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Aseptic processing of health care products —

Part 2: **Filtration**

Traitement aseptique des produits de santé —

Partie 2: Filtration

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Foreword

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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 13408-2 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*

The following parts are under preparation:

— *Part 3: Freeze-drying*

— *Part 4: Sterilization in place*

— *Part 5: Cleaning in place*

— *Part 6: Isolator/barrier technology*

Introduction

During the process of preparing ISO 13408-1:1998, which addresses general requirements, several items, e.g. filtration, freeze-drying and steam-in-place, were found to be in need of supplementary information which was too large to be given in corresponding Annexes. This part of ISO 13408 includes requirements and guidance that are to be observed when aseptically manufacturing health care products by filtration.

ISO 13408-1:1998 will be revised soon after the publication of this part of ISO 13408, as clause 20 of ISO 13408-1:1998 is replaced by this part of ISO 13408.

Aseptic processing of health care products —

Part 2:
Filtration

1 Scope

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

This part of ISO 13408 is not applicable to removal of viruses. Sterilizing filtration is not applicable to fluids containing particles as effective ingredient larger than the pore size of a filter (e.g. bacterial whole-cell vaccines).

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 13408-1:1998, *Aseptic processing of health care products — Part 1: General requirements*

ISO/TS 11139:2001, *Sterilization of health care products — Vocabulary*

3 Terms and definitions

For the purposes of this document, the terms and definitions given in ISO 13408-1, ISO/TS 11139 and the following apply.

3.1
bacterial challenge test
test to evaluate the capability of a filter to retain organisms from a bacterial suspension under defined conditions

3.2
bioburden
population of viable microorganisms in a fluid prior to sterilizing filtration

NOTE For the purposes of this part of ISO 13408, the definition of bioburden is narrower than that in ISO/TS 11139.

3.3
chemical compatibility
ability of the process fluids not to adversely affect the properties of filter materials and/or filter assembly components and vice versa

3.4
fibre
particle having an aspect (length-to-width) ratio of 10 or more

[ISO 14644-1:1999, 2.2.7]

3.5
fibre-releasing filter
filter which, even after any appropriate treatment such as washing or flushing, will release fibres into the filtrate

3.6
filter
porous material through which a liquid or a gas is passed to remove viable and non-viable particles

3.7
filter assembly
filter cartridge(s) or filter material installed into a housing or holder

NOTE This can be done by the filter user or by the filter manufacturer, e.g. in the form of pre-assembled filter units.

3.8
filter cartridge
filter material assembled into a unit

3.9
filter equipment
gauge, valve and other items attached to filter assembly

3.10
filtration
process to remove viable and/or non-viable particles from liquids and/or gases by passage through a porous material

3.11
filtration system
filter assembly equipped with filter equipment

cf. **filter equipment** (3.9)

3.12
fluid
liquid or a gas

NOTE The fluid subjected to the filtration process may be the formulation to be produced, or a part of the formulation, or a process fluid.

3.13
fluid-sterilizing filter
filter that is capable of removing a defined challenge of microorganisms from a fluid under defined filtration process conditions

NOTE Typically, such a filter has a nominal pore size rating of less than or equal to 0,22 µm.

3.14
integrity test
non-destructive physical test which can be correlated to the bacterial retention capability of a filter/filter assembly

3.15
microorganism
entity, encompassing bacteria, fungi, protozoa and viruses

NOTE For the purposes of this part of ISO 13408, viruses are not addressed.

3.16
nominal pore size rating
pore size of a filter as claimed and stated by the filter manufacturer

3.17
worst case
most challenging pre-determined condition(s) and specification(s) applied in a process to be validated

4 General requirements

The requirements of ISO 13408-1:1998 shall apply.

5 Selection of filters and filter assemblies based on filter manufacturer's data

5.1 Selection shall document the choice of the most suitable type(s) of filter, taking into account the chemical and physical characteristics of the filters as established by the filter manufacturers.

NOTE For further information see A.1.

5.2 The filters selected shall have a quality certificate.

NOTE For further information see A.2.

5.3 Filters shall not contain asbestos and shall not be fibre-releasing. Where the use of fibre-releasing filters is dictated by product need, it shall be demonstrated that the fibres are removed downstream of filtration.

6 Fluid-specific selection criteria based on filter user's data

6.1 The filter user shall evaluate filter characteristics following a documented filter evaluation programme that takes into account the fluid to be filtered and the process used for filtration. Filter characteristics shall not be adversely affected by the fluid to be filtered; conversely, the product shall not be adversely affected by the filter. Adsorption of fluid components and extraction of filter components shall be evaluated.

6.2 For filter characterization, the following shall be taken into account:

a) compatibility between filter and fluid;

   1) effects of the formulation and process conditions on the chemical and physical attributes and performance of the filter;

   2) effects of the filter on the relevant biological, chemical and physical attributes of the product;

b) process characteristics;

   1) effective filter surface area required;

   2) pre-filtration requirements for reduction of particulate matter and reduction of bioburden.

Compatibility and process criteria, as applicable, should also be applied to pre-filters in view of their intended use.

7 Filtration process

7.1 Process parameters

7.1.1 Process parameters shall be established, qualified and documented, and the process validated by the filter user. Factors to be defined or specified include:

a) flushing procedures, including filter(s) and downstream flow path (or justification for lack of flushing);

The flushing process applied should ensure that the filtrate meets acceptable limits for extractables, insoluble particles and oxidizable substances.

NOTE 1 Information from the filter manufacturer can be useful in designing and validating a flushing procedure.

NOTE 2 Results from a permanganate reduction test and/or total organic carbon (TOC) test can be useful in designing and validating a flushing procedure.

b) sterilization procedures for the filter assembly, filtration system and fluid path, including the permissible limit for cumulative sterilization time and/or number of cycles at applicable sterilization conditions in case of multiple sterilizations and re-use;

c) filtration process conditions;

1) fluid pre-filtration holding time and effect on bioburden;

2) filter conditioning, with fluid if necessary;

3) filtration time/total time filter is in contact with fluid;

4) maximum number of repeated filtrations;

5) flowrate;

6) filtration volume;

7) temperature;

8) differential pressure;

d) cleaning procedures for the filtration system.

7.1.2 Written integrity test procedures shall be established, including acceptance criteria and methods of failure investigation and conditions under which the filter integrity test can be repeated.

It should be demonstrated that the integrity test procedure(s) can be supported by bacterial-retention testing. The standardized bacterial-retention tests should use a challenge level of at least 10^7 colony-forming units per square centimetre of effective filtration area, with filters representative of standard production filters as close as possible to the minimum integrity test specification.

NOTE Information from the filter manufacturer can be useful in designing and validating integrity test procedure(s) based on gas flow through a wetted filter.

7.1.3 One or more appropriate wetting fluids shall be selected. These shall be the filter manufacturer's recommended reference wetting fluid or the fluid to be filtered. In the latter case, the appropriate integrity test value specification shall be established and validated. The wetting fluid shall be compatible with, and shall not impart impurities to, the fluid to be filtered or the filter assembly.

7.1.4 For air and gas filters, an appropriate frequency for physical integrity testing shall be established.

7.2 Validation of fluid-specific microbial retention by filters

7.2.1 Bacterial challenge test

7.2.1.1 Fluid-sterilizing filtration shall be validated during initial process qualification by an appropriate bacterial challenge test using at least one filter from not less than three lots of filters with three consecutive successful outcomes. All failures shall be investigated.

NOTE 1 This testing is usually performed in a scaled-down model system (which can include a different cartridge or disc size) in a laboratory environment to avoid jeopardizing the quality of the manufacturing environment.

NOTE 2 In case of an unsuccessful validation test, any further course of action depends on the outcome of the failure investigation.

7.2.1.2 Bacterial-retention performance of filters shall be validated in a fluid-specific manner or for fluid groups under worst-case conditions. Justification for grouping fluids for validation shall be by a documented rationale.

7.2.1.3 For fluid-specific bacterial challenge testing, membranes of the same type as that used for production shall be obtained from the filter manufacturer and shall have been found to be close to the limit of acceptance in filter integrity testing (typically within 10 % of the limit).

7.2.1.4 For the selection of the challenge conditions to simulate worst-case conditions in production, the following shall be taken into account:

a) pH;

b) viscosity;

c) ionic strength;

d) osmolarity;

e) concentration of active ingredient and/or excipients;

f) surface activity/tension;

g) effect of fluid on challenge organisms;

h) characteristics of process bioburden;

i) filtration time/total time filter is in contact with fluid;

j) filtration volume per unit area of filter;

k) flowrate/flux across the filter;

l) differential pressure;

m) temperature;

n) sterilization conditions;

o) effect of repeated sterilizations where relevant.

7.2.1.5 Revalidation shall be performed whenever filters or filtration conditions are altered to be outside the worst-case conditions tested during validation.

7.2.2 Challenge fluid and challenge microorganisms

7.2.2.1 The testing fluid shall be the fluid to be filtered. If the fluid to be filtered cannot be used due to antimicrobial or other properties, a simulation fluid or a change in simulation conditions shall be used.

In determining the simulation, the following shall be considered:

a) modifying the fluid to be filtered (e.g. reducing or eliminating the antimicrobial compound);

   The simulation fluid shall mimic as closely as possible the formulation and the following fluid specific characteristics: pH, viscosity, ionic strength, osmolarity, surface activity/tension, and the effects of the fluid on the challenge organisms.

b) reducing fluid-organism exposure time;

c) reducing the fluid temperature;

d) using a diminutive organism that is resistant to the antimicrobial properties of the fluid or process;

e) exposing the filter to the fluid with the anticipated fluid contact time, followed by a challenge in a modification of fluid as in a) to d) above.

7.2.2.2 Unless a rationale for a lower challenge level is given, an acceptable challenge level of *Brevundimonas diminuta* (e.g. ATCC 19146 or DSM 1635) is at least 10^7 colony-forming units per square centimetre of effective filter surface area.

If there is concern that there may be more penetrating microorganisms than *Brevundimonas diminuta*, an appropriate microorganism should be considered for use.

NOTE Factors of potential concern can be:

— presence of biological material;

— use of water from systems that are not operated under self-sanitizing conditions;

— presence of microorganisms known to penetrate filters;

— presence of pleomorphic organisms (e. g. L forms in penicillin solution, mycoplasma).

Where it is not possible to use *Brevundimonas diminuta* and where no more penetrating microorganisms have been identified as potential challenge organisms, the user shall justify the choice of an alternative challenge microorganism.

Where alternative organisms are cultivated as challenge organisms, cultivation conditions shall be chosen appropriately to yield cells of a small size (see [2] and [3]).

7.2.2.3 Validation of the microbial aspects of the challenge test shall ensure that

a) the challenge organisms are dispersed in a volume of the fluid representative for batch size and available filter area, unless antimicrobial properties require a different approach;

b) the viable count of the challenge suspension during the test is determined on an appropriate number of samples taken throughout that time to show that the intended challenge is actually delivered and that the challenge remains viable for the duration of the test;

c) the challenge is recoverable from the filtrate if present;

d) the test method is capable of recovering a small number of challenge organisms from the filtrate.

7.2.3 Acceptance criteria

Acceptance criteria: no growth of the challenge organism in the filtrate following a microbial challenge.

8 Filtration system design

8.1 The selection of components for the filtration system (including air and gas filters), and their interconnection and arrangement within the filtration system, shall be documented and justified.

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

a) piping systems and connections;

b) valves;

c) gauges and/or other instruments;

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

e) filter materials (see A.1).

8.3 In air and gas filtration, attention should be paid to avoidance of unintended moistening or wetting of the filter or filter equipment.

8.4 Filtration system design shall allow operation within validated process parameters.

8.5 The system shall be designed to maintain the sterility of the filtrate. Environmental conditions shall be defined. See ISO 13408-1:1998, Clause 14.

8.6 The filtration system shall be designed so that the number of aseptic connections is minimized.

8.7 A sterilizing filter should be installed as close as possible to the point of fill.

8.8 The filtration system shall be designed to allow cleaning procedures to be conducted as necessary.

8.9 The filtration system shall be designed to allow sterilization procedures to be conducted as necessary. The sterilization procedures shall be validated to a sterilization assurance level (SAL) of not less than 10^{-6}.

NOTE Acceptable approaches to sterilization can include:

— sterilization in place;

— sterilization of disassembled components followed by aseptic assembly.

8.10 The filtration system should be designed to permit in-place integrity testing as a closed system prior to filtration.

Care should be taken not to compromise the sterility of the filter.

9 Routine process

9.1 The routine process for filtration shall be documented in a written procedure.

9.2 The written procedures shall include processing requirements for:

a) inspection of components;

b) assembly of the filtration system;

c) cleaning, sterilization or flushing;

d) time between cleaning and sterilization;

e) time between sterilization and use;

f) control testing including integrity test testing;

g) monitoring of parameters such as temperature, differential pressure, flowrate, etc.

9.3 Pre-sterilization bioburden shall be determined for every batch, unless all aspects of aseptic manufacture are well controlled and previous test results have shown bioburden to be low and consistent.

9.4 Procedures shall be in place to minimize the number of microorganisms prior to sterile filtration, thus minimizing the challenge to the sterilizing filter.

9.5 The validated physical integrity test of a sterilizing filter shall be conducted after each use without disturbing the filter in its housing. Physical integrity testing of a sterilizing filter *in situ* should be conducted before use after sterilization where the design of the filtration system permits.

Care should be taken not to compromise the sterility of the filter.

10 Process documentation

10.1 All critical defined process parameters shall be documented and maintained in a report. The documentation shall become part of a batch record.

10.2 Batch manufacturing records shall include, where appropriate:

a) dates of fluid preparation and filtration;

b) name and batch number of the fluid;

c) operator's name(s);

d) filter manufacturer, filter type and filter manufacturer's lot and/or serial number(s);

e) cleaning of filtration system;

f) sterilization conditions for the filtration system;

g) filtration process conditions (differential pressure, upstream pressure, downstream pressure, flowrate, operation temperature, time, etc.);

h) filter integrity test result and assessment;

i) reference to sterilization cycles used for components employed in the filtration process;

j) any deviations to the written procedure that have occurred.

11 Maintenance and change control

11.1 The filter user shall establish, document and execute calibration and maintenance procedures for the filter and filtration system and test instruments. A change-control procedure shall be defined and documented for any change of the defined process parameters.

11.2 Any change in filter manufacturing conditions as reported by the filter manufacturer shall be evaluated with respect to their potential effect to the defined product and process parameters. See 7.1.1 c) and 7.2.1.4.

11.3 There shall be a written agreement between the filter user and filter manufacturer that they will comply with this requirement. This should be verified by the filter user through audits of the filter manufacturer.

12 Operator training

Filtration-specific operator training shall be implemented and documented, for:

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

b) integrity test theory;

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.

Annex A
(informative)

Basic information and quality certificates for filter cartridges

A.1 The following basic information is typically available from filter manufacturers:

a) materials of the filter assembly;

b) hydrophilic/hydrophobic characteristics;

c) extractables in model solvents (e.g. water);

d) general chemical compatibility;

e) recommended sterilization procedure(s) (cumulative time, number of cycles and sterilization conditions);

f) thermal resistance;

g) maximum acceptable pressure differential;

h) flow characteristics;

i) particle and/or fibre shedding (filter media migration) characteristics in a model solvent (e.g. water);

j) microbial retentivity and correlation to integrity test data under stated test conditions;

k) nominal pore-size rating;

l) recommended integrity test procedures;

m) biological safety data.

A.2 Lot-specific quality certificates for filter cartridges may include information on:

a) integrity test result;

b) endotoxin or pyrogen;

c) bacterial challenge testing results;

d) oxidizable substances or total organic carbon;

e) extractable substances;

f) fibre- and particle-release characteristics;

g) biological safety data;

h) water flowrate;

i) hydraulic stress resistance;

j) thermal stress resistance.

NOTE 1 Items a), b), c) and d) are typically reported based on tests performed for each lot.

NOTE 2 The quality certificates are generally applied to filter cartridges, but can also be applied to filter discs or filter sheets.

Bibliography

[1] ISO 14644-1:1999, *Cleanrooms and associated controlled environments — Part 1: Classification of air cleanliness*

[2] ASTM F 838, Standard Test Method for Determining Bacterial Retention of Membrane Filters Utilized for Liquid Filtration

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