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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

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 13408-6 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*

— *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 by using appropriate and validated methods. When a health care product is intended to be sterile and cannot be terminally sterilized, aseptic processing provides an alternative. This applies to the aseptic preparation and filling of solutions, suspensions, emulsions, and solids, as well as to the aseptic handling, transfer and filling of those products which cannot be terminally sterilized.

Aseptic processing is an exacting and demanding discipline. It is essential that manufacturers make use of qualified/validated systems, adequately trained personnel, controlled environments and well-documented systematic processes to assure a sterile finished product.

Aseptic processing of health care products —

Part 6:
Isolator systems

1 Scope

This part of ISO 13408 specifies the requirements for isolator systems used for aseptic processing and offers guidance on qualification, bio-decontamination, validation, operation and control of isolator systems used for aseptic processing of health care products.

This part of ISO 13408 is focused on the use of isolator systems to maintain aseptic conditions; this may include applications for hazardous materials.

This part of ISO 13408 does not supersede or replace national regulatory requirements, such as Good Manufacturing Practices (GMPs) and/or compendial requirements that pertain in particular to 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 13408-1:1998, *Aseptic processing of health care products — Part 1: General requirements*

ISO 13408-4:—[1)], *Aseptic processing of health care products — Part 4: Clean-in-place technologies*

ISO 13408-5:—[1)], *Aseptic processing of health care products — Part 5: Sterilization in place*

ISO 14644-7:2004, *Cleanrooms and associated controlled environments — Part 7: Separative devices (clean air hoods, gloveboxes, isolators and mini-environments)*

ISO/IEC 90003, *Software engineering — Guidelines for the application of ISO 9001:2000 to computer software*

3 Terms and definitions

For the purposes of this document, the terms and definitions given in ISO 13408-1:1998 and the following apply.

3.1
bio-decontamination
removal of microbiological contamination or its reduction to an acceptable level

1) To be published.

3.2
design qualification
documented verification that the proposed design of the facilities, equipment or system is suitable for the intended use

3.3
isolator
sealed enclosure capable of preventing ingress of contaminants by means of total physical interior/exterior separation, and capable of being subject to reproducible interior bio-decontamination

NOTE 1 An isolator can range in size from a small box to a large room.

NOTE 2 Physical separation can be achieved by an absolute solid wall completely surrounding the entire interior, where any discontinuities in such wall are equipped to physically prevent ingress of contaminants. Examples of such physical protection include pass-through air locks for sterile or bio-decontaminated goods, (HEPA)-filtered (high efficiency particulate air-filter) or sterilized inflow air, and high flow rate of outflow air through a minimal-sized orifice. Operators always remain totally separated from the interior of an isolator by means of an absolute physical barrier.

3.4
isolator system
isolator with transfer system(s) and ancillary equipment used for aseptic processing

3.5
leak test
physical test to identify a quantifiable leakage rate under repeatable test conditions

3.6
material safety data sheet
document specifying the properties of a material, its potential hazardous effects for humans and the environment, and the precautions necessary to handle and dispose of the material safely

3.7
risk assessment
overall process comprising a risk analysis and a risk evaluation

[ISO 14971:2000, 2.15]

3.8
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, glove boxes, isolators and mini-environments

[ISO 14644-7:2004, 3.17]

EXAMPLES For the aseptic processing industry: mouse-hole and cooling zone.

3.9
surrounding environment
specific, characterized and controlled area in which an isolator system has been qualified and is operated

3.10
transfer device
mechanism to effect movement of material into or out of separative devices while minimizing ingress or egress of unwanted matter

[ISO 14644-7:2004, 3.18]

EXAMPLES Transfer isolator, transfer container, and transfer system.

3.11
transfer port
interface between the interiors of an isolator and a transfer device that can be attached to and detached from this equipment without any ingress or egress of unwanted matter

3.12
transfer system
system allowing ingress and/or egress of material to an isolator without compromising the environmental quality of the critical processing zone

EXAMPLES Autoclave, oven, depyrogenation tunnel, freeze dryer.

3.13
worst-case conditions
set of conditions which represent the highest challenge to product integrity and safety which will be accepted during validation and routine production

4 Quality system elements

4.1 General

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

4.1.2 Documented procedures for each phase of the development, validation, routine monitoring and control of isolator systems 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 Management responsibility

4.2.1 The responsibilities and authority for implementing and performing the procedures described in this part of ISO 13408 shall be specified.

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

4.3 Design control

The design of isolator systems shall be undertaken in accordance with a documented plan. At defined stages design reviews shall be planned, conducted and documented.

4.4 Measuring instruments and measuring systems

4.4.1 A documented system shall be specified for the calibration of all measuring instruments or measuring systems.

4.4.2 Procedures for control of all measuring instruments or measuring systems designated as non-conforming and for corrective action shall be specified.

4.4.3 The accuracy and tolerance of the measuring instrument shall be justified for the process to be measured.

5 Design of isolator systems

5.1 General

5.1.1 For the design of isolator systems, ISO 14644-7 shall apply.

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

5.1.2 The design of isolator systems shall be justified and documented to establish important operational parameters or key specifications. This shall include a risk assessment to identify critical steps.

NOTE 1 Equipment and material transfer is one of the greatest challenges to the isolator processes.

NOTE 2 In applications which require both aseptic conditions and protection of the operator, such as the manufacture of bio-hazard, cytotoxic or radioactive products, the design of the isolator system will address pressure (negative or positive) and location and integrity of the isolator system. The design, based on risk assessment, typically considers safety-specific requirements for location and surrounding environment.

5.2 Types of isolators

5.2.1 Closed

Closed isolators are operated to exclude exterior contamination from air or other sources. Air from the room shall first pass through a filter, usually a HEPA, before entering the isolator. All materials used in the isolator shall be decontaminated or sterilized. The operator is located exterior to the isolator and works indirectly with material located on the interior of the isolator. Closed isolators shall remain closed during the ingress/egress of materials during operation.

5.2.2 Open

Open isolators are similar to closed isolators, except that they shall allow for the continuous or semi-continuous ingress/egress of materials during operation. Design considerations shall include protective measures for the integrity of the isolator's interior environment. Openings shall be protected by unidirectional air flow and/or air over-pressure.

5.3 Materials of construction

5.3.1 Materials used in the construction, including gasket materials, fans, ventilation systems, piping, viewing windows, and associated fittings shall be chemically and mechanically compatible with the intended processes, process materials, and application. The materials shall be compatible with the cleaning and bio-decontaminating agents and be cleanable. Construction materials shall be considered for protection against corrosion, degradation, and heat/fire resistance, where appropriate. Where appropriate, materials used shall be checked for thermal characteristics, sorption and out-gassing properties. Viewing window (panel) materials shall remain transparent and resistant to degradation and shall allow for proper interior lighting.

5.3.2 Flexible walls should be thick enough to resist puncture and flexible enough to allow the operator to work safely and efficiently.

5.4 Air-handling system

5.4.1 Air change rate

The rate of air change shall be appropriate for the specific application. The rate shall be sufficient to ventilate the isolator to avoid the build-up of particulates, contaminants and heat.

NOTE An increased rate of air changes is typically used to aid in the removal of the bio-decontaminating agent in a timely manner.

5.4.2 Air flow pattern

The air flow pattern shall be demonstrated to maintain the isolator's interior environmental quality.

5.4.3 Temperature/humidity

Temperature and humidity shall be controlled within minimum and maximum ranges appropriate for the specific process for which the isolator system is being used.

NOTE These ranges can be different depending on the stage of use (e.g. operational, bio-decontamination, etc.).

5.4.4 Particulate air specifications

The air quality shall meet the predefined user requirement specifications and shall be (HEPA)-filtered (as a minimum).

Generally, the critical processing zone is classified as ISO Class 5 (particles equal to and larger than 0,5 µm), according to ISO 14644-1:1999, at rest and in operation.

In some situations, filters in series can be appropriate.

5.4.5 Recirculation of air

Air to be recirculated in the isolator shall pass through a HEPA filter (as a minimum) before re-entering the isolator.

Exhaust air is typically (HEPA)-filtered.

5.4.6 Pressure differentials

The pressure differentials shall be monitored, at least during operation and bio-decontamination. An alarm or other warning device shall notify the operator when the differential pressure is out of range.

Most isolators are operated under positive pressure conditions. A negative pressure differential is usually applied for isolators used for hazardous material.

5.4.7 Filter maintenance

Air filters shall be subject to routine maintenance. Filters shall be changed on a regular basis. See 9.6.2.

5.5 Operator interface

5.5.1 Isolator gloves/sleeves

5.5.1.1 Isolator gloves and sleeves shall be designed to allow for flexibility and easy movement for the operator while working, but shall still be resistant to tear and puncture. The isolator gloves/sleeves shall be compatible with the cleaning and bio-decontamination agents. Isolator gloves/sleeves shall be checked regularly based on frequency of use to determine if their integrity has been compromised.

5.5.1.2 To minimize the possibility of a tear or hole allowing contamination into the isolator system and for hygienic reasons, the operator may use double gloving. Double gloving involves wearing gloves under the isolator gloves.

5.5.1.3 If a second pair of gloves is worn over the isolator gloves for mechanical protection, they should be of suitable material and sterilized according to validated processes.