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Aseptic processing of health care products —

Part 6: Isolator systems

Traitement aseptique des produits de santé —

Partie 6: Systèmes isolateurs

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Foreword

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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).

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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*.

This second edition cancels and replaces the first edition (ISO 13408-6:2005), which has been technically revised. It also incorporates the Amendment ISO 13408-6:2005/Amd.1:2013. The main changes compared to the previous edition are as follows:

— changes to the Introduction;

— changes to the Scope;

— addition of the new Clause 5 "Basic principle of Isolator system";

— addition of risk management approach in Clause 6 "Isolator system specification";

— addition of new informative Annex A "Devices acting as transfer ports for portable and mobile equipment";

— addition of new informative Annex B "Isolator system – Explanation of terms used and flow of air and material";

— addition of new informative Annex C "Isolator system – Direct/indirect product contact surfaces "

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

A health care product that is labelled “sterile” is manufactured using suitably designed, validated and controlled processes. Wherever possible, it is terminally sterilized in its final, sealed container. When this is not possible, the product is aseptically processed.

Aseptic processing is an exacting and demanding discipline designed to maintain sterility through all stages of preparation, manufacturing, filling and sealing in final containers. It relies on a number of independent factors for prevention of recontamination of previously sterilized components during the assembly or filling of product into a final container.

An effective risk management system addressing aseptic processing design (including the use of barrier separation technology), validation and control, and which identifies, assesses, eliminates (where applicable) and controls contamination risks is a prerequisite to provide assurance of sterility for aseptically processed product.

Various separation systems exist to protect the critical processing zone of an aseptic processing area from non-viable particulate and microbiological contamination and to separate process operators from the critical processing zone.

These systems range from controlled airflow devices based on aerodynamic protection through to separation barriers that combine physical and aerodynamic protection to separate the external cleanroom environment from the critical processing zone, minimizing exposure of this zone to process operators and thereby reducing the opportunities for contamination during processing.

Isolator systems provide physical separation whilst facilitating operator intervention into the controlled processing environment under barrier conditions typically via sealed glove-sleeve systems that are physically connected with glove-ports to the isolator barrier screen(s). To establish a controlled environment, reduction of viable and non-viable particulates within isolators is achieved by validated and reproducible cleaning and bio-decontamination processes, principally achieved through the use of automated methods.

In addition to control of bio-contamination and non-viable particulates, isolator systems can include control features, which together with operating practices provide product containment to control cross contamination between process contaminants and product batches, and to manage risk to operators.

Aseptic processing of health care products —

Part 6:
Isolator systems

1 Scope

This document specifies the requirements for and provides guidance on the specification, selection, qualification, bio-decontamination, validation, operation and control of isolator systems related to aseptic processing of health care products and processing of cell-based health care products.

This document does not specify requirements for restricted access barrier systems (RABS).

This document does not supersede or replace national regulatory requirements such as Good Manufacturing Practices (GMPs) and/or compendia requirements that pertain in particular to national or regional jurisdictions.

This document does not specify requirements for isolators used for sterility testing; however, some of the principles and information in this document could be applicable to this application.

This document does not define biosafety containment requirements.

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 13408-1:2008, *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 13408-7, *Aseptic processing of health care products — Part 7: Alternative processes for medical devices and combination products*

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

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

ISO 18362, *Manufacture of cell-based health care products — Control of microbial risks during processing*

ISO/IEC 90003, *Software engineering — Guidelines for the application of ISO 9001:2015 to computer software*

ISO 11139, *Sterilization of health care products — Vocabulary of terms used in sterilization and related equipment and process standards*

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:

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

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

3.1
ancillary isolator equipment
equipment that can be attached to or detached from the isolator whilst ensuring separation of the internal and external environment

3.2
bio-decontamination
removal and/or reduction of biological contaminants to an acceptable level

[SOURCE: ISO 11139:2018, 3.27]

3.3
decontamination device
means used to deliver the agent for the decontamination process

3.4
isolator
<aseptic processing> 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]

3.5
isolator system
isolator (3.4) with transfer system(s), and *ancillary isolator equipment* (3.1)

[SOURCE: ISO 11139:2018, 3.150]

3.6
safety data sheet
SDS
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

[SOURCE: ISO 11139:2018, 3.239]

3.7
sterile barrier system
SBS
device acting as interface between the interiors of an isolator and *ancillary isolator equipment* (3.1) minimum package that minimizes the risk of ingress of microorganisms and allows aseptic presentation of the sterile contents at the point of use

[SOURCE: ISO 11139:2018, 3.272]

3.8
transfer port
interface between the interior of an *isolator* (3.4) and *ancillary isolator equipment* (3.1)

Note 1 to entry: See example figures in Annex A.

[SOURCE: ISO 11139:2018, 3.304]

3.9
transfer system
equipment and process that allows ingress and/or egress of material to an *isolator* (3.4) without compromising its environmental quality

4 Quality system elements

Quality elements as defined in ISO 13408-1:2008, Clause 4 shall be implemented to assure control over all activities affecting isolator systems.

5 Basic principle of isolator systems

5.1 General

An isolator system comprises a piece of equipment, or collection of equipment and control systems that provides a controlled environment suitable for aseptic processing that shall be separated from the operator and the surrounding environment using barrier technologies. An isolator system consists of an isolator, its utilities and its surrounding environment, and can include transfer systems and ancillary isolator equipment.

Movement of materials in and out of the isolator is a principal risk in maintaining the quality of the controlled environment. Materials are generally loaded into the isolator before bio-decontamination. After bio-decontamination of the isolator and during operation, ingress of materials to and egress from the isolator shall occur via transfer systems that maintain the quality of the controlled environment.

All components, materials and equipment parts shall be sterile/bio-decontaminated before being transferred into a bio-decontaminated isolator, unless bio-decontamination is conducted inside the device acting as a transfer port.

Isolator systems shall be classified into open and closed systems according to the construction and operation of their transfer systems.

Closed isolator systems shall exclusively incorporate transfer systems that separate the controlled environment from the surrounding environment during operation through the use of a solid physical barrier. A closed system shall restrict the movement of materials through the system to defined batches.

EXAMPLE 1 Autoclaves, pass-through chambers and rapid transfer port (RTP) containers.

Open isolator systems shall incorporate at least one transfer system that provides separation of the controlled environment from the surrounding environment through use of a fluid barrier. Open systems shall allow for the continuous movement of material through the isolator system.

EXAMPLE 2 Exit mouse holes, depyrogenation tunnels and electron beam systems.

NOTE 1 Portable and mobile equipment with aseptic transfer ports can allow for connection of an isolator to another aseptic environment during operation.

Specification of a transfer system shall consider the quality of the surrounding environment, whether the transfer system is for ingress and/or egress of items and the characteristics of the items to be transferred.

Isolator system design shall include protective measures for maintaining the quality of the controlled environment based on risk management.

Air supplied to the isolator and the transfer systems shall pass through a filter, usually a high efficiency particulate air (HEPA) or better, which shall render the air at a cleanliness level equivalent to the controlled environment. Surfaces of the isolator system shall be bio-decontaminated. Materials

entering the controlled environment shall possess a level of cleanliness equivalent to or better than the controlled environment.

Direct product contact surfaces of items within the controlled environment shall be sterilized. Operators shall access items located within the isolator system via a physical barrier (e.g. glove). Direct product contact surfaces of items within the controlled environment shall be sterilized by a validated process (see 8.2.1).

NOTE 2 Most isolators are operated under positive pressure conditions.

NOTE 3 See Annex B for an example layout of an isolator system.

5.2 Negative pressure isolators

A negative pressure isolator protects the operator and the surrounding environment by providing containment during the processing of hazardous or potent product. It can be used to assist in the management of product quality, containment, bio-contamination risk (where applicable) and safety issues. To effect containment, the critical work zone within the isolator shall be maintained at a negative pressure to the environment surrounding the isolator system. Risk management shall consider the impact of the quality of the surrounding environment, the transfer systems of the isolator and its degree of integrity or leak tightness in relation to the maintenance of the controlled environment.

6 Isolator system specification

6.1 General

The purpose of this activity is to define the isolator system for aseptic processing. The design specification is driven by the risk assessment of the intended use(s) of the isolator system.

6.2 Risk management

6.2.1 General

The following additional requirements to ISO 13408-1:2008, 5.2, and ISO 18362:2016 concerning risk management apply:

The risk management process shall consist of a continuous cycle of risk assessment, risk control and risk review. Risk assessment shall be used during the development, specification, validation and operation of the isolator system.

NOTE ICH Q9 and ISO 14971 can be a reference as they provide requirements and guidance on risk management for medicinal products and medical devices.

The risk assessment for the isolator system shall include, but is not limited to, the following:

a) surrounding environment;

b) materials of construction;

c) configuration including suitability for its intended purpose;

d) isolator;

e) transfer system (especially where mouse hole and/or portable mobile equipment exist);

f) operator interface;

g) air handling system;

h) operating control system;

i) internal environmental monitoring;

j) cleaning;

k) bio-decontamination;

l) maintenance;

m) the use of suitable safeguards to maintain assurance of sterility and achieve isolator operator safety objectives;

n) containment.

6.2.2 Negative pressure isolator systems

The risk assessment for a negative pressure isolator system shall address additional risks that are specific to this type of isolator system, including (but not restricted to), the risk that air containing microorganisms and particulates can enter the isolator system and contaminate product, as well as the risk that air and material exiting the isolator system can pose a contamination risk to the operator and surrounding environment. The rationale for the decision concerning the surrounding room classification shall be documented in the risk assessment.

6.3 User requirement specification

The specification details the design requirement of the isolator system according to the output of the risk assessment process.

This shall include but is not limited to:

a) physical size and weight constraints;

b) material transfer requirements;

c) the airflow requirements;

d) bio-decontamination requirements;

e) the requirements for monitoring and detection of contamination;

f) required operator interactions/interfaces;

g) materials of construction;

h) cleaning requirements;

i) maintenance requirements.

7 Design of isolator systems

7.1 General

7.1.1 ISO 14644-7 shall apply to the design of isolator systems.

For design principles of containment enclosures, see ISO 10648-1.

7.1.2 The documentation of the isolator systems design shall include:

— all necessary specifications;

— important operational parameters;