement regarding the absence of microorganisms can be proven (see sterilization).

3.22 sterilization: Validated process used to render a product free of all forms of viable microorganisms.

NOTE 7 In a sterilization process, the nature of microbiological death is described by an exponential function. Therefore, the presence of microorganisms on any individual item may be expressed in terms of probability. While this probability may be reduced to a very low number, it can never be reduced to zero.

3.23 sterilization cycle: Automatic sequence of operating stages performed in the sterilizer.

3.24 sterilization process development: Studies conducted to develop a reproducible process by which the product may be sterilized to the desired probability of a non-sterile unit without damage.

3.25 validation: Documented procedure for obtaining, recording and interpreting the results required to establish that a process will consistently yield product complying with predetermined specifications.

NOTE 8 Validation covers three activities: commissioning, verification of process specification and performance qualification.

3.26 z value: Number of degrees of temperature required for a 1-logarithm change in the D value.

4 General

4.1 Responsibilities and training of personnel

Responsibility for the installation and maintenance of moist heat sterilizers, for the validation and routine

control of moist heat sterilization, and for the release of sterilized product shall be assigned to qualified personnel as specified in ISO 9001 or ISO 9002.

4.2 Product considerations

The product shall be designed to comply with its specification and requirements for safety and efficacy following exposure to the maximum number of sterilization cycles specified for the product. If any treatment is required prior to sterilization (for example, cleaning) this shall also be validated as part of the resterilization procedure. The product shall be designed and materials shall be selected to be compatible with environmental changes occurring in the sterilization chamber during the sterilization cycle.

4.3 Packaging considerations

4.3.1 General

The packaging shall consist of at least a primary package and a secondary package.

The primary package and, if present at the time of sterilization, the secondary package shall comply with its specification following sterilization.

4.3.2 Packaging permeability

The packaging shall permit the attainment of sterilizing conditions on or within the product either by the removal of air and penetration of steam or, for non-permeable packaging (e.g. for vials containing liquids), by heat transfer.

5 Equipment

5.1 Documentation

5.1.1 Identification

Each sterilization system shall have one or more information plates, permanently fastened and marked, that provide the following information in the language agreed to by the user:

a) name and address of the manufacturer;

b) serial number or other system identification;

c) chamber design pressure and maximum working temperature;

d) jacket pressure rating (if applicable);

e) stamp of inspection authority and vessel identification mark;

f) date of primary construction of the vessel.

5.1.2 Safety

Documentary evidence shall be provided to demonstrate that the sterilization system complies with the safety requirements specified in IEC 1010-1 and IEC 1010-2 and any other standards or regulatory requirements applicable in the country of use.

5.1.3 Manuals and instructions

As a minimum, the following information shall be available for each identified sterilizer in the language agreed to by the user:

a) instructions for the installation of the sterilization system sufficient to ensure safe and effective operation of the equipment;

b) a list of materials of construction exposed to the sterilant or to inadvertent contact with the product;

c) instructions for safe and effective operation, including recommendations for vessel temperature and pressure limits as well as safety precautions;

d) instructions and recommended schedules for routine preventive maintenance;

e) a repair manual including a list of recommended replacement parts;

f) chamber drawings sufficient to define configuration and hardware, pipe-work and control system schematic drawings, recommended installation drawings, and a parts list defining all significant system components;

g) process-control logic and/or software documentation necessary to operate and maintain the equipment control system (see 5.2.6). Any software supplied shall be accompanied by proof of validation of its release and revision level.

5.1.4 Additional information

The specifications for a sterilizer to be used for moist heat sterilization, including its installation and installation tests, shall be documented.

5.2 Sterilizer performance, utilities, components, accessories and controls

5.2.1 Performance

Sterilization systems used to process health care products by moist heat shall be provided in accordance with regulations or standards for sterilization equipment performance applying in the country of use.

5.2.2 Utilities

5.2.2.1 Steam purity and quality shall be specified and demonstrated to be adequate for its intended use.

5.2.2.2 The purity of the compressed air used in the sterilization chamber shall be such that the safety of the product is not impaired.

5.2.2.3 Ambient air admitted to the chamber to relieve the vacuum shall pass through a microbiological-retentive filter for all products with packaging that is permeable by air.

5.2.2.4 Water used in the sterilizer as a means of direct cooling of product shall be specified and verified to meet the requirements established during product development. This shall be documented.

5.2.2.5 Electrical power supplied to the sterilization system shall comply with the manufacturer's specification.

5.2.3 Components

The materials and components used in the construction of the sterilization system shall be selected to minimize the potential for microbiological or chemical contamination.

5.2.4 Accessories

The system designed to support the product in the chamber shall be designed to allow uniform steam penetration and/or heat transfer. The carrier system shall also allow drainage of condensate and/or cooling water, prevent damage to the product and retain the integrity of the load.

5.2.5 Control and recording systems

The following process parameters shall be automatically controlled and recorded:

a) temperature;

b) time;

c) pressure;

d) rate of change of temperature and pressure, if required for product integrity.

The recorder and process control systems shall either be independent or designed in a manner that will cause a warning to occur should the difference between a controlled and recorded variable exceed specified limits.

5.2.6 Control programmes

Programmes used to execute and control the sterilization process, whether microprocessor or electromechanically based, shall be validated. The documented control programme shall be evaluated by procedures designed to demonstrate the correctness of the programme logic in both process simulated conditions and actual sterilizer use. Any subsequent changes shall be similarly documented, be evaluated to assess whether revalidation is required and be approved by the user.

5.3 Performance of instruments

5.3.1 Instrument accuracy

5.3.1.1 Accuracy of instruments used for validation shall exceed the accuracy of the controller and recorder system.

5.3.1.2 Temperature and pressure sensors shall be selected, installed and used in a manner which will ensure that the stated accuracy is maintained.

5.3.2 Calibration standards

The accuracy of standards used to calibrate process measurement instruments shall be specified and calibration shall be traceable to a national reference standard as specified in ISO 9003.

5.3.3 Sterilizer reference instruments

The sterilizer shall be equipped with a separate measuring system to verify that values measured by controlling instruments are within the specified temperature and pressure limits during each cycle.

5.3.4 Calibration programme

An effective procedure shall be established, documented and maintained for the calibration of all controlling, indicating and recording instruments used for validation and routine control of the sterilization cycle. The procedure shall comply with the requirements of ISO 9001, ISO 9002 and, for instruments used for validation, ISO 9003.

5.4 Maintenance

5.4.1 A sterilizer shall be maintained in accordance with a documented planned preventive maintenance scheme.

5.4.2 Person(s) carrying out maintenance shall have documentary evidence to demonstrate successful training in the skills needed to maintain the specified sterilizer(s).

5.4.3 The procedure for each planned maintenance task and the frequency with which it is carried out shall be specified and documented.

5.4.4 A sterilizer shall not be used to process health care products until scheduled and unscheduled maintenance tasks have been satisfactorily completed and recorded accordingly.

5.4.5 Records of maintenance shall be retained in an equipment file.

5.4.6 The maintenance scheme, maintenance procedures and maintenance records shall be reviewed periodically by a designated person.

6 Sterilization process development

6.1 Except where compliance with the product specification would be compromised, sterilization by saturated steam shall be used. Where other methods are to be used (e.g. air-steam mixtures) reproducibility of the environment within the chamber shall be demonstrated.

Air-steam mixtures shall only be used in combination with effective circulation that creates a uniform heating medium throughout the sterilizer. Where air-steam mixtures are used and steam penetration is required, the circulation system shall create a uniform air-steam mixture within the load.

6.2 The sterilization cycle shall be developed to be reproducible during routine processing.

6.3 The attainment of sterilizing conditions in the product processed in newly-developed moist heat sterilization cycles shall be demonstrated.

6.4 Any product handling or storage after sterilization at the site of sterilization shall not compromise the qualities of the product.

6.5 The probability of a non-sterile product unit shall be selected to ensure that the sterile health care product has a sufficiently low probability of a surviving microorganism to be safe for its intended use.

6.6 If indicator microorganisms are used, they shall be selected with reference to the sterilization process and shall meet the requirements of ISO 11138-1.

6.7 Data generated during cycle development shall demonstrate that the required probability of survival of the bioburden has been achieved.

6.8 For sterilization processes based upon bioburden, there shall be a bioburden programme which determines the numbers and resistance of the bioburden prior to sterilization.

7 Sterilization process validation

7.1 The validation programme shall be performed using an approved protocol that conforms to the principles outlined in ISO 9002.

7.2 Each production sterilizer shall be commissioned upon installation. New products and new sterilization equipment or process conditions shall be validated.

7.3 Validation activities shall be assigned to a designated person experienced in this task.

7.4 The process validation shall consist of a commissioning of the systems, a performance qualification, and certification.

7.4.1 The commissioning shall include:

a) demonstration of compliance with design performance specifications;

b) documentation of the equipment (see 5.1.3);

c) demonstration of conformance of the quality and capacity of utilities;

d) calibration of both operating and test instrumentation; and

e) when applicable, demonstration of efficacy of air removal.

7.4.2 The performance qualification shall include:

a) demonstration of process reproducibility (through the use of sufficient cycles);

b) demonstration of uniformity within specified limits throughout the chamber and load (through the use of sufficient cycles and sensors);

c) demonstration of the relationship between control and load parameters;

d) demonstration of the correlation of physical parameters to microbiological lethality by data taken from established literature or from original research;

e) demonstration that both maximum and minimum loading (or specified product mix) are compatible;

f) if simulated product loads are used, demonstration that the simulated product loads are representative of actual products;

g) demonstration that qualification loads that will be re-used have returned to specified conditions before re-use; and

h) demonstration that the product and packaging comply with the specification after sterilization and, where applicable, resterilization.

7.4.3 The number of temperature sensors to be used for performance qualification and performance requalification shall be specified. Documented evidence shall be provided to demonstrate that this number is sufficient to establish that the process conforms to specifications generated during process development.

7.4.4 The calibration of temperature measurement systems used for validation shall be verified before and after each programme of sequential tests.

7.5 At the completion of the validation there shall be a formal review and approval of the recorded data.

7.6 Revalidation shall be done whenever there has been a major repair to the sterilization system that could affect the efficacy of the process. Revalidation shall also be performed at least once every 12 months.

7.7 Procedures for revalidation, review and implementation of changes to the process, sterilization system (hardware and software), product or packaging shall be documented. The procedures shall include the assignment of responsibility for determining the necessity and extent of repeating elements of the original validation studies.

Modifications to equipment or control systems shall be evaluated to confirm that the process conditions delivered to the product load are comparable to those originally qualified.

8 Routine moist heat sterilization

8.1 Steam sterilization process control

8.1.1 The accuracy and reliability of instrumentation used to monitor each production cycle shall be periodically checked for compliance with their specification.

8.1.2 Documented procedures for the routine monitoring of the sterilization cycle shall be provided.

8.1.3 For each cycle, a record shall be retained of the following:

a) date;

b) sterilizer identification;

c) cycle identification;

d) operator identification and signature;

e) cycle start time (real time);

f) chamber pressure throughout the cycle;

g) chamber temperature throughout the cycle;

h) timing of critical process parameters.

8.2 Change control

There shall be documented procedures in place to ensure that no changes take place in equipment, process or materials that could affect the sterilization process. If such changes do occur as a planned event, the new sterilization cycle shall be validated. Process failures that cannot be attributed to lack of adherence to process specifications shall be examined to determine the need for requalification.

8.3 Periodic testing

Sterilizers shall be tested periodically in accordance with a documented plan.

8.4 Microbiological testing

If the efficacy of the process cycle is based on a study or estimate of the bioburden on the product,

a) the method used to determine the bioburden or the estimate of the bioburden shall be validated and documented;

b) means shall be provided to ensure that the limits specified for bioburden are not exceeded; and

c) a continuing programme of product bioburden monitoring shall be carried out at a prescribed frequency and the rationale documented.

8.5 Release of sterilized products

To release the product, the process parameters monitored during routine sterilization shall be within the validated limits. A system to differentiate between processed and unprocessed items shall be used. Only authorized persons shall release products after sterilization.

8.6 Audit of operations

Production and quality control procedures and records shall be reviewed in accordance with ISO 9001 at least annually. Competent personnel not directly involved in these procedures shall ensure that the process specifications established during qualification testing are followed and remain valid.

8.7 Corrective action

Procedures and documentation for corrective action shall comply with ISO 9001. Any deviations from specifications or procedures uncovered during operations, audits, calibrations or maintenance shall be reviewed by a designated person to determine the proper steps and corrective action required.

8.8 Records

Records to demonstrate that the product has been sterilized in accordance with all specifications shall be produced and maintained as specified in ISO 9001.