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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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ISO copyright office
CP 401 • Ch. de Blandonnet 8
CH-1214 Vernier, Geneva
Phone: +41 22 749 01 11
Email: copyright@iso.org
Website: www.iso.org

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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.

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).

ISO draws attention to the possibility that the implementation of this document may involve the use of (a) patent(s). ISO takes no position concerning the evidence, validity or applicability of any claimed patent rights in respect thereof. As of the date of publication of this document, ISO had not received notice of (a) patent(s) which may be required to implement this document. However, implementers are cautioned that this may not represent the latest information, which may be obtained from the patent database available at www.iso.org/patents. ISO shall not be held responsible for identifying any or all such patent rights.

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

For an explanation of 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 www.iso.org/iso/foreword.html.

This document was prepared by Technical Committee ISO/TC 198, *Sterilization of health care products,* in collaboration with the European Committee for Standardization (CEN) Technical Committee CEN/TC 204, *Sterilization of medical devices,* in accordance with the Agreement on technical cooperation between ISO and CEN (Vienna Agreement).

This third edition cancels and replaces the second edition (ISO 13408-1:2008) which has been technically revised. It also incorporates ISO 13408-1:2008/Amd 1: 2013.

The main changes are as follows:

— a complete restructuring of the document;

— inclusion of a diagram to explain the relationship between the ISO 13408 series and ISO 18362;

— revision of the normative references;

— alignment of definitions with ISO 11139:2018;

— positioning of the document to recognize current and future advances in sterile manufacturing technology, acknowledging that new approaches to aseptic processing are transforming classical aseptic processing;

— promotion of aseptic processing principles and the systematic implementation of quality risk management (QRM), including for aseptic process design, and microbiological contamination and particulate contamination control;

— provision of guidance for different types of aseptic processing, for example, manual processing systems to automated robotic processing systems;

— deletion of tables from the previous edition of this document referring to acceptance criteria for process simulation (media fill) qualification and requalification;

— encouraging adoption of advanced aseptic processing technologies and continuous process improvement to improve assurance of sterility;

— recognition that alternative or rapid microbiological methods (RMMs) provide timely microbiological data vital for process monitoring and control, and for product release;

— inclusion of a series of informative annexes providing guidance on defining an aseptic process, including risks to be considered, aseptic processing areas (APAs), classification of cleanrooms, aseptic process flow, closed systems and robotics, and qualification of a cleanroom clothing system.

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

Any feedback or questions on this document should be directed to the user's national standards body. A complete listing of these bodies can be found at www.iso.org/members.html.

Introduction

Wherever possible, health care products intended to be sterile should be terminally sterilized in their final sealed container by a terminal sterilization process, which has been validated to achieve a specified sterility assurance level (SAL). ISO/TC 198 has developed standards for terminal sterilization of health care products, for example (but not restricted to): the ISO 11137 series (radiation sterilization), ISO 17665-1 (moist heat sterilization), ISO 20857 (dry heat sterilization), ISO 11135 (ethylene oxide sterilization) and ISO 14160 (liquid chemical sterilization).

Where a health care product is intended to be sterile and cannot withstand terminal sterilization in its final container, aseptic processing provides an acceptable alternative for product manufacture.

ISO/TC 198 also developed ISO/TS 19930, which provides guidance on aspects of a risk-based approach to assuring sterility of terminally sterilized, single-use health care product that is unable to withstand processing to achieve maximally a 10^{-6} SAL.

Aseptic processing produces a sterile product in its final container by the assembly of component parts (e.g. product, container and container closure) that have been sterilized separately by validated and controlled processes suitable for each component part. Each of these assembly processes can introduce error that can result in product contamination. Furthermore, contamination can be introduced from the personnel, equipment or environment when the sterilized components are brought together to create the final product. It is important to control all possible sources of contamination so that the aseptic manufacturing process maintains sterility of previously-sterilized components during product filling or assembly, and sealing. Fundamentally, aseptic processing minimises the probability of a chance event of microbial contamination occurring. The rationale to use aseptic processing is product dependent and is not based solely on manufacturing considerations.

Examples of applications in which aseptic processing is 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 (e.g. vaccines).

Sterilization processes for product and components used as a prerequisite for aseptic processing are established and validated separately to aseptic processing activities.

Traditionally, aseptic processing has been carried out in cleanrooms and associated controlled environments to provide an environment in which the air supply, materials, equipment and operators are regulated to maintain sterility of previously-sterilized components. Advances in aseptic processing include systems that prevent the direct intervention of operators with open-product containers or exposed-product contact surfaces in the critical processing zone, for example, the use of fully enclosed barrier systems (e.g. isolators), automation and robotics. This can mean that a traditional cleanroom is not always appropriate for aseptic processing activities.

To provide assurance of sterility for an aseptically processed product, this document identifies three key activities in the development and operation of an aseptic process to reduce and control particulate and microbial contamination risks:

— process design;

— risk assessment;

— contamination control strategy (CCS).

An effective risk management approach is an essential tool for the development, validation and control of aseptic processing. Only when risks of particulate and microbiological contamination have been

identified, and where possible eliminated, or minimized and controlled, can an aseptic process be considered suitable for its intended purpose.

Controls for some infectious agents, e.g. protozoa or parasites, can require a multifaceted approach to assure component or product safety. These types of infectious agents are not considered in the ISO/TC 198 standards for terminal sterilization or aseptic processing. Guidance can be found in ISO 18362 applicable good manufacturing practice (GMP) regulations and the EDQM guide[28].

This document describes the fundamental requirements of aseptic processing regardless of the nature of the aseptic process, e.g. small-scale versus large-scale, open- versus closed-processing, single-use, disposable sterile systems, traditional cleanroom versus isolator systems, manual versus automated or robotic systems, autologous sterile products, processes with post-aseptic lethal treatments and processes using real-time microbiological monitoring. It does not, however, describe the requirements for other manufacturing processes upstream or downstream of aseptic processing activities. This document acknowledges the different geographical regulatory approaches to aseptic processing and recognizes that new approaches to aseptic processing are transforming classical aseptic processing. It recognizes that future improvements in aseptic processing rely on improved use of technology for both existing and new products, for example, sterile advanced therapy medicinal products.

To encourage adoption of suitable, advanced aseptic processing technologies and continuous process monitoring, this document introduces the concept of recognising efforts in risk-based process design, particulate and microbiological contamination control and risk management, to justify consideration of alternative approaches to demonstrating ongoing process effectiveness, for instance reduced frequency of requalification, sampling, or for real-time release of finished product.

Assurance of sterility for an aseptically processed product should not be confused with the term, ‘sterility assurance level (SAL)’. SAL is a mathematical extrapolation applicable only to a validated and controlled terminal sterilization process of known microbial lethality and which is delivered to each individual sealed unit of product subject to that process. Due to the variability and chance nature of occurrence of microbial contamination during aseptic processing, aseptic process simulation (APS) does not result in a mathematical probability of there being a single, viable microorganism in a contaminated unit, but rather results in an indication of what can happen in the routine processing of subsequent product batches (see ISO/TS 19930:2017, Clause 4).

This document specifies the requirements for general aspects of aseptic processing of health care products. Requirements and guidance for other processes often employed during aseptic processing are specified in ISO 13408-2 to ISO 13408-7, i.e. sterilizing filtration (ISO 13408-2), lyophilization (ISO 13408-3), clean-in-place (CIP) technologies (ISO 13408-4), sterilization in place (SIP) (ISO 13408-5), isolator systems (ISO 13408-6) and alternative processes for medical devices and combination products (ISO 13408-7).

ISO 18362 specifies the minimum requirements for, and provides guidance on, a risk-based approach for the processing of cell-based health care products (CBHPs) requiring control of viable and non-viable microbial contamination. It is applicable to CBHPs labelled ‘sterile’, as well as to those that are not labelled ‘sterile’. For aseptic processing of CBHPs to be labelled sterile, ISO 18362 refers normatively to this document and ISO 13408-7. A CBHP that incorporates non-sterile starting material cannot meet the ISO 11139 definition of aseptic processing, which amongst other things, requires the use of sterile product and components. ISO 18362, therefore also includes requirements and guidance for the processing of such products to reduce and control microbial contamination risks.

The relationship between the ISO 13408 series and ISO 18362 is shown in Figure 1.

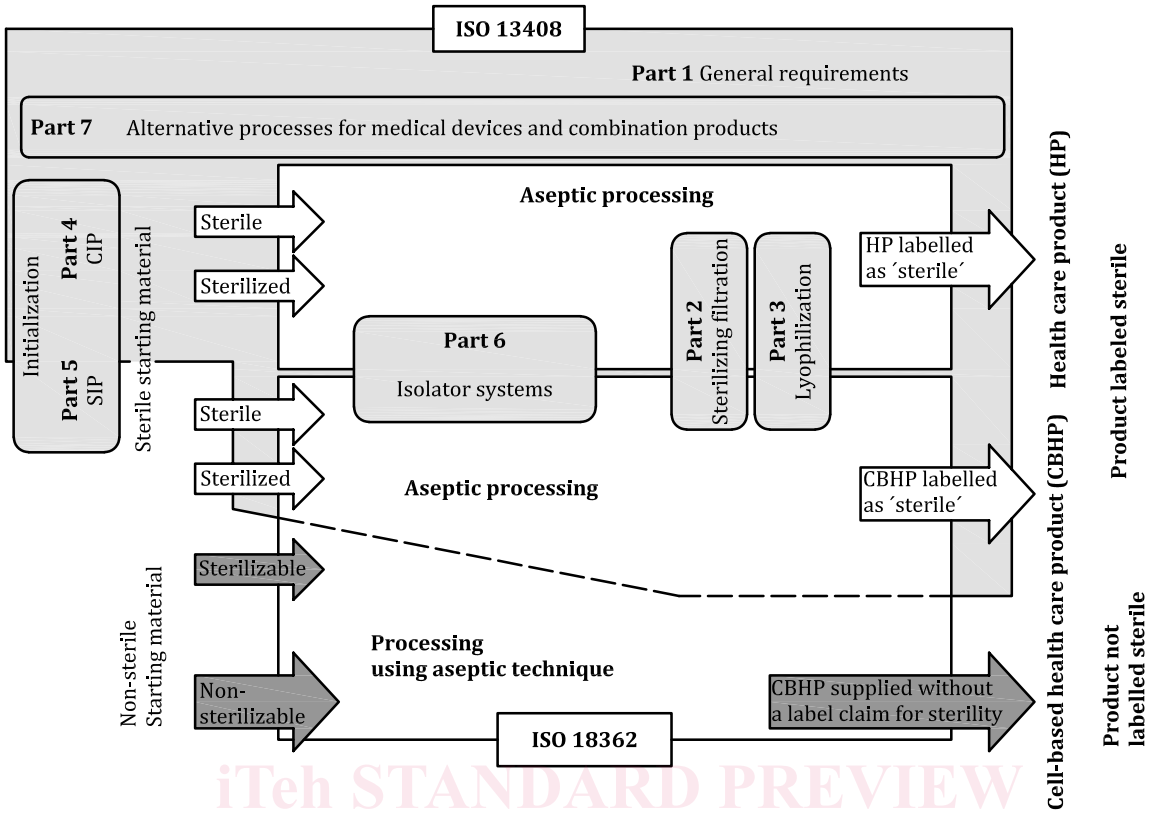

Figure 1 — Relationship between the ISO 13408 series and ISO 18362

Aseptic processing of health care products —

Part 1:
General requirements

1 Scope

This document specifies the general requirements for, and offers guidance on, processes, programs and procedures for development, validation and routine control of aseptic processing of health care products.

This document includes requirements and guidance relative to the overall topic of aseptic processing.

Specific requirements and guidance on various specialized processes and methods related to sterilizing filtration, lyophilization, clean-in place (CIP) technologies, sterilization in place (SIP) and isolator systems are given in the other parts of the ISO 13408 series.

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 13408-2, *Aseptic processing of health care products — Part 2: Sterilizing filtration*

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

ISO 14644-1:2015, *Cleanrooms and associated controlled environments — Part 1: Classification of air cleanliness by particle concentration*

ISO 14644-2, *Cleanrooms and associated controlled environments — Part 2: Monitoring to provide evidence of cleanroom performance related to air cleanliness by particle concentration*

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

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

3 Terms and definitions

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

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

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

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

3.1
action level
value from monitoring that necessitates immediate intervention

[SOURCE: ISO 11139:2018, 3.5]

3.2
advanced aseptic processing
aseptic processing (3.5) where direct intervention by personnel wearing cleanroom garments with open product containers or exposed product contact surfaces, in the critical processing zone, is not necessary or is not allowed

3.3
airlock
enclosure with interlocked doors designed to maintain pressure control between adjacent areas

[SOURCE: ISO 11139:2018, 3.10]

3.4
alert level
value from monitoring providing early warning of deviation from specified conditions

[SOURCE: ISO 11139:2018, 3.11]

3.5
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

[SOURCE: ISO 11139:2018, 3.14]

3.6
aseptic processing area
APA
facilities for *aseptic processing* (3.5), consisting of several zones

[SOURCE: ISO 11139:2018, 3.15]

3.7
bioburden
population of viable microorganisms on or in a product and/or sterile barrier system

Note 1 to entry: 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 materials, intermediates, other components and equipment.

[SOURCE: ISO 11139:2018, 3.23, modified – Note 1 to entry added.]

3.8
bio-decontamination
removal and/or reduction of biological contaminants to an acceptable level

[SOURCE: ISO 11139:2018, 3.27]

3.9
cleaning
removal of contaminants to the extent necessary for further processing or for intended use

[SOURCE: ISO 11139:2018, 3.46]

3.10
cleanroom clothing system
combination of reusable or single-use cleanroom garments and other accessories (e.g. undergarments, footwear, socks, head coverings, face masks, eye coverings, gloves) designed to minimize the risk of contamination during activities performed in *aseptic processing area (APA)* (3.6)

Note 1 to entry: The cleanroom clothing system can also protect personnel against other hazards (e.g. chemical, biological) depending on the products handled in the aseptic environment.

3.11
closed system
<*aseptic processing*> (3.5) means to prevent egress of hazardous agents and ingress of extrinsic contamination

[SOURCE: ISO 11139:2018, 3.50]

3.12
combination product
entity presented as a single health care product that physically, chemically, or otherwise brings together or mixes items regulated under separate legislation

Note 1 to entry: The entity could be a combination of medical device and medicinal product or biopharmaceutical product.

[SOURCE: ISO 11139:2018, 3.54]

3.13
correction
action to eliminate a detected nonconformity

Note 1 to entry: A correction can be made in advance of, in conjunction with or after a *corrective action* (3.14).

Note 2 to entry: A correction can be, for example, rework or regrade.

[SOURCE: ISO 9000:2015, 3.12.3]

3.14
corrective action
action to eliminate the cause of a nonconformity and to prevent recurrence

Note 1 to entry: There can be more than one cause for a nonconformity.

Note 2 to entry: *Corrective action* (3.14) is taken to prevent recurrence whereas *preventive action* (3.32) is taken to prevent occurrence.

Note 3 to entry: This constitutes one of the common terms and core definitions for ISO management system standards given in Annex SL of the Consolidated ISO Supplement to the ISO/IEC Directives, Part 1. The original definition has been modified by adding Notes 1 and 2 to entry.

[SOURCE: ISO 9000:2015, 3.12.2]

3.15
critical control point
point, step or procedure of an aseptic process at which control can be applied and is essential to prevent or eliminate a hazard or reduce it to an acceptable level

[SOURCE: ISO 5667-13:2011, 3.3, modified — Added "of an aseptic process" to the definition.]

3.16
critical processing zone
location within the aseptic processing area in which product and critical surfaces are exposed to the environment

[SOURCE: ISO 11139:2018, 3.67]

3.17
critical surface
surface that might come into direct contact with a product, including its containers or closures, posing a risk of contamination

[SOURCE: ISO 11139:2018, 3.68]

3.18
depyrogenation
process used to remove or deactivate pyrogenic substances to a specified level

Note 1 to entry: Pyrogenic substances include bacterial *endotoxins* (3.23).

[SOURCE: ISO 11139:2018, 3.77]

3.19
design qualification
process for verification that the proposed specification for the facility, equipment or system meets the expectation for the intended use

[SOURCE: ISO 11139:2018, 3.220.1]

3.20
direct support zone
protective area directly surrounding a critical processing zone

[SOURCE: ISO 11139:2018, 3.81]

3.21
disinfectant
chemical or combination of chemicals used for disinfection

[SOURCE: ISO 11139:2018, 3.82]

3.22
disinfection
process to inactivate viable microorganisms to a level previously specified as being appropriate for a defined purpose

Note 1 to entry: Level could be a log reduction or an absolute value.

[SOURCE: ISO 11139:2018, 3.84, modified — Added Note 1 to entry.]

3.23
endotoxin
lipopolysaccharide component of the cell wall of Gram-negative bacteria that is heat stable and elicits a variety of inflammatory responses in animals and humans

[SOURCE: ISO 11139:2018, 3.101]

3.24
gowning procedure
specified actions for putting on protective garments in a manner commensurate with the cleanliness level of the room

[SOURCE: ISO 11139:2018, 3.127]

3.25
health care product
medical device, including in vitro diagnostic medical device, or medicinal product, including biopharmaceutical

[SOURCE: ISO 11139:2018, 3.132]

3.26
indirect support zone
location within the aseptic processing area that protects the direct support zone

Note 1 to entry: The required grade of cleanliness of the indirect support zone depends on the aseptic processing technologies and activities performed.

[SOURCE: ISO 11139:2018, 3.142]

3.27
installation qualification
IQ
process of establishing by objective evidence that all key aspects of the process equipment and ancillary system installation comply with the approved specification

[SOURCE: ISO 11139:2018, 3.220.2]

3.28
isolator
<*aseptic processing*> (3.5) enclosure capable of preventing ingress of contaminants by means of physical separation of the interior from the exterior that is capable of being subject to reproducible interior bio-decontamination and where operators always remain separated from the interior of the enclosure by means of an absolute physical barrier

Note 1 to entry: If containment requirements apply (i.e. aseptic processing of hazardous materials) egress also has to be prevented.

[SOURCE: ISO 11139:2018, 3.149, modified — Note 1 to entry added.]

3.29
operational qualification
OQ
process of obtaining and documenting evidence that installed equipment operates within predetermined limits when used in accordance with its operational procedures

[SOURCE: ISO 11139:2018, 3.220.3]

3.30
packaging system
combination of a sterile barrier system and protective packaging

[SOURCE: ISO 11139:2018, 3.192]

3.31
performance qualification
PQ
process of establishing by objective evidence that the process, under anticipated conditions, consistently produces a product which meets all predetermined requirements

[SOURCE: ISO 11139:2018, 3.220.4]

3.32
preventive action
action to eliminate the cause of a potential nonconformity or other potential undesirable situation

Note 1 to entry: There can be more than one cause for a potential nonconformity.

Note 2 to entry: Preventive action is taken to prevent occurrence whereas *corrective action* (3.14) is taken to prevent recurrence.

[SOURCE: ISO 9000:2015, 3.12.1]