INTERNATIONAL STANDARD

ISO 13408-5

First edition
2006-11-15

Aseptic processing of health care products —

Part 5: Sterilization in place

Traitement aseptique des produits de santé —

Partie 5: Stérilisation sur place

Reference number
ISO 13408-5:2006(E)

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Published in Switzerland

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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.

International Standards are drafted in accordance with the rules given in the ISO/IEC Directives, Part 2.

The main task of technical committees is to prepare International Standards. 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.

Attention is drawn to the possibility that some of the elements of this document may be the subject of patent rights. ISO shall not be held responsible for identifying any or all such patent rights.

ISO 13408-5 was prepared by Technical Committee ISO/TC 198, *Sterilization of health care products*.

ISO 13408 consists of the following parts, under the general title *Aseptic processing of health care products*:

- *Part 1: General requirements*
- *Part 2: Filtration*
- *Part 3: Lyophilization*
- *Part 4: Clean-in-place technologies*
- *Part 5: Sterilization in place*
- *Part 6: Isolator systems*

Introduction

During the process of preparing ISO 13408-1, several items, e.g. filtration, freeze drying and sterilization in place, were found to be in need of supplementary information which was too voluminous to be given in corresponding annexes.

This part of ISO 13408 includes requirements and guidance that are to be observed during sterilization in place. The purpose of this part of ISO 13408 is to achieve standardization in the field of validation and routine control of sterilization in place processes used in the manufacture of health care products.

Sterilization in place is, in most instances, preceded by cleaning in place which is described in ISO 13408-4. While methods of cleaning in place and sterilization in place differ considerably in technology, the concept of *in situ* treatment is similar.

The most important issue to consider in establishing sterilization-in-place technology is the design of the system(s) to ensure that they be able to successfully sterilize manufacturing equipment to the desired level of sterility assurance.

Aseptic processing of health care products —

Part 5:
Sterilization in place

1 Scope

1.1 This part of ISO 13408 specifies the general requirements for sterilization in place (SIP) applied to product contact surfaces of the equipment used in the manufacture of sterile health care products by aseptic processing and offers guidance on qualification, validation, operation and control.

NOTE SIP can be achieved by using steam or other gaseous or liquid sterilizing agents. Specific guidance on steam sterilization in place, which is the most common method used, is given in Annex A.

1.2 This part of ISO 13408 applies to processes where sterilizing agents are delivered to the internal surfaces of equipment that can come in contact with the product.

1.3 This part of ISO 13408 does not apply to processes where equipment is dismantled and delivered to a sterilizer.

1.4 This part of ISO 13408 does not supersede or replace national regulatory requirements, such as Good Manufacturing Practices (GMPs) and/or compendial requirements that pertain in particular national or regional jurisdictions.

1.5 This part of ISO 13408 does not specify requirements for development, validation and routine control of a process for inactivating the causative agents of spongiform encephalopathies, such as scrapie, bovine spongiform encephalopathy and Creutzfeldt-Jakob disease. Specific recommendations have been produced in particular countries for the processing of materials potentially contaminated with these agents.

NOTE See also ISO 22442-1, ISO 22442-2 and ISO 22442-3.

2 Normative references

The following referenced documents are indispensable for the application of this document. For dated references, only the edition cited applies. For undated references, the latest edition of the referenced document (including any amendments) applies.

ISO 11138 (all parts), *Sterilization of health care products — Biological indicators*

ISO 11140 (all parts), *Sterilization of health care products — Chemical indicators*

ISO 13408-1, *Aseptic processing of health care products — Part 1: General requirements*

ISO 13408-4, *Aseptic processing of health care products — Part 4: Clean-in-place technologies*

ISO 14161, *Sterilization of health care products — Biological indicators — Guidance for the selection, use and interpretation of results*

ISO 14937, *Sterilization of health care products — General requirements for characterization of a sterilizing agent and the development, validation and routine control of a sterilization process for medical devices*

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

ISO/IEC 90003, *Software engineering — Guidelines for the application of ISO 9001:2000 to computer software*

3 Terms and definitions

For the purposes of this document, the terms and definitions given in ISO 13408-1 and the following apply.

3.1
dead leg
location which, by design, does not permit adequate accessibility of the sterilizing agent

3.2
design qualification
verification that the proposed specification for the facility, equipment or system is suitable for the intended use

[ISO/TS 11139:2006, definition 2.12]

3.3
material safety data sheet
MSDS
document specifying the properties of a substance, its potential hazardous effects for humans and the environment, and the precautions necessary to handle and dispose of the substance safely

[ISO/TS 11139:2006, definition 2.23]

3.4
process parameter
specified value for a process variable

NOTE The specification for a sterilization process includes the process parameters and their tolerances.

[ISO/TS 11139:2006, definition 2.34]

3.5
process variable
condition within a sterilization process, changes in which alter microbicidal effectiveness

EXAMPLE Time, temperature, pressure, concentration, humidity, wavelength.

[ISO/TS 11139:2006, definition 2.35]

3.6
sterilization in place
SIP
method of sterilization of the internal surfaces of parts of the equipment or an entire process system *in situ*, without disassembly, using appropriate sterilizing agents

NOTE The term “Steam in place” is used in ISO 13408-1, Clause 19, and this term is sometimes abbreviated as SIP. However, in this part of ISO 13408, “SIP” is used with a wider meaning and includes not only steam in place, but all kinds of sterilization used for the sterilization “in place” or “in situ”. In this part of ISO 13408, “Steam sterilization in place” is referred to as “Steam SIP”.

3.7
sterility assurance level
SAL
probability of a single viable microorganism occurring on an item after sterilization

NOTE 1 The term SAL takes a quantitative value, generally 10^{-6}or 10^{-3}. When applying this quantitative value to assurance of sterility, an SAL of 10^{-6} provides a greater assurance of sterility than an SAL of 10^{-3}.

[ISO/TS 11139:2006, definition 2.46]

NOTE 2 For the purposes of this part of ISO 13408, the product is considered to be product contact surfaces subject to SIP.

3.8
sterilization process
series of actions or operations needed to achieve the specified requirements for sterility

[ISO/TS 11139:2006, definition 2.49]

3.9
sterilizing agent
physical or chemical entity, or combination of entities, having sufficient microbicidal activity to achieve sterility under defined conditions

[ISO/TS 11139:2006, definition 2.50]

4 Quality system elements

4.1 General

4.1.1 The requirements of ISO 13408-1 shall apply.

4.1.2 Documented procedures for each phase of the development, validation, routine monitoring and control of the SIP process shall be prepared and implemented.

4.1.3 Documents required by this part of ISO 13408 shall be reviewed and approved by designated personnel.

4.1.4 Records of development, validation, routine control and monitoring shall be maintained to provide evidence of conformity to the requirements of this part of ISO 13408.

4.2 Management responsibility

4.2.1 The responsibilities and authority for implementing and performing the procedures described in this part of ISO 13408 shall be specified.

4.2.2 If the requirements of this part of ISO 13408 are undertaken by organizations with separate quality management systems, the responsibilities and authority of each party shall be specified.

4.3 Design control

Characterization of the sterilizing agent, sterilization process, equipment to deliver SIP and equipment to be subject to SIP shall be undertaken in accordance with a documented plan. At defined stages, design reviews shall be planned, conducted and documented.

4.4 Measuring instruments and measuring systems

4.4.1 A documented system shall be specified for the calibration of all measuring instruments or measuring systems.

4.4.2 The accuracy and tolerance of the measuring instrument shall be adequate to the process to be measured.

5 Process and equipment characterization

5.1 General concepts

5.1.1 Specifications for the SIP process shall include, but not be limited to:

a) compatibility of the equipment with the sterilizing agent(s) and processing conditions;

b) pre-requisite cleaning procedure, where necessary;

c) introduction, homogeneity, distribution and contact time with the sterilizing agent;

d) physical and/or chemical characteristics of sterilizing agent(s);

e) demonstration of the efficacy of the process;

f) sterilizing agent residuals or degradation products;

g) drying of product contact surfaces, where necessary;

h) maintenance of sterility after the completion of the process;

i) acceptable tolerances for any potential residues from the process in the product to be made in the equipment;

j) physical integrity testing and establishing limits.

5.1.2 Process parameters and their tolerances shall be specified, documented and reviewed.

5.1.3 During production processes, the sterilizing conditions achieved shall be monitored, maintained within specified tolerances, and documented throughout the duration of the sterilization process.

5.1.4 Although the entire processing system can be sterilized as a single entity in SIP, it can be advantageous to divide the system into several parts in order to simplify the sterilization procedures. When a large system is sterilized by dividing it into several segments, the segments should overlap to ensure that all portions of the system are adequately and effectively sterilized.

5.1.5 Complex sequences of opening and shutting of valves in the pipes of a system could be required. Where this is controlled manually, detailed documentation of individual steps is required. Where automation is used, electronic automation systems should be carefully designed and validated.

5.2 Effectiveness of sterilization in place (SIP)

The sterility assurance level of the process shall be established and documented. Justification of the process parameters shall be included in the documentation.

5.3 Equipment

5.3.1 Equipment to be subjected to SIP

5.3.1.1 The equipment shall be designed and manufactured to facilitate SIP and to ensure that the sterilizing agent(s) can enter all internal product contact parts of the equipment to be sterilized (such as filter housings, pipe branches, and valves).

Design considerations shall include, but not be limited to:

a) smoothness of inner surface of equipment;

b) accessibility of the sterilizing agent to all relevant surfaces;

c) correct placement of ports to admit the sterilizing agent(s) and, where applicable, to allow bleeding to facilitate sterilizing agent distribution;

d) absence of dead legs in piping systems;

e) drainability of the system (e.g. slope of piping to ensure the complete removal of remaining liquid in the system);

f) correct placement of ports to permit inclusion of process monitoring devices;

g) where applicable, exhaust port for safe removal of gaseous sterilizing agent;

h) where applicable, resistance of the equipment to pressure, vacuum and heat;

i) compatibility of materials of construction (e.g. pipes, tanks, valves, nozzles, filters, gaskets, sensors) with the sterilizing agent, over the anticipated number of sterilization cycles;

j) provisions for maintenance of sterility during and after completion of SIP (e.g. by elevated pressure).

Materials made of resin, such as gaskets, require particular attention.

Inner corners or shoulders of the tank and/or vessel of the system should be designed so that they do not entrap air and thereby cause incomplete sterilization in the resulting air pocket.

Valves, connections and other equipment (such as heat exchangers) should be designed and oriented to reduce the inaccessible surfaces and entrapment of air.

5.3.1.2 Specification of the equipment shall include, but not be limited to:

a) physical description of the equipment, together with any necessary ancillary items (including materials of construction and “as-built” drawings);

b) specifications of the sterilizing agent and means by which it is provided, including any additives or precursors necessary for its delivery;

c) description of instrumentation for monitoring and controlling the sterilization process, including sensor characteristics and their locations, indicating instruments and recording instruments;

NOTE Temperature monitoring will normally be at the slowest-to-heat locations.

d) description of safety features, including those for personnel and environmental protection;

e) description of installation requirements, if applicable;

f) documented evidence that the software used to control and/or monitor the process is prepared in accordance with a quality system and that the software meets its design intention;

g) a process flow diagram that outlines the processing equipment layout to be sterilized, including valve sequencing.

5.3.2 Equipment to be used for SIP

5.3.2.1 The equipment shall be designed and manufactured to effectively perform and control SIP of the equipment to be sterilized. Its primary functions to be verified in qualification shall include but not be limited to:

a) generation of the sterilizing agent, where applicable;

b) admittance of the sterilizing agent into the equipment to be sterilized in a controlled and safe manner;

c) distribution of the sterilizing agent within the equipment to be sterilized;

d) maintenance of effective sterilization conditions throughout the equipment to be sterilized;

e) controlling and monitoring of the sterilization conditions in the defined locations;

f) safe removal of the sterilizing agent;

g) maintenance of the sterility of the equipment.