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

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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 re-sterilization 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.

Annex A
(informative)

Guidance for validation and routine control of industrial moist heat sterilization

NOTE 9 The clauses in this annex provide guidance on the related clause in the body of the Standard.

A.1 Scope

No guidance is offered.

A.2 Normative references

No guidance is offered.

A.3 Definitions

No guidance is offered.

A.4 General

A.4.1 Responsibilities and training of personnel

No guidance is offered.

A.4.2 Product considerations

A.4.2.1 Product design

When moist heat is to be used to sterilize health care products, the product should

a) be able to withstand moisture and the relative high values and rates of changes in temperature and pressure;

b) facilitate the contact between the sterilant and all the surfaces to be sterilized;

c) remain sterile (for those parts intended to be sterile) when properly stored.

These points should be considered when the product is designed. Simple design changes that do not affect product performance could possibly prevent sterilization and validation problems.

Any change in design should not be implemented before the factors mentioned above are considered and, if necessary, validated.

A.4.2.2 Selection of materials

In selecting materials, the ability to withstand the physical stresses inherent in moist heat sterilization is essential. For some materials, it is also essential that the material be readily permeable by air and steam. Procedures should be specified and followed to ensure that the materials used in the production are of equivalent qualities as those used in the validated products. As improving one quality can lead to a negative effect on another quality, any change could require revalidation.

A.4.3 Packaging considerations

The same considerations given to product design (see A.4.2.1) and selection of materials (see A.4.2.2) apply to packaging. Also, to allow proper transportation and handling of the sterile product, the packaging should be designed to accommodate shelf-life requirements. The product and its packaging should withstand the rates of change of temperatures and pressures occurring during the sterilization cycle.

This packaging design should consist of not less than two layers, which may include:

a) **primary packaging** containing the product, or the product itself where only the inside is considered sterile (such as the fluid path of tubing);

NOTES

10 Fittings and closures intended to keep the inside of the product sterile are designed and validated to at least the same standards as the primary packaging materials.

11 The primary packaging may consist of more than one layer to ensure that, after the outer layer has been removed and the product is presented to the user, particulate and biological carryover is at a minimum.

b) **secondary packaging** containing one or more primary packages intended to facilitate proper storage and internal transport by the user;

c) **transport packaging** protecting the product(s) and the primary and secondary packaging during external transport.

For sterile products, the total packaging configuration should perform the functions of a primary package, secondary package and transport package as described above. For sterile fluid path products, the packaging should perform at least the functions of a secondary package and transport package. Also, all packaging configurations should be strong enough to protect the product during intended handling and shipping.

During sterilization, the product will be contained in at least the primary packaging but sterilizing products in the secondary or transport package is not uncommon.

The properties needed for a good packaging design for sterilization are, in general, in contradiction with those needed for optimum protection of the product. A compromise may be made in either the selection of packaging materials or in the level to which the product is packed prior to and during sterilization.

In contract sterilization, the use of temporary second and third packaging layers should be considered during transport prior to sterilization.

A.5 Equipment

A.5.1 Documentation

A.5.1.1 Identification

No guidance is offered.

A.5.1.2 Safety

Written instructions should be available to alert the user of potential hazards associated with equipment use.

The equipment, including the pressure vessel, should comply with IEC 1010-1 and IEC 1010-2 and additionally, where appropriate, to national safety regulations applying in the country of intended use.

Means should be provided to ensure that the system cannot be accidentally operated unless the chamber door(s) is (are) closed, sealed and locked. The sterilizer should be provided with means to prevent the door(s) from being unsealed when the chamber is pressurized. Unless a fault condition is indicated, the sterilizer door(s) should only be able to be unsealed, unlocked and opened at the end of a sterilization cycle. The sterilizer should also be provided with means to return the chamber to atmospheric condition and open the loading door(s) if a breakdown of the automatic cycle occurs.

If a loading, unloading or maintenance operation requires entrance into the chamber, means should be provided to enable the door(s) to be locked open and the key removed and retained by the operator before entry into the chamber, or means should be provided to allow the emergency shutdown from inside the chamber.

A.5.1.3 Manuals and instructions

Information should be supplied to enable the purchaser to prepare for installation, to install and operate the sterilizer system, and to perform routine maintenance.

A.5.1.3.1 The installation instructions should include

a) the overall dimensions and mass of the sterilizer system;

b) the type of electrical supply, voltage, frequency and power;

c) the flow and pressure for steam, water and compressed air supplies;

d) sound power.

A.5.1.3.2 The instructions for safe and effective system operation should include

a) the range of application, type of load, kind of packing;

b) the capacity;

c) a description of the available sterilizing cycles;

d) a description of controls and indicating devices;

e) a description of safety devices;

f) safety instructions;

g) instructions in the event of a malfunction.

A.5.1.3.3 The maintenance/repair instructions should include

a) maintenance procedures;

b) the recommended maintenance interval or timetable;

c) electrical diagrams and circuits;

d) hydraulic plans and circuits;

e) a spare parts list;

f) safety procedures.

A.5.1.3.4 The process-control logic and/or software documentation necessary to operate and maintain the equipment control system (or any other software supplied) should be provided and should be accompanied by proof of validation. This validation may be

performed either by an independent party or by the manufacturer of the software in accordance with the requirements of the appropriate Standards in the ISO 9000 series.

A.5.1.4 Installation

A series of checks and tests should be performed after installation of the sterilizers in the location of intended use. The manufacturer, the supplier and the purchaser should agree upon the assignment of responsibility for performing these checks and tests.

A.5.2 Sterilizer performance, utilities, components, accessories and controls

A.5.2.1 Performance

The performance of the sterilizer should be checked through a test programme that complies with appropriate national regulations or standards.

A.5.2.2 Utilities

A.5.2.2.1 Steam

The sterilizer should be designed to operate with saturated steam or preset air-steam mixtures. Where saturated steam is used, the steam should have a dryness value not less than 0,95 containing not more than 3,5 % (*V/V*) of non-condensable gases and not superheated more than 5 °C. To ensure continued steam quality, the steam, on condensing, should not contain contaminants in a quantity that could impair the sterilization process, harm the sterilizer or compromise the product integrity. The steam pressure fluctuation before the sterilizer pressure reduction valve should not exceed 10 % and the reduction ratio should not be greater than 2 to 1.

A.5.2.2.2 Air

A.5.2.2.2.1 The sterilizer should be designed to operate with a compressed air supply, free of liquid water, filtered to 5 µm and containing not more than 0,5 mg of oil per cubic metre of free air. Compressed air should be passed through a microbiological retentive filter at the point of use. The filter should retain not less than 99,5 % of particles greater than 0,3 µm.

A.5.2.2.2.2 For sterilizers where the operating cycle requires the admission of air directly from the atmosphere into the chamber, the air should be admitted through a filter that retains not less than 99,5 % of particles greater than 0,3 µm.

A.5.2.2.2.3 Sealed products may not require air admitted to the chamber to be microbiologically filtered. Permeable packaging under conditions of vacuum, heat and humidity may, however, allow microbiological penetration which would not occur under normal conditions. Also, normally sealed packaging can breathe if heat-induced expansion of components and/or internal vacuums, caused by cooling of air in the product, occur.

A.5.2.2.3 Water

The feed water for steam production and the water for direct cooling should be free from contaminants in a concentration that could impair the sterilization process, harm the sterilizer or damage the products to be sterilized. See table A.1 for typical limiting values of contaminants. The water for the vacuum system should be of potable quality, supplied at a temperature not exceeding 15 °C, and should be of a hardness value less than or equal to 0,2 mmol/l.

Table A.1 — Typical limiting values of contaminants of steam and/or water in contact with product and/or product packaging

Contaminant	Limiting value
evaporation residue	⩽ 15 mg/l
silicie	⩽ 2 mg/l
iron	⩽ 0,2 mg/l
cadmium	⩽ 0,005 mg/l
lead	⩽ 0,05 mg/l
rest of heavy metals	⩽ 0,1 mg/l
chloride	⩽ 3 mg/l
phosphate	⩽ 0,5 mg/l
conductivity	⩽ 50 µs/cm
pH	6,5 to 8
appearance	colourless, clean, without sediment
hardness	⩽ 0,1 mmol/l

A.5.2.2.4 Electrical power

The sterilizer should be designed to operate when the main voltage is maintained with ± 10 % of the nominal supply voltage. The sterilizer should be designed to operate with an electrical supply provided with means simultaneously to isolate all poles from the mains supply and where each pole is separately fused.

A.5.2.3 Components

The materials used should resist the attack of steam and condensate, should not lead to deterioration of the quality of the steam and should not release any substances known to be toxic in quantities that could create a health hazard.

Pipe joints and fittings should be pressure-tight and vacuum-tight. The pipe-work for steam or water at a temperature greater than 70 °C should be thermally insulated. The cold water pipe-work should be insulated. The design of the piping system should take into account the needs of drainage and sterilization.

Lines should not connect directly to a drain without means to avoid back-syphoning. Heat exchangers should prevent leakage of external media into the air

The performance of the sterilizer should be checked through a test programme that complies with appropriate national regulations or standards.

A.5.2.2 Utilities

A.5.2.2.1 Steam

The sterilizer should be designed to operate with saturated steam or preset air-steam mixtures. Where saturated steam is used, the steam should have a dryness value not less than 0,95 containing not more than 3,5 % (*V/V*) of non-condensable gases and not superheated more than 5 °C. To ensure continued steam quality, the steam, on condensing, should not contain contaminants in a quantity that could impair the sterilization process, harm the sterilizer or compromise the product integrity. The steam pressure fluctuation before the sterilizer pressure reduction valve should not exceed 10 % and the reduction ratio should not be greater than 2 to 1.

A.5.2.2.2 Air

A.5.2.2.2.1 The sterilizer should be designed to operate with a compressed air supply, free of liquid water, filtered to 5 µm and containing not more than 0,5 mg of oil per cubic metre of free air. Compressed air should be passed through a microbiological retentive filter at the point of use. The filter should retain not less than 99,5 % of particles greater than 0,3 µm.

A.5.2.2.2.2 For sterilizers where the operating cycle requires the admission of air directly from the atmosphere into the chamber, the air should be admitted through a filter that retains not less than 99,5 % of particles greater than 0,3 µm.

A.5.2.2.2.3 Sealed products may not require air admitted to the chamber to be microbiologically filtered. Permeable packaging under conditions of vacuum, heat and humidity may, however, allow microbiological and to which standard(s) the validation was performed.

The logic of electromechanical or other means of control should also be validated.

A.5.3 Performance of instruments

A.5.3.1 Instrument accuracy

A.5.3.1.1 The temperature control device should

a) be either digital or analogue;

b) have an accuracy of ± 1 % over the scale range 50 °C to 150 °C;

Table A.1 — Typical limiting values of contaminants of steam and/or water in contact with product and/or product packaging

Contaminant	Limiting value
evaporation residue	⩽ 15 mg/l
silicie	⩽ 2 mg/l
iron	⩽ 0,2 mg/l
cadmium	⩽ 0,005 mg/l
lead	⩽ 0,05 mg/l
rest of heavy metals	⩽ 0,1 mg/l
chloride	⩽ 3 mg/l
phosphate	⩽ 0,5 mg/l
conductivity	⩽ 50 µs/cm
pH	6,5 to 8
appearance	colourless, clean, without sediment
hardness	⩽ 0,1 mmol/l

A.5.2.2.4 Electrical power

The sterilizer should be designed to operate when the main voltage is maintained with ± 10 % of the nominal supply voltage. The sterilizer should be designed to operate with an electrical supply provided with means simultaneously to isolate all poles from the mains supply and where each pole is separately fused.

qualification phase. The measurement system should be recalibrated if the deviation between the two measurements exceeds the specified limit.

A.5.3.4 Calibration programme

A documented calibration programme should be established to ensure that accurate and valid measurements are obtained. The calibration programme should address standards requirements, use written calibration procedures, and specify the accuracy and precision of the instruments.

Instruments should be calibrated in accordance with the manufacturer's instructions and calibration should include a value within 2 K of sterilization temperature.

The organization providing calibration services should be evaluated to determine whether personnel are competent and capable of performing calibration to the degree of accuracy required. Written procedures and adequate documentation of the work performed are required.

A.5.4 Maintenance

A maintenance scheme should be developed from the schedules provided by the sterilizer manufacturer, instrument manufacturer(s) and equipment manufacturer(s), from the generic tasks and tests carried out in the plant and as a result of experience. The maintenance scheme and frequency with which each task is carried out should be based on the recommendations given by the manufacturer and persons with specialized experience. In addition, usage, risk to safety and the need to maximize utilization should be considered.

The procedure for each maintenance task should be based on manufacturer's instructions.

The designated person should sign and date all entries relating to maintenance, both scheduled and unscheduled, stating that all the necessary work and tests have been completed and are satisfactory. Recurring faults should be identified and corrective action taken.

The review of maintenance records should aim to identify

a) emerging defects;

b) changes required in the maintenance scheme;

c) changes to any maintenance procedure;

d) additional training required by maintenance persons;

e) whether records have been completed satisfactorily, signed and dated.

A.6 Sterilization process development

NOTE 12 See also annex B.

A.6.1 Selection of the type of sterilization cycle to be used depends upon the product configuration and the ability of the product and package to withstand temperatures, pressure stresses and total heat input.

A.6.1.1 Moist heat sterilization of health care products can be complex because of the heterogeneity of product types, product packaging and vessel loading configurations that may be encountered. Factors that can influence moist heat sterilization of health care products are listed in table A.2.

Multicomponent products may have matted surfaces where the steam penetration necessary for sterilization might not occur. A dry heat sterilization situation could exist and cycle development using dry heat techniques (e.g. indicator organisms) could be necessary.

A.6.1.2 Cycle development studies may be performed in a research vessel if process equivalency with the product vessel is demonstrated.

Moist heat processes should be developed with the narrowest practical range of temperatures within the sterilization chamber. Prevacuum saturated steam processes are inherently easier to control while, for example, an air-steam or pressurized water cycle can potentially have a greater temperature band. The validation process in terms of the number of repetitive cycles might have to be adjusted based on the process to demonstrate adequately the control desired. Throughout the holding time, the temperature in the chamber

a) should be within a 3 K temperature band with the sterilization temperature as the lower limit;

b) should not fluctuate by more than $\pm$ 1 K;

c) should not differ from one another by more than $\pm$ 2 K.

During moist heat sterilization of a device or component, the item will be subjected to temperature, pressure and perhaps evacuation stresses. If packaged devices are moist heat sterilized, consideration should be given to adequate poststerilization drying of the packaging material in order to maintain sterile barrier properties.

Table A.2 — Factors that may influence or be affected by moist heat sterilization of devices and components

Variables	Factor(s)	Considerations
Packaging	Density per unit volume Hermetic seals Porosity Labelling	Moisture penetration, ability to dry adequately prior to cycle termination, seal strengths, retained moisture or condensation, maintenance of sterility, and retention of product labels during the process
Device or component	Composition Complexity Design	Moisture absorption, thermal degradation, appropriateness of venting for air removal and moisture permeation and subsequent drying, maintenance of sterility potential and loss of function
Sterilizer loading	Sterilizer density, e.g. fully loaded or partially loaded sterilizer	Rate of steam penetration, thoroughness of moisture penetration, and rate of poststerilization drying

A.6.1.3 The moist heat process that is easiest to control and validate is a saturated steam process with mechanical air removal. Such processes involve a single component, single phase process, which is inherently simpler to control. The two variables of greatest concern in these processes are the ability to remove air from dense porous loads and the maintenance of saturated steam conditions. Excessive moisture can result in wet porous loads, packaging damage or spotting.

Producing a saturated steam environment by air venting or gravity displacement of air leads to some uncertainty about achieving a single component (steam) atmosphere. Removal of air from porous materials is a greater concern. The loading pattern in the sterilizer chamber is critical both to ensure air removal from a package and to permit adequate steam flow for the displacement of the air. The latter, for example, requires sufficient vertical channels in the product load. Additional validation or inclusion of a denser pattern of temperature monitors may be required for such cycles.

A.6.1.4 Moist heat sterilization of sealed containers with liquid and gas phase may require external pressures greater than those provided for just heating. If the contained liquid is water (or a solution with similar physical properties), the vapour pressure produced by heating cannot, during the heat-up and exposure phase, exceed the pressure of the heating media. However, additional pressure is produced by heating of the vapour space (e.g. air) and by expansion of the liquid which compresses the vapour. It is typical to add external pressure greater than required to compensate for these heat-up and exposure phases. This compensates for interior pressures caused by the interior temperatures and vapour pressure being greater than the cooling media.

Addition of air to the steam can be used to produce the required overpressure. These systems are, however, very difficult to run and validate. Adequate mixing of the steam and air requires a forced mixing device in the chamber. A load configuration that permits effective circulation between packages is also vital.

A.6.1.5 Pressurized water spray of submerged water processes may be used. These processes avoid the air-steam mixing problems but not the problem of adequate distribution and flow of the heating media, and so are often run with high water flowrates to limit heat transfer to the product and prevent significant top to bottom temperature and heat input deficiencies. The large volumes of water employed also require that water treatment, both microbiological (e.g. for pyrogen control) and chemical, be performed to prevent substantial deposits on packaging.

A.6.2 The rate of microbiological destruction associated with moist heat sterilized devices and components may be influenced by the temperature of the steam, the chamber pressure during sterilization, the permeability of the packaging material to steam and air, the accessibility of the device's or the component's fluid pathway to steam and air, or by the physiological state of the bioburden associated with the product.

A.6.2.1 Mathematical techniques and graphing methods have been developed whereby the process lethality (often expressed as F-Physical) can be calculated from product temperature data. The calculation of an F value derived from physical process parameters is explained in publications by the National Canners Association[2], the Parenteral Drug Association[3], and I.J. Pflug[4]. Definitions of F value, F_0 value, D value and z value are given in clause 3. Both the D value and the z value are needed to select the F value.

The larger the D value, the more resistant the microorganism is to thermal destruction. The value may be derived by plotting the logarithm of the number of

microbiological survivors against sterilization exposure time; the time corresponding to a 1-logarithm reduction in numbers may then be directly measured.

Use of F_0 to express cycle lethality assumes a reference temperature of 121,1 °C and a z value of 10 K. Product temperature data accumulated during the entire process (heating, exposure, cooling) are converted to the equivalent lethality at 121,1 °C and mathematically or graphically integrated to derive a physical lethality value expressed as the equivalent minutes of exposure at 121,1 °C. For example, each minute at 114 °C has a lethal rate equivalent to 0,2 min at 121,1 °C, if z = 10 K. Some software programmes can calculate the process F value continuously during the sterilization cycle using input from one or more temperature sensors in the product. Specific techniques are described in references to this practice and in other literature.

Preliminary studies should be conducted to select the locations for monitoring temperatures to calculate F-Physical, so the F values used in cycle development represent the best challenge to the system. These should include temperature distribution studies in the loaded sterilizer to find slow-to-heat regions within the chamber sterilizing zone, to determine whether they are reproducible, and to find the lowest-temperature regions within the sterilizing zone during exposure. These studies should demonstrate that the temperature sensor is in the product low-temperature zone, or a documented technical rationale should be given for the selected location of the temperature sensor. If the size of the package or container, or the volume of fill is small, consideration should be given to the possible effects of heat conduction along the probe and into the product, and to the need to insert the probe to the proper depth in order to minimize steam conduction errors. Small-gauge sensor wire can be used to minimize this heating effect.

Accurate estimation of a process F-Physical value requires that the temperature measurement system be properly calibrated. Correction factors need to be applied to individual readings before calculating cycle lethality. The validity of the F-Physical value is based on the assumption that the resistant species in the product bioburden have a z value of approximately 10 K. Validation depends upon first-order death kinetics and the presence of a saturated steam environment.

The relationship between the F-Physical and the F value of organisms in the product/sterilization environment (D and z values) should be determined.

Lethality using physical process data should be determined in conjunction with appropriate microbiological studies.

A.6.2.2 Temperature data are collected during replicate runs performed at the parameter set points known to result in the lowest process lethality (e.g. at minimum time and temperature). Other variables that may affect the calculated process lethality derived during these studies include, but are not limited to, initial product temperature, chamber/jacket temperature, duration of heat-up and cool-down periods, and load configuration.

A.6.3 Many similarities exist among devices and packages to be sterilized. For example, the only difference among several devices could be a slight modification in the length of tubing, or the presence of some accessory that has no effect on the product's suitability for sterilization. In addition, many product packages can be composed of the same material with only slight modifications in size. The general approach is to classify products and packages by their similarities and then to evaluate what conditions within a given classification provide the greatest challenge. Families of products and packages may be used in the development of product sterilization cycles and the selection of microbiological challenges, in the certification or validation of sterilizers, and in the development of other quality assurance or product tests. Documentation of studies or sound rationales should justify placement of the most difficult-to-sterilize product and package in its family category. Different methods may be applied to validation of the sterilization process for packaged surgical products and devices, components, commodities, solutions, other products, containers and closures. Therefore, different sterilization specifications may be required to moist heat sterilize these varied products.

Two approaches can be used in the development and use of effective steam sterilization cycles: the overkill method and the bioburden method.

A.6.3.1 "Overkill" methods traditionally have been used to establish industrial steam sterilization cycles. This approach is based on the premise that the sterilization process will inactivate a high microbiological challenge, which is not necessarily related to the pre-sterilization bioburden. This method is called "overkill" because the cycle conditions established to kill the microbiological challenge, with an additional safety factor, should be much more severe than those required to inactivate the product bioburden.

It should be realized that the D value of microbiological challenge and product bioburden microorganisms can vary in different environments, such as solutions, and at different sites, such as closures. Thus, the initial count or challenge concentration is selected on the basis of the resistance of the spore population under the conditions of use.

When using the overkill method, the potential thermal degradation of the product and its package or container should be considered. Increased chemical degradation, increased particulate formation and lim-

ited product shelf-life may result from excessive thermal exposure.

The manufacturer should obtain data for the typical bioburden loading associated with the product. These data need not be as extensive or obtained as frequently as when using bioburden cycle development methods.

A.6.3.2 The bioburden method involves two distinctive approaches. One methodology is described as the absolute bioburden method; the other is referred to as the combined biological indicator/bioburden method.

The absolute bioburden method involves screening of the product for thermally resistant microorganisms; for example, by using a bioburden isolate (recovered for purposes of challenging product sterilization) that is representative of the most resistant bioburden population. The isolate may be propagated, inoculated on or into the product, and used in product sterilization challenge studies to demonstrate directly the desired probability of survival for the product bioburden. Typical bioburden counts used in the calculation are based on the mean bioburden count plus three times the standard deviation.

In the combined biological indicator/bioburden method, the microbiological sterilization challenge of the product may necessitate inactivation of the initial inoculum concentration to an established logarithmic level. The relative resistance and population of the initial challenge inoculum of the microbiological challenge microorganism should be compared with the mean number and thermal resistance of the bioburden typically associated with the product. The comparison should demonstrate that inactivation of a predetermined level of microbiological challenge ensures that the desired probability of a bioburden survivor is achieved. This method is considered to be based on bioburden; therefore, the bioburden should be enumerated and the resistance determined as in the absolute bioburden method.

A.6.4 Sterilized products should not be stored in areas subject to large humidity, pressure and temperature changes.

A.6.5 Moist heat sterilization is a probability function dependent on thermal energy, time, moisture content, the number of microorganisms associated with the product (bioburden) and the thermal resistance of those microorganisms.

A.6.6 Strains of microorganisms that demonstrate high moist heat resistance with respect to bioburden are *Clostridium sporogenes, Bacillus coagulans, B. subtilis,* and *B. stearothermophilus.*

Factors such as entrapment of microorganisms in the product, product contact with contaminated liquids during manufacturing, and/or use of materials that could support microbiological growth should be considered.

Recovery of heat-treated spores can also vary with time between treatment and culturing and with culturing conditions. Therefore, such conditions should be carefully controlled and documented.

The overkill method is based on the concept that the sterilization process will inactivate the microbiological challenge with an additional safety factor. The microbiological challenge will consist of selected numbers (e.g. between 10^3 and 10^6) of moist-heat-resistant spores. The challenge population is not necessarily related to the bioburden. If dry heat conditions (a relative humidity of less than 100 %) exist in the product, an organism such as *B. subtilis* 5230 or *B. subtilis* subsp. *niger* (ATCC 9372) should also be used. The cycle conditions established to kill the microbiological challenge by the overkill method are more severe than those required to kill the bioburden.

The microenvironment within many systems may not be a true moist heat environment as encountered within a solution. Resulting microbiological inactivation rates may lag behind. In certain cases, the attainment of an overkill of 12 D inactivation of microbiological challenge will result in excessive thermal exposure.

The microbiological challenge resistance may be evaluated at fractional exposure times to determine the degree of lethality as a function of proposed process parameters. The degree of lethality may be measured either by recovering and counting surviving microorganisms to develop a death rate curve or by performing an endpoint analysis when sterility test methods are used. In the latter case, exposure times are selected so that the shortest exposure results in growth of all test samples, the longest exposure results in no growth and the intermediate exposures result in growth of some of the samples.

A.6.7 Biological indicators have been widely used to evaluate the lethality of the various combinations of process parameters, products and packaging. A microbiological challenge system of known resistance directly measures the achieved lethality at certain product sites as a result of the variable employed.

The indicator mircroorganisms used for production are generally more resistant to sterilization than typical bioburden. However, as part of cycle development, studies should be conducted to demonstrate this resistance. Procedures that can be applied include isolation, propagation and resistance evaluation of recovered bioburden organisms or exposure of product with typical bioburden to short cycles together with product sterility testing.

The number and resistance of isolates can be used to calculate the lethality of the sterilization process relative to the bioburden. However, the propagation of bioburden organisms can change their resistance.

If short exposure cycles are used, they should be selected to allow extrapolation of the results.

A.6.8 The absolute bioburden method necessitates an actual product count and a resistance screening programme. Sufficient bioburden data should be obtained to establish a historical record. The frequency of bioburden screening depends on the quality and variability of the historical data, the kind of products being sterilized, the manufacturing process and the type of sterilization process. If a change in the manufacturing environment occurs, additional bioburden monitoring should be considered.

Bioburden resistance may be determined by exposing product samples containing the bioburden to fractional exposure time increments at proposed cycle conditions and then conducting sterility tests to determine the number of survivors or fractional positives present at various durations of exposure (Halvorson and Ziegler[1], Pflug and Holcomb[5]). As an alternative, the resistance of bioburden organisms may be determined by isolation and propagation, followed by inoculation onto the product or an appropriate carrier; however, propagation can change the resistance of the bioburden. The resistance of other microbiological challenge systems that could be used for routine biological monitoring should also be determined.

A cycle based on bioburden requires frequent bioburden screening to determine bioburden counts and species associated with the products. Representative products from each manufacturing facility should be sampled during routine production. A bioburden monitoring programme should be designed to evaluate any changes in product components and manufacturing, in the environment, or in production processes that could significantly affect bioburden.

A.7 Sterilization process validation

Validation of moist heat sterilization processes is, in fact, validation of the sterilizer, the product and the loading concepts. Validation activity involves

a) checking the performance of the sterilizer against its designed sterilization specifications;

b) establishing the actual effectiveness and reproducibility of the cycle in relation to the product and the loading concepts;

c) assessing possible changes in the product that could have occurred during sterilization.

If any change, even one regarded as an improvement, is made to the product, packaging, loading configuration, sterilization cycle or sterilizer, validation results obtained under prior conditions should be considered void until the impact of the change has been evaluated.

The work associated with validation may be extensive because of the high number of measuring points and the repetition needed to demonstrate process reproducibility. By setting stricter tolerances for physical parameters (thus ensuring uniformity within the chamber and the load), the work may be reduced. Process lethality data generated in another sterilizer (e.g. research vessel) using the same sterilization method and cycle should be related to the production vessel being validated.

A dependable and lasting validation requires that changes only be made after thorough evaluation of the consequences. If any factor involved is not accurately documented, changes may occur over time that might not be noted and the need to revalidate might not be considered.

The designated person referred to in 7.3 should be required to demonstrate competence in the field of validation and sterilization.

A.8 Routine moist heat sterilization

A.8.1 Steam sterilization process control

Upon completion of development studies and the validation programme, the manufacturer should specify the sterilization facilities, equipment and procedures required to ensure product sterility and efficacy.

Persons responsible for sterilization should ensure that, before a sterilizer is used for production, evidence exists to show that all maintenance and instrument calibration have been successfully completed and that the performance qualification report(s) include the type(s) of load(s) to be sterilized.

Plans for routine monitoring should include the tests and checks (and the frequency with which these test and checks should be performed) required to ensure that the parameters of the sterilization cycle are within limits equivalent to or correlated to those determined during performance qualification.

Under certain circumstances, it is advisable to employ special additional process monitoring techniques, such as the direct measurement of product temperature, to supplement routine monitoring.

A.8.2 Change control

A change control system should be employed that establishes when operational or performance qualification testing should be repeated. Requalification is recommended if significant changes are made in the sterilization system (hardware or software), process, product or packaging that could affect sterilization efficacy. The following are examples (not necessarily all-inclusive) of changes that could necessitate performance requalification unless data are available to establish equivalency:

a) **product tolerances** – significant change in the product material or design tolerances that could affect the heating rate of the product;

b) **product venting** – significant change in the sterile barrier venting (e.g. from a vented to a nonvented closure or from one type of filter or filter porosity to another);

c) **product design** – significant change in product design including product materials composition or thickness (where heat penetration is required) that could affect the efficacy of the sterilization process;

d) **packaging** – changes that could affect microbiological barrier efficacy, substantive changes in packaging design (e.g. from a rigid container to a flexible pouch), or changes in vendors that could significantly affect physical properties and heat transfer;

e) **equipment** – changes that could affect ability to maintain specified operating parameters or that could substantially change the rate of heat transfer or steam penetration into the product;

f) **process** – alterations in the process that could substantially change the manner in which process parameters are achieved and controlled (e.g. changes in process control software);

g) **product loading or density** – changes in the previously validated loading configurations that could affect heat and moisture transfer into the load;

h) **heating medium** – changes in the ratio of steam to air, where applicable in air-steam processes.

A.8.3 Periodic testing

To guard against unreported or inadvertent changes, consideration should be given to periodic repetition of all or parts of the operational and performance qualification. The interval between periodic requalifications should be determined by the sterilization process characteristics and by the amount of process data routinely documented. The interval may be varied based on existing historical data that demonstrate process reproducibility and conformance with established parameter specifications.

A.8.4 Microbiological testing

Consideration should be given to previously identified factors, such as seasonal and manufacturing influences, that may result in fluctuations in the types, magnitude and process resistance of microorganisms. When moist heat cycle selection is based on overkill, the data need not be as extensive and need not be obtained as frequently.

If cycles are based on bioburden, the selection and use of biological indicators for routine monitoring should be consistent with the microbiological testing previously conducted during cycle development and validation studies. The species of microorganism selected for routine monitoring should be the same as, or have moist heat resistance correlated to, the species used previously. This will allow correlation of microbiological inactivation between the routine process cycle and the data used to establish and verify the cycle. The number of indicators used in routine monitoring will ordinarily be fewer than required for performance qualification.

A.8.5 Release of sterilized products

Product release should be based on evaluation of all available data including acceptable cycle data for critical process parameters. In addition for terminally sterilized products, finished product testing or biological indicator testing might be required by some regulatory authorities.

Colour change: Chemical indicators may be used to differentiate between processed and unprocessed items. However, a system of physical separation or an administrative label process may also be used.

A.8.6 Audit of operations

No guidance is offered.

A.8.7 Corrective action

No guidance is offered.

A.8.8 Records

Records of preventive maintenance and instrument calibrations should be detailed enough to facilitate change control, thus ensuring that operating parameters are maintained within prescribed, validated limits.

Annex B
(informative)

Sterilization cycles

NOTE 13 This annex describes cycles typically used in the moist heat sterilization process. Figures are conceptual and give examples only.

B.1 Saturated steam — vented systems

B.1.1 General cycle description

This sterilization process is used for products than can tolerate process temperature at saturated steam pressure. It is primarily intended for surface contact sterilization, as air removal from fabrics and cavities is uncertain. An example of a chamber temperature and pressure profile for a vented, saturated steam cycle is given in figure B.1.

The process consists of three major phases.

a) **Heating phase.** With the vent open, saturated steam is admitted or generated in the chamber until the desired conditions are met — normally determined by the measurement of temperature. The vent then closes and saturated steam continues to be admitted or generated in the chamber until the exposure temperature and corresponding saturated steam pressure are attained.

b) **Exposure phase.** The sterilizing temperature is maintained in the chamber by saturated steam for the prescribed exposure time.

c) **Cooling phase.** This phase can differ for various types of product. Supply air to vent the chamber to atmosphere or, when solutions in sealed containers are cooled to admit filtered compressed air into the chamber, to prevent rapid depressurization. This phase is completed when the pressure in the chamber is at atmosphere and also, in the case of sealed containers, when a safe temperature is reached.

B.2 Saturated steam — forced air removal

B.2.1 General cycle description

This process is intended to sterilize products consisting of porous materials, and/or items having cavities where air is difficult to remove. An example of a chamber temperature and pressure profile is given in figure B.2.

a) **Air removal phase.** Air is removed from the chamber and load by either a deep vacuum, a number of vacuum pulses, or a combination of vacuum or steam pulses.

b) **Charge phase.** Saturated steam enters the chamber until the sterilization temperature and pressure are attained.

c) **Exposure phase.** The sterilizing temperature and pressure are maintained in the chamber by saturated steam for the specified exposure time.

d) **Exhaust phase.** Steam is exhausted from the chamber, and a vacuum is drawn to a predetermined level.

e) **Drying phase.** For products that are required to be dry, the temperature in the jacket and the vacuum in the chamber are maintained for a predetermined period.

f) **Vacuum relief phase.** Air is admitted to the chamber through a microbiologically-retentive filter until atmospheric pressure is reached.

B.3 Air pressurization system

Some products cannot withstand the vapour pressure related to the intended sterilization temperature and for this reason, a number of processes are available where compressed air that has been passed through a microbiologically-retentive filter is used to ensure that, for part or for the duration of the sterilization cycle, the pressure on the outside of the product equals or exceeds the inside pressure.

B.3.1 Air-steam mixtures

a) **Heating phase.** The first part of this stage is the same as for the vented system except that, where the product integrity can be affected by rising steam pressure, venting is precluded.

Steam continues to enter the chamber until the prescribed sterilizing temperature is attained. When products require overpressure during this phase and where the partial pressure caused by the entrapped air is insufficient, compressed air is

introduced. Circulation is normally required to maintain a uniform environment.

b) **Exposure phase.** The sterilizing temperature is maintained in the chamber by saturated steam and, where overpressure is required, compressed air will also be used.

c) **Cooling phase.** Product cooling can be accomplished with cooled, compressed air or with water spray. To maintain product integrity, rapid depressurization is prevented by maintaining the required chamber pressure with compressed air. The pressure is maintained until the product has been sufficiently cooled, then it is vented to atmosphere.

An example of chamber temperature and pressure profiles is given in figure B.3.

B.3.2 Water spray

a) **Fill phase.** At the beginning of the cycle, a quantity of water is introduced into the sterilizer system or produced as condensate from the steam. It is then sprayed over the product.

b) **Heating phase.** Heating to the required sterilizing temperature is achieved either by introducing air and steam into the circulating system or by heating the water through a heat exchanger and introducing compressed air into the chamber.

c) **Exposure phase.** The circulating system is operated and the water is maintained at the required sterilizing temperature for the desired time.

d) **Cooling phase.** The pressure in the chamber is maintained by compressed air and the product is cooled by reducing the temperature of the circulating water at a controlled rate. The chamber is depressurized when the product has been reduced to a safe temperature.

An example of chamber temperature and pressure profiles is shown in figure B.4.

B.3.3 Water immersion

This process is similar to the water spray system except that the product is totally immersed in water. This process is used to maintain product shape.

An example of chamber temperature and pressure is given in figure B.5.

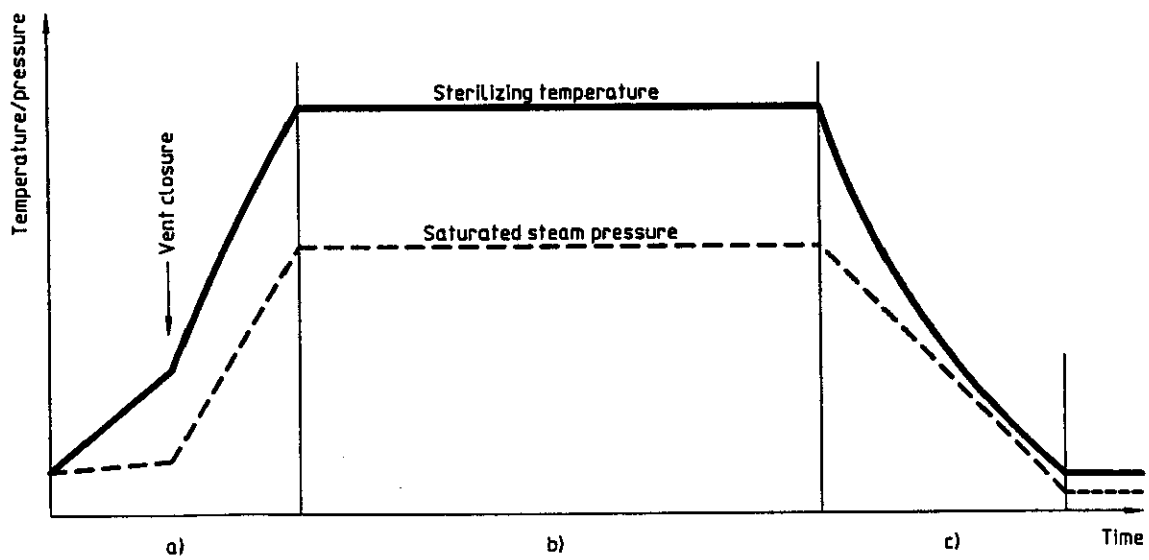

Figure B.1 — Example of saturated steam — vented cycle

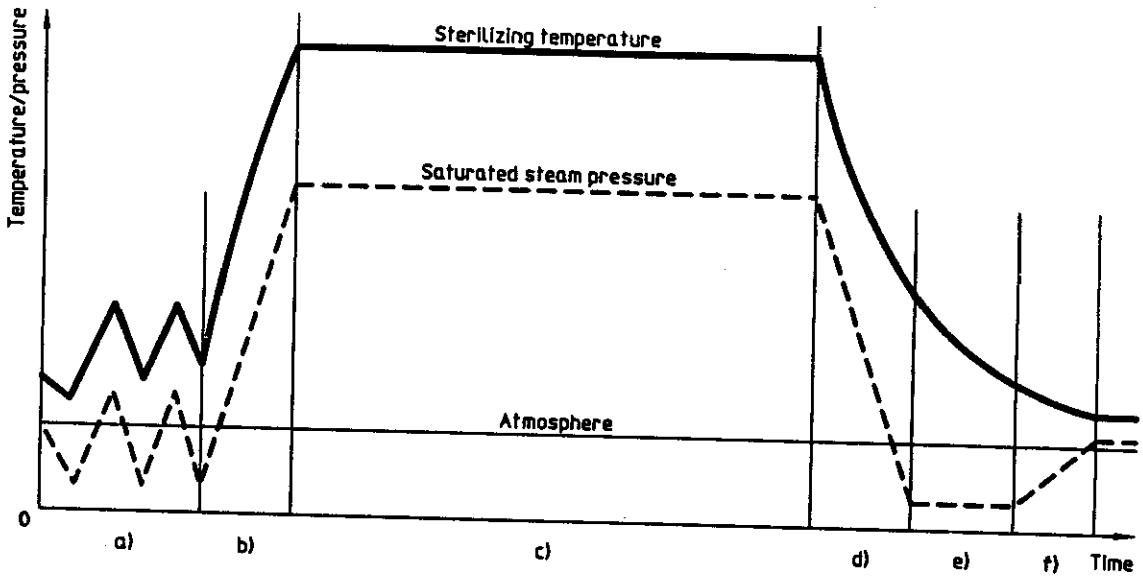

Figure B.2 — Example of saturated steam with forced air removal cycle

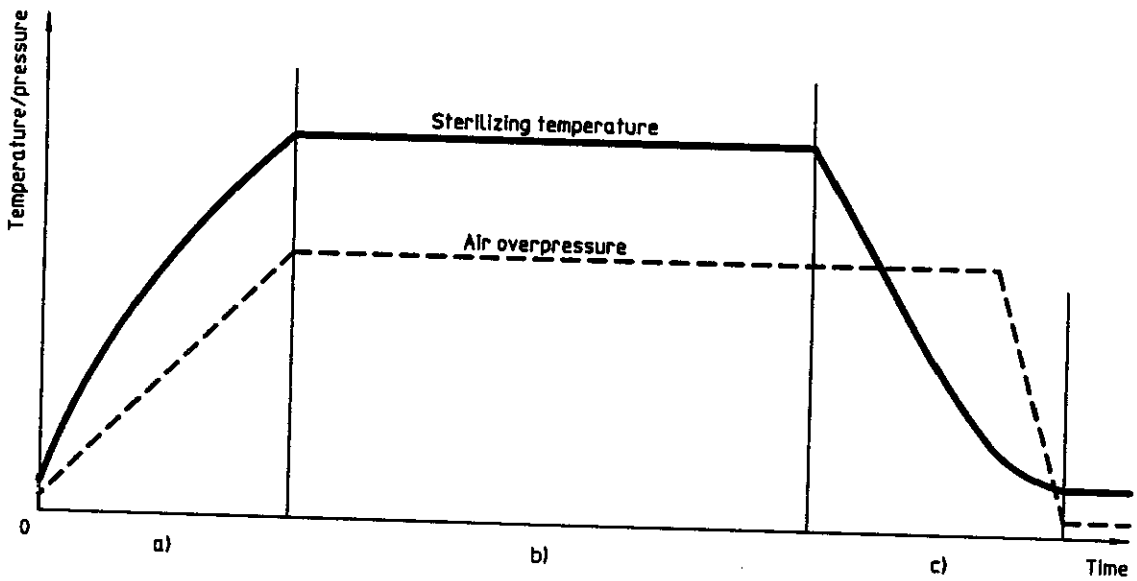

Figure B.3 — Example of air-steam mixture cycle

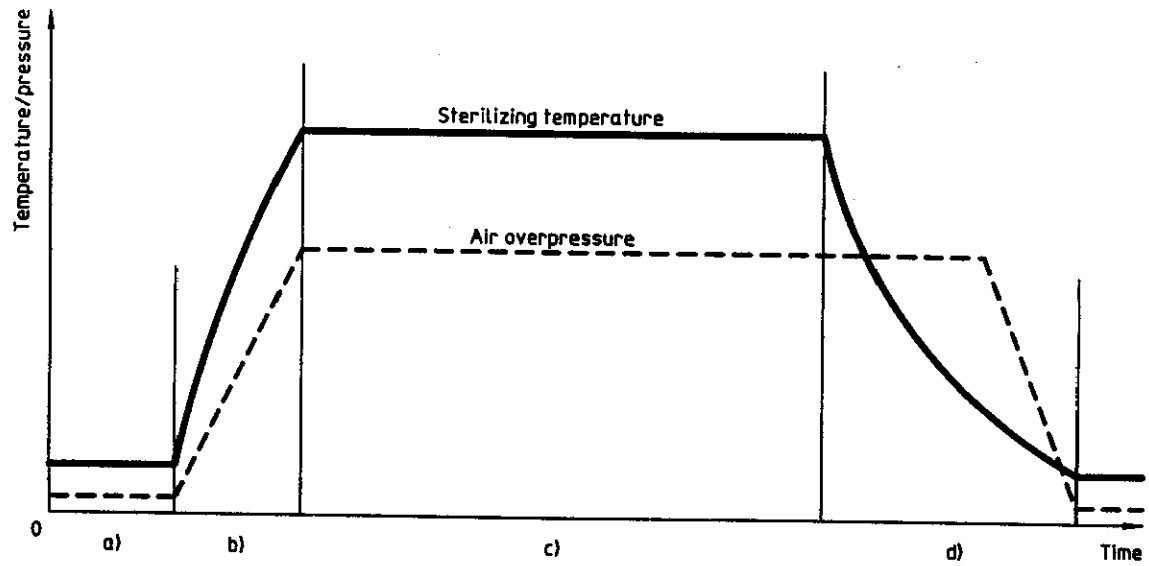

Figure B.4 — Example of water spray cycle

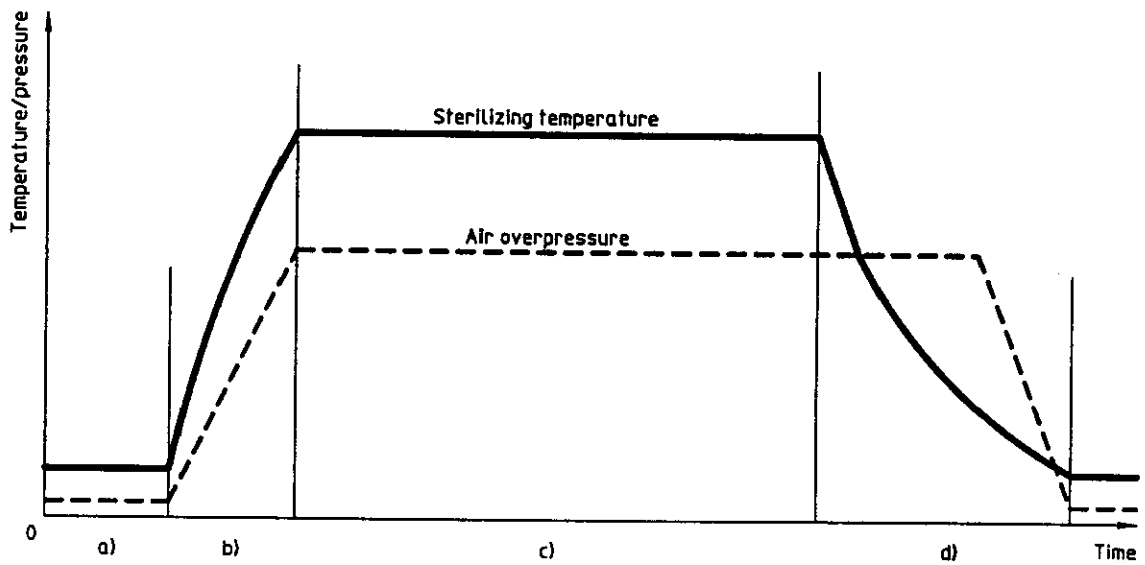

Figure B.5 — Example of water immersion cycle

Annex C
(informative)

Bibliography

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