INTERNATIONAL STANDARD

ISO 13408-1

Second edition
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Aseptic processing of health care products —

Part 1: General requirements

Traitement aseptique des produits de santé —

Partie 1: Exigences générales

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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 13408-1 was prepared by Technical Committee ISO/TC 198, *Sterilization of health care products*.

This second edition cancels and replaces the first edition (ISO 13408-1:1998), which has been technically revised. Any normative and informative clauses on subjects which have meanwhile been addressed in Part 2 to Part 6 of ISO 13408 have been removed from this part.

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

Health care products that are labelled “sterile” are prepared using appropriate and validated methods under stringent control as part of a quality management system. For pharmaceuticals and medical devices there might be various requirements including compliance with ISO standards, GMP regulations and pharmacopoeial requirements.

Wherever possible, healthcare products intended to be sterile should be sterilized in their final sealed container (terminal sterilization). ISO/TC 198 has prepared standards for terminal sterilization of health care products by irradiation (series ISO 11137), by moist heat (ISO 17665-1), by dry heat (ISO 20857, in preparation) and by ethylene oxide (ISO 11135-1).

When a health care product is intended to be sterile and cannot be terminally sterilized, aseptic processing provides an alternative. Presterilization of product, product parts and/or components and all equipment coming into direct contact with the aseptically-processed product is required. Aseptic processing intends to maintain the sterility of the pre-sterilized components and products during assembling. The resulting product is required to be sterile in its final container. Aseptic processing can also be used to prevent contamination of biological product or biological systems (e.g. tissues, vaccines).

While terminal sterilization involves the control of a well-defined process of known lethality delivered to the product and a sterility assurance level (SAL) can be extrapolated from sterilization data, this is not applicable to aseptic processing.

Examples of applications in which aseptic processing are used include:

— aseptic handling and filling of solutions, suspensions, semisolids and powders;

— aseptic handling, transfer and packaging of solid products including solid medical devices;

— aseptic handling, transfer and packaging of combination products;

— aseptic handling of tissues or biological production systems.

Sterilization procedures which render components and/or parts sterile as a prerequisite for further aseptic processing can be treated as separate procedures. They have to be evaluated and validated separately and it is important that their risk of failure is minimal. The aseptic process definition encompasses all production steps following the sterilization of product and components until the final container or package is sealed. To keep the aseptic process definition clear and workable, this part of ISO 13408 is focused on the risks to the maintenance of sterility.

It is important to control all possible sources of contamination in order to maintain the sterility of each and every component. To achieve this, a risk-based aseptic process definition is established encompassing each product and applied in a comprehensive way considering product, package design, environment and manufacturing process designs. The product is processed in a controlled environment where microbial and particulate levels are maintained at defined minimal levels and where human intervention is minimized. Validated systems, adequately trained personnel, controlled environments and well-documented systematic processes are applied to assure a sterile finished product.

The aseptic process is divided into unit operations (e.g. sterilization of product or components including sterile filtration, assembly of components, handling and storage of sterilized product) and it is necessary that potential sources of contamination from materials, components, product, personnel, facility, equipment and utilities such as water systems be considered and minimized. Only if all risks of contamination have been recognised, wherever possible minimized, eliminated or controlled and finally have been evaluated as

acceptable, can the controls on the aseptic process be considered to be acceptable. Appropriate validation of the specified elements of the aseptic process is needed, of which process simulation studies are an essential.

This revision of ISO 13408-1:1998 is intended to adopt this International Standard to the actual state of technology in the field.

Aseptic processing of health care products —

Part 1:
General requirements

1 Scope

1.1 This part of ISO 13408 specifies the general requirements for, and offers guidance on, processes, programmes and procedures for development, validation and routine control of the manufacturing process for aseptically-processed health care products.

1.2 This part of ISO 13408 includes requirements and guidance relative to the overall topic of aseptic processing. Specific requirements and guidance on various specialized processes and methods related to filtration, lyophilization, clean-in place (CIP) technologies, sterilization in place (SIP) and isolator systems are given in other parts of ISO 13408.

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

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 9001, *Quality management systems — Requirements*

ISO 11135-1, *Sterilization of health care products — Ethylene oxide — Part 1: Requirements for 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 11137-2, *Sterilization of health care products — Radiation — Part 2: Establishing the sterilization dose*

ISO 13408-2, *Aseptic processing of health care products — Part 2: Filtration*

ISO 13408-3, *Aseptic processing of health care products — Part 3: Lyophilization*

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

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

ISO 13408-6, *Aseptic processing of health care products — Part 6: Isolator systems*

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

ISO 14160, *Sterilization of single-use medical devices incorporating materials of animal origin — Validation and routine control of sterilization by liquid chemical sterilants*

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

ISO 14644-2, *Cleanrooms and associated controlled environments — Part 2: Specifications for testing and monitoring to prove continued compliance with ISO 14644-1*

ISO 14644-3, *Cleanrooms and associated controlled environments — Part 3: Test methods*

ISO 14644-4, *Cleanrooms and associated controlled environments — Part 4: Design, construction and start-up*

ISO 14644-5, *Cleanrooms and associated controlled environments — Part 5: Operations*

ISO 14644-7, *Cleanrooms and associated controlled environments — Part 7: Separative devices (clean air hoods, gloveboxes, isolators and mini-environments)*

ISO 14698-1, *Cleanrooms and associated controlled environments — Biocontamination control — Part 1: General principles and methods*

ISO 14698-2, *Cleanrooms and associated controlled environments — Biocontamination control — Part 2: Evaluation and interpretation of biocontamination data*

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 14971, *Medical devices — Application of risk management to 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 20857[1)], *Sterilization of health care products — Dry heat — Requirements for the development, validation and routine control of a sterilization process for medical devices*

ICH *Guidance for Industry — Q9 Quality Risk Management* [2)]

3 Terms and definitions

For the purposes of this document, the following terms and definitions apply:

3.1
action level
established microbial or particulate monitoring results requiring immediate follow-up and corrective action

3.2
airlock
room with interlocked doors designed to maintain pressure control between adjacent rooms of different cleanliness class

3.3
alert level
established microbial or particulate monitoring results giving early warning of potential drift from normal operating conditions which are not necessarily grounds for definitive corrective action but which could require follow-up investigation

1) To be published.

2) Available at: http://www.ich.org

3.4
aseptic processing
handling of sterile product, containers and/or devices in a controlled environment, in which the air supply, materials, equipment and personnel are regulated to maintain sterility

NOTE This includes sterilization by membrane filtration which cannot be separated from the subsequent aseptic process.

3.5
aseptic processing area
APA
facilities for **aseptic processing** (3.4), consisting of several zones

3.6
bioburden
population of viable microorganisms on or in product and/or sterile barrier system

[ISO/TS 11139:2006, definition 2.2]

NOTE For the purposes of aseptic processing, the bioburden of concern is that on or in the product including all factors affecting it such as raw material, intermediates, other components and equipment.

3.7
bio-decontamination
removal of microbiological contamination or its reduction to an acceptable level

[ISO 13408-6:2005, definition 3.1]

3.8
cleaning
removal of contamination from an item to the extent necessary for further processing or for intended use

[ISO/TS 11139:2006, definition 2.7]

3.9
combination product
product comprised of drug/device, biologic/device, drug/biologic or drug/device/biologic, that are physically, chemically, or otherwise combined or mixed and produced as a single entity

3.10
correction
action to eliminate a detected nonconformity

NOTE A correction can be made in conjunction with a corrective action.

[ISO 9000:2005; definition 3.6.6]

3.11
corrective action
action to eliminate the cause of a detected nonconformity or other undesirable situation

[ISO 9000:2005, definition 3.6.5]

NOTE 1 There can be more than one cause for a nonconformity.

NOTE 2 Corrective action is taken to prevent recurrence whereas **preventive action** (3.29) is taken to prevent occurrence.

NOTE 3 There is a distinction between correction and corrective action.

NOTE 4 Corrective actions might be subject to change control.

3.12
critical processing zone
location within the aseptic processing area in which product and critical surfaces are exposed to the environment

3.13
critical surface
surface that may come into contact with or directly affect a product or its containers or closures

3.14
depyrogentation
validated process designed to remove or deactivate endotoxins

3.15
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]

3.16
direct support zone
protective area directly surrounding a critical processing zone

3.17
disinfectant
chemical agent that is able to reduce the number of viable microorganisms

3.18
disinfection
removal, destruction or de-activation of microorganisms on objects or surfaces

[ISO 14644-5:2004;definition 3.1.4]

3.19
endotoxin
lipopolysaccharide component of the cell wall of Gram-negative bacteria which is heat stable and elicits a variety of inflammatory responses in animals and humans

3.20
environmental isolates
microorganisms present in and/or isolated from processing or manufacturing environments

3.21
gowning procedure
defined steps to reduce the risk of contamination while putting on the protective garments needed to enter the **APA** (3.5)

3.22
health care product
medical device(s), including *in vitro* diagnostic medical device(s), or medicinal product(s), including biopharmaceutical(s)

[ISO/TS 11139:2006, definition 2.20]

3.23
high efficiency particulate air filter
HEPA filter
retentive matrix having a minimum particle-collection efficiency of 99,97 % (that is, a maximum particle penetration of 0,03 % for 0,3 µm particles)

3.24
indirect support zone
location within the aseptic processing area which protects the direct support zone

NOTE The required grade of cleanliness of the indirect support zone depends on the aseptic processing activities performed in the indirect processing zone.

3.25
installation qualification
IQ
process of obtaining and documenting evidence that equipment has been provided and installed in accordance with its specification

[ISO/TS 11139:2006, definition 2.22]

3.26
isolator
enclosure capable of preventing ingress of contaminants by means of physical interior/exterior separation, and capable of being subject to reproducible interior bio-decontamination

NOTE An isolator can range in size from a small box to a large room.

3.27
operational qualification
OQ
process of obtaining and documenting evidence that installed equipment operates within predetermined limits when used in accordance with its operational procedures

[ISO/TS 11139:2006, definition 2.27]

3.28
performance qualification
PQ
process of obtaining and documenting evidence that the equipment, as installed and operated in accordance with operational procedures, consistently performs in accordance with predetermined criteria and thereby yields product meeting its specification

[ISO/TS 11139:2006, definition 2.30]

3.29
preventive action
action to eliminate the cause of a potential nonconformity or other undesirable potential situation

[ISO 9000:2005, definition 3.6.4]

NOTE 1 There can be more than one cause for a potential nonconformity.

NOTE 2 Preventive action is taken to prevent occurrence whereas **corrective action** (3.11) is taken to prevent recurrence.

3.30
qualification
documented process used by the health care product manufacturer to assure the reliability and capability of equipment and/or processes before approval for use in manufacturing

NOTE Qualification of equipment and/or processes generally includes **installation qualification** (3.25), **operational qualification** (3.27) and **performance qualification** (3.28).

3.31
risk control
process in which decisions are made and measures implemented by which risks are reduced to, or maintained within, specified levels

[ISO 14971:2007, definition 2.19]

3.32
separative device
equipment utilizing constructional and dynamic means to create assured levels of separation between the inside and outside of a defined volume

NOTE Some industry-specific examples of separative devices are clean air hoods, containment enclosures, gloveboxes, isolators and mini-environments.

[ISO 14644-7:2004, definition 3.17]

3.33
shift
scheduled period of work or production staffed by a single defined group of workers

NOTE This is usually not more than 12 h in length.

3.34
sterile
free from viable microorganisms

[ISO/TS 11139:2006, definition 2.43]

NOTE In practice, no such absolute statement regarding the absence of microorganisms can be proven, see **sterilization** (3.35).

3.35
sterilization
validated process used to render a product free from viable microorganisms

[ISO/TS 11139:2006, definition 2.47]

3.36
terminal sterilization
process whereby product is sterilized within its sterile barrier system

[ISO/TS 11139:2006, definition 2.52]

3.37
ultra low penetration air filter
ULPA filter
matrix with minimum 0,3 µm particle retaining efficiency of 99,999 %

3.38
unidirectional airflow
air stream which has a defined direction

3.39
unit operation
defined chemical or physical step in a manufacturing process

NOTE See example of a flowchart in Annex A.

3.40
validation
documented procedure for obtaining, recording and interpreting the results required to establish that a process will consistently yield product complying with predetermined specifications

[ISO/TS 11139:2006, definition 2.55]

3.41
worst case
set of conditions that represent the greatest challenge to product integrity and safety which will be accepted during routine production

4 Quality system elements

4.1 General

4.1.1 A quality management system, appropriate to the nature of the operations, shall be implemented to assure control over all activities affecting aseptic processing. Unless a superseding national, regional, or International Good Manufacturing Practice (e.g. the World Health Organization GMPs) is employed, the quality management system shall be in conformance with the requirements of ISO 9001 and/or ISO 13485.

NOTE Guidance on selecting a suitable model is given in ISO 9004 and ISO/TR 14969.

4.1.2 Documented procedures for each phase of the development, validation, routine monitoring and control of the aseptic 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 Assignment of responsibilities

4.2.1 The responsibilities and authority for implementing, performing and monitoring the procedures described in this part of ISO 13408 shall be assigned to qualified personnel as specified in ISO 13485.

4.2.2 Management shall be responsible for ensuring that there is an adequate number of qualified employees to perform required work and that supervision is provided. Management shall periodically review the performance of the quality management system to assess any areas needing improvement.

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

4.3 Calibration

4.3.1 A documented procedure shall be specified for the calibration of all measuring instruments or measuring systems.

4.3.2 The accuracy and tolerance of all measuring instruments shall be adequate for the process to be measured.