INTERNATIONAL STANDARD

ISO 13408-2

Second edition
2018-01

Aseptic processing of health care products —

Part 2: Sterilizing filtration

Traitement aseptique des produits de santé —
Partie 2: Filtration stérilisante

Reference number
ISO 13408-2:2018(E)

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Published in Switzerland

Contents

Page

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.

The procedures used to develop this document and those intended for its further maintenance are described in the ISO/IEC Directives, Part 1. In particular the different approval criteria needed for the different types of ISO documents should be noted. This document was drafted in accordance with the editorial rules of the ISO/IEC Directives, Part 2 (see www.iso.org/directives).

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. Details of any patent rights identified during the development of the document will be in the Introduction and/or on the ISO list of patent declarations received (see www.iso.org/patents).

Any trade name used in this document is information given for the convenience of users and does not constitute an endorsement.

For an explanation on the voluntary nature of standards, the meaning of ISO specific terms and expressions related to conformity assessment, as well as information about ISO's adherence to the World Trade Organization (WTO) principles in the Technical Barriers to Trade (TBT) see the following URL: www.iso.org/iso/foreword.html.

This document was prepared by Technical Committee ISO/TC 198, *Sterilization of health care products*.

This second edition cancels and replaces the first edition (ISO 13408-2:2003), which has been technically revised.

A list of all parts in the ISO 13408 series can be found on the ISO website.

Introduction

ISO 13408-1 covers general aspects of aseptic processing. Several processes including sterilizing filtration, lyophilization, clean and sterilization in place, isolator systems, and alternative processes for medical devices and combination products were found to be in need of supplementary information, which was too extensive to be included in the corresponding annexes to ISO 13408-1. This information is presented in ISO 13408-2 to ISO 13408-7.

Sterilizing filtration is a critical step in an aseptic manufacturing process. Validation of sterilizing filtration processes can be complex and is generally conducted in both a process and product specific manner. This document describes requirements that, if met, will provide a sterilizing filtration process that consistently removes microorganisms from a fluid (liquid or gas) without negatively affecting the quality of the filtrate. Furthermore, conformity with the requirements ensures that a sterilizing filtration process is both reliable and reproducible so that a determination can be made, with reasonable confidence, that the sterilizing grade filter/s will provide a sterile filtrate under specified operational conditions. This (the reliability and reproducibility of the filtration process) is essential, as unlike a micro-biocidal sterilization process where process variables can be monitored continuously, microbial retention and physical integrity of a sterilising grade filter cannot be monitored on a continuous basis throughout a filtration process.

Where validation establishes a reproducible relationship between the product-specific bacterial retention capability of a sterilizing grade filter and the physical integrity of that filter, then suitable non-destructive pre-use and post-use filter integrity tests are used to determine whether a full-scale sterilizing filtration process has been conducted successfully. During terminal sterilization the kinetics of inactivation follows a mathematical order and allow calculation of a sterility assurance level (SAL). Removal of organisms from a fluid by filtration does not follow such mathematical order and so the use of the term “sterility assurance level” is not appropriate for product sterilized by filtration.

There has been a significant increase in the development and availability of biopharmaceuticals, biologic-based medical devices and cell-based health care products since publication of the initial 2003 edition of this document. This second edition emphasizes the importance of a thorough understanding of the nature of the indigenous bioburden of a fluid that is to be sterilized by filtration, including its relationship to the test microorganism used to determine microbial retention capability of the sterilizing grade filter. For example, Mycoplasma can cause serious contamination problems during the manufacturing of biopharmaceutical, biotechnological and cell-based health care products. A thorough understanding of the indigenous bioburden enables suitable safeguards to be implemented during development, validation and control of a sterilizing filtration process to ensure the safety and quality of the filtered fluid.

While the activities required by this document have been grouped together and are presented in a particular order, this document does not require that the activities be performed in the order that they are presented. The activities required are not necessarily sequential, as the programme of development and validation may be iterative. It is possible that performing these different activities will involve a number of separate individuals and/or organizations, each of whom undertake one or more of these activities. This document does not specify the particular individuals or organizations to carry out the activities.

Guidance on the application of this document is given in Annex A.

Aseptic processing of health care products —

Part 2:
Sterilizing filtration

1 Scope

This document specifies requirements for sterilizing filtration as part of aseptic processing of health care products conducted in accordance with ISO 13408-1. It also offers guidance to filter users concerning general requirements for set-up, validation and routine operation of a sterilizing filtration process.

This document is not applicable to removal of viruses.

Sterilizing filtration is not applicable to fluids that intentionally contain particles larger than the pore size of the filter (e.g. bacterial whole-cell vaccines).

This document is not applicable to high efficiency particulate air (HEPA) filters.

This document does not specify requirements for the development, validation and routine control of a process for removing 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.

2 Normative references

The following documents are referred to in the text in such a way that some or all of their content constitutes requirements 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 11135, *Sterilization of health-care products — Ethylene oxide — Requirements for the development, validation and routine control of a sterilization process for medical devices*

ISO 11137-1, *Sterilization of health care products — Radiation — Part 1: Requirements for development, validation and routine control of a sterilization process for medical devices*

ISO 11139,[1)] *Sterilization of health care products — Vocabulary — Terms used in sterilization and related equipment and process standards*

ISO 13408-1:2008, *Aseptic processing of health care products — Part 1: General requirements*

ISO 13408-1:2008/Amd. 1:2013, *Aseptic processing of health care products — Part 1: General requirements — Amendment 1*

ISO 13408-5, *Aseptic processing of health care products — Part 5: Sterilization in place*

ISO 13485, *Medical devices — Quality management systems — Requirements for regulatory purposes*

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*

1) Under preparation. Stage at the time of publication: ISO/DIS 11139:2017(E).

3 Terms and definitions

For the purposes of this document, the terms and definitions given in ISO 11139 and the following apply.

ISO and IEC maintain terminological databases for use in standardization at the following addresses:

— IEC Electropedia: available at https://www.electropedia.org/

— ISO Online browsing platform: available at https://www.iso.org/obp

3.1
bacterial challenge test
technical operation performed to evaluate the capability of a *filter* (3.5) to retain organisms from liquid bacterial suspension under defined conditions

3.2
bioburden
population of viable *microorganisms* (3.9) on or in product and/or sterile barrier system

Note 1 to entry: For the purposes of this document, the definition of bioburden is the population of viable microorganisms in a *fluid* (3.6) prior to *sterilizing filtration* (3.11).

3.3
chemical compatibility
<filter> capability of process *fluids* (3.6) and *filter* (3.5) materials to be used together, under the specified process conditions, without adverse effects on either the fluids or filter materials

3.4
extractable
substance that can be released from a *filter* (3.5) or material using extraction solvents and/or extraction conditions that are expected to be at least as aggressive as the normal use conditions

[SOURCE: ISO 10993-12:2012, 3.8, modified — The wording has been modified.]

3.5
filter
construct of porous material through which a *fluid* (3.6) is passed to remove viable and/or non-viable particles

3.6
fluid
substance that continually deforms (flows) under applied shear force

EXAMPLE Liquid, gas, vapour or plasma.

Note 1 to entry: The filtrate of the fluid subjected to the *sterilizing filtration* (3.11) process might be the product to be produced, a part of the formulation, a gas used to provide overpressure or a process gas released into the aseptic processing area (e.g. gases released from air actuated valves).

3.7
filter integrity test
non-destructive physical test that can be correlated to the bacterial retention capability of a filter assembly

3.8
leachable
substance that can be released from a *filter* (3.5) or filter assembly during normal use conditions

3.9
microorganism
entity of microscopic size, encompassing bacteria, fungi, protozoa and viruses

Note 1 to entry: Viruses are not addressed in this document.

3.10
pore size rating
nominal pore size of a *filter* (3.5) as claimed and stated in the labelling

Note 1 to entry: The pore size rating is determined by retention performance with a model particle. The pore size rating is not necessarily the physical diameter of the pores but is a rating based on the size of particles which might not pass through the filter.

3.11
sterilizing filtration
removal of viable *microorganisms* (3.9) from *fluids* (3.6) by passage of the fluid through a *filter* (3.5) under specified process conditions resulting in a sterile filtrate

4 Quality system elements

4.1 General

A quality management system as defined in ISO 13408-1:2008, Clause 4, and ISO 13408-1:2008/Amd. 1:2013 shall be implemented to ensure control over all activities affecting sterilizing filtration. Additionally the requirements in 4.2 and 4.3 shall apply.

4.2 Management responsibility

Operator training specific to filtration activities shall be implemented and documented for the following:

a) filtration procedures, modes of failure and needed precautions;

b) integrity test theory and practice;

c) failure investigation procedures and measures taken in case of integrity test deviations;

d) filter assembly procedure (including aseptic technique if required);

e) filter installation, cleaning and sterilization procedures.

4.3 Procurement of filters

4.3.1 Procedures for purchasing filters and filtration equipment shall be specified. These procedures shall conform with the applicable clauses of ISO 13485 or equivalent quality system.

4.3.2 There shall be a written agreement between the filter user and filter manufacturer that the filter manufacturer will notify the filter user of any changes in the filter manufacturing conditions with potential to affect the defined fluid and process parameters.

4.3.3 Procedures for identification and traceability of filters shall be specified. These procedures shall conform with the applicable clauses of ISO 13485 or equivalent quality system.

5 Sterilizing filter characterization

5.1 General

Sterilizing filter characterization is the process of determining which filters might be suitable for use as a sterilizing filter in a sterilizing filtration process for a given fluid. This is usually carried out by the filter user considering information available from the filter manufacturer.

Sterilizing filter formats include, but are not limited to the following:

a) membrane filter discs for the user to assemble into filter holders/housings;

b) cartridge filters for the user to assemble into filter holders/housings;

c) units supplied pre-assembled by the filter manufacturer (capsules).

The specification for the filters used in production shall be justified against the specification of those used in the product and process validation.

5.2 Microbial removal effectiveness

5.2.1 Microbial removal effectiveness data shall be developed for each combination of sterilizing grade filter and fluid type. This is usually by demonstration of retention of a

a) product specific microbial challenge for liquid filtration, and

b) generic aerosol challenge for gas filtration.

5.2.2 The variables that affect the effectiveness of the microbial removal and the interactions of these variables in relation to this effectiveness shall be identified. Such variables include, but are not limited to the following:

a) filter membrane characteristics, such as the pore size distribution, surface chemistry, structure and polymer type of the membrane (see 8.2.1);

b) filtration equipment characteristics (see 6.4);

c) fluid characteristics, such as the effects of surfactants or additives; including the absorptive influence of the fluid on microorganisms, pH, viscosity, osmolarity, surface tension and ionic strength (see 7.1.2);

d) fluid bioburden; number, type and cell size of organisms present in the fluid and process conditions or formulations which might affect cell size (see 7.1.2);

e) process conditions, such as batch size, temperature, differential pressure, flow rate, hold times and processing times (see 8.3.1);

f) the effect of the sterilization process for the filter on the filter performance.

For the sterilization of gases by filtration, some of the above may not be applicable.

5.3 Material effects

5.3.1 The effects of materials extracted or leached from the filter on the fluids being filtered shall be evaluated (see 8.2.2.2 and 8.2.2.3).

5.3.2 The effects of adsorption of product or product components onto the filter material shall be evaluated (see 8.2.2.4).

5.3.3 Filters shall not be fibre-releasing.

NOTE A fibre is generally considered to be a particle having an aspect (length-to-width) ratio of 10 or more.

5.3.4 Where filters are reused, the processes for disassembly, cleaning, rinsing, storage, reassembly, flushing and sterilization shall be justified. The effects of these processes on microbial removal effectiveness and filter materials shall be evaluated (for further details see 8.2.3.2).

5.4 Environmental considerations

Procedures for the disposal of used filter material shall take into consideration the materials filtered and shall ensure safe disposal.

NOTE Local waste disposal requirements can apply.

6 Process and equipment characterization

6.1 General

The purpose of this activity is to define the entire sterilizing filtration process so that it is both safe and reproducible.

6.2 Risk management

6.2.1 The following additional requirements to ISO 13408-1:2008, 5.2, and ISO 13408-1:2008/Amd. 1:2013 concerning risk management apply.

6.2.2 A risk assessment shall be performed during the selection of the filter and filtration equipment. The risk assessment shall include, but is not limited to the following:

a) effects of variables identified in 5.2.2;

b) the design of the sterilizing filtration system in terms of the incorporation of, and location within the system of particulate reduction or bioburden reduction filters, single or sterilizing filters in series, redundant sterilizing grade filters or parallel sterilizing grade filters;

c) the risk to the sterility of the filtration system when pre-use post-sterilization integrity testing (PUPSIT) is carried out;

d) the risks associated with filter reuse for the sterilizing filtration process for a given fluid.

6.2.3 Risk management shall include assessment and management of risks associated with the outsourcing of sterilization of critical sterile components, for example, where filters are purchased sterile.

For single use filtration systems this shall include an evaluation of the following:

a) the supplier's assembly design (including the filter user's need for single, serial, redundant or parallel filter design), materials of construction, manufacturing and sterilization processes;

b) filter location, i.e. inside or outside of an isolator;

c) the ability to conduct a pre-use post-sterilization integrity test (if required);

d) how the assembly performs in the filtration process for the fluid, including requirements for filter flushing or wetting;

e) maintenance of downstream sterility;

f) integrity testing of closed systems;

g) how the assembly impacts the filtered fluid.

6.2.4 The estimation of risk by quantitative methods and the verification of effectiveness of risk mitigation procedures shall be determined. Methods might include microbiological and particulate monitoring of the fluid.

6.2.5 The outcome of the risk assessment shall be used in the design of the sterilizing filtration validation study.

6.2.6 Risk management shall be applied iteratively. The risk assessment shall be updated as necessary if the sterilizing filtration process changes during development and validation.

6.3 Process characterization

6.3.1 The process parameters and their tolerances shall be specified. These tolerances shall be based upon knowledge of the combination of process parameters yielding minimal acceptable microbial removal effectiveness. Processing within such process parameters shall routinely yield safe and functional sterile filtrate.

The establishment of tolerances for process parameters shall be based upon analyses of process variables (see Clause 8).

6.3.2 Means of controlling and monitoring the process variables shall be determined.

6.3.3 Any treatment of fluid that is required prior to exposure to the sterilizing filter to ensure effectiveness of the sterilizing filtration process shall be specified (for example, the use of a bioburden reduction filter).

6.3.4 Following sterilizing filtration subsequent aseptic handling of sterile filtrate shall be as specified in ISO 13408-1.

6.4 Equipment characterization

6.4.1 The equipment to deliver the process in a safe manner within the parameters stipulated for the process variables shall be specified.

6.4.2 The specification shall include, but is not limited to a physical description of the equipment and necessary ancillary items, including materials of construction.

6.4.3 The selection of components for the filtration system and their interconnection and arrangement within the filtration system shall be documented and justified.

The filtration system components shall not impart impurities to or otherwise alter the quality of the fluid. Such components can include the following:

a) piping systems and connections;

b) valves;

c) gauges and/or other instruments;

d) gaskets, O-rings and/or packings;

e) filter materials.

6.4.4 In gas filtration, unintended wetting of the filter or accumulation of liquid in the filter equipment shall be avoided.

6.4.5 The filtration system shall be designed in accordance with the following requirements.

a) To allow operation within validated process parameters.