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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.

5.5.2 Suits/half-suits

5.5.2.1 Suits/half-suits shall be designed to allow for comfort, flexibility and easy movement for the operator while working. They shall be resistant to tear and puncture. The materials used to make the suits/half-suits shall be compatible with the cleaning and bio-decontamination agents. Suits/half-suits, including gloves, shall be checked regularly based on frequency of use to determine if their integrity has been compromised.

5.5.2.2 The suits/half suits should be cleaned, not only on the exterior surface of the suit (exposed to the interior of the isolator), but also on the interior surface for hygienic reasons.

5.5.3 Access to the isolator

5.5.3.1 When designing an isolator, consideration shall be given to how materials (including in-process product), equipment, and other items enter and exit the isolator.

Generally, items enter/exit through transfer systems (e.g. autoclave, oven, depyrogenation tunnel, freeze-dryer) and/or transfer ports.

5.5.3.2 If required, access ports shall be provided to allow the monitoring equipment to be used during the operation of the isolator without the entire piece of equipment being placed into the isolator. These ports shall be kept to a minimum number.

5.6 Ancillary equipment

5.6.1 Portable and mobile equipment

5.6.1.1 Portable and mobile equipment to be used with the isolator shall be designed to be compatible with the required cleaning, sterilization, and/or bio-decontamination procedures used for the preparation and staging of in-process product, supplies, goods and other items that need to be aseptically transferred to the isolator.

Portable and mobile equipment includes transfer devices that can be docked to the isolator by use of transfer ports.

5.6.1.2 Waste containers shall be designed in such a way that the waste does not re-enter the isolator and that the interior isolator environment is not compromised when the waste container is removed.

5.6.2 Transfer ports

5.6.2.1 Interface transfer ports shall allow the easy attachment/docking of portable or mobile equipment to the isolator without compromising the isolator's interior environment. The ports shall provide an airtight seal against the surrounding environment.

NOTE Transfer ports can be contaminated by exposure to the surrounding environment.

5.6.2.2 Transfer ports should be disinfected/cleaned before the transfer process of materials occurs. Operators should aseptically move the materials through the transfer port to avoid possible contamination and damage to the port.

6 Facility requirements

6.1 Surrounding room classification

6.1.1 The room in which the isolator system is located shall have restricted access and shall be maintained as a clean zone.

Typically an ISO Class 8, in accordance with ISO 14644-1:1999 or better, is used, based on the application of the isolator system. Special considerations for the room (surrounding environment) apply for negative pressure isolators.

Temperature and humidity of the room affect the bio-decontamination process of the isolator unless these factors are specifically controlled by the isolator and/or by the surrounding room.

6.1.2 Isolator systems dedicated to sterility testing may be located in a non-classified room with restricted access.

6.2 Process utilities

All utility connections to the isolator shall be designed to prevent contamination during connection and use. Sterilizing filters shall be used for all fluids and compressed gases. Filters shall be integrity tested on a regular basis and changed accordingly. Vacuum systems, when existing, shall be equipped to prevent backflow. All process utilities access ports shall be tested for leaks and backflow. Electrical requirements in the room shall be based on those of the isolator and ancillary equipment.

7 User requirements

7.1 Product/process application

The product/process application shall be developed before designing the isolator. The process conditions shall be defined so that the use of the isolator and the ancillary equipment will produce a reliable and safe product. Risk assessment shall be conducted to determine potential process control or equipment factors that could compromise the quality of the isolator system or of the product.

7.2 Ergonomics

Isolators, operator interfaces, and ancillary equipment shall be designed to allow for necessary access to all working areas without compromising the quality of the product, the safety and comfort of the operator, or the integrity of the isolator.

NOTE Mock-up models of the isolator and other equipment, or the use of computer simulations, can aid in ergonomic evaluations.

7.3 Cleaning

7.3.1 General

All pre-determined, internal surfaces of the isolator shall be cleaned at a defined frequency. Cleaning processes shall be specified and validated to achieve a known, quantified, reproducible reduction of residues from worst-case locations.

7.3.2 Clean-in-place

When cleaning surfaces in contact with the product using a clean-in-place (CIP) process, ISO 13408-4 applies.

An automated CIP procedure is preferred over a manual one to improve process reliability and personnel safety.

7.3.3 Manual cleaning

Where manual cleaning of the isolator and equipment is performed, it shall be done according to a validated cleaning method. It is preferred to undertake cleaning without dismantling the isolator.

7.3.4 Cleaning agent

7.3.4.1 The cleaning agent(s) shall be compatible with all materials (including gloves, gaskets, interior surfaces, etc.) used in the isolator system. Agent residues shall be removed to acceptable levels before initiating bio-decontamination. For selection of the most suitable cleaning agent(s), at least the following considerations shall be addressed:

a) physical and chemical characteristics of potential cleaning agent(s);

b) compatibility with the isolator system;

c) physical and chemical characteristics of agent residual substances to be removed;

d) ability to remove residual cleaning agent(s); and

e) cleaning efficacy.

7.3.4.2 Any remaining residuals of cleaning agent(s) can be removed, for example, by using water of defined quality (e.g. distilled water, water for injection).

7.4 Bio-decontamination

7.4.1 General

7.4.1.1 The bio-decontamination process shall be developed and validated for the isolator and any transfer device(s).

7.4.1.2 For the development and validation of bio-decontamination processes, at least the following items shall be considered:

a) previous cleaning and drying of interior isolator surfaces;

b) appropriate choice/selection of biological indicator (BI) or inoculated carrier;

c) appropriate choice/selection of chemical indicator;

d) temperature tolerances;

e) humidity tolerances and dew point;

f) exposure time, concentration, and internal isolator pressure;

g) accessibility and uniform distribution of bio-decontaminating agent to all surfaces (especially gloves, suits, and choice/selection of sleeves);

h) biocontamination;

i) predetermined loading pattern of additional material.

7.4.2 Sterilization-in-place

When sterilizing surfaces in contact with the product using a sterilization-in-place process, ISO 13408-5 applies.

7.4.3 Selection of bio-decontamination agent

7.4.3.1 The bio-decontamination agent selected shall be compatible with the materials of the isolator, the cleaning agent, the process application, the volume and configuration of the load, and the biocontamination of

the internal isolator environment. Personnel safety shall be assessed. Material safety data sheets (MSDS) shall be available in the immediate area where the bio-decontamination agent is being used.

NOTE The most common bio-decontamination agent is vapour-phase hydrogen peroxide. Other examples are peracetic acid, chlorine dioxide, and ozone.

7.4.3.2 Other safety issues to be assessed can include, but are not limited to:

a) installation of a specific flammable cabinet for hydrogen peroxide;

b) use of a self-contained breathing apparatus;

c) availability of personal protective equipment (goggles, gloves, ear protection, etc.);

d) emergency eye-wash station installed in the immediate area;

e) warning signs for the specific bio-decontamination agent in use;

f) warning signs about ambient noise level posted outside the room;

g) availability of a fire extinguisher installed in the room.

7.4.4 Bio-decontamination agent generation and testing

7.4.4.1 The identity, composition, and concentration of the bio-decontamination agent shall be verified. The concentration of the agent shall be verified during the bio-decontamination process, when possible. Equipment for dispersing bio-decontamination agents (generators) are considered independent equipment and each shall be qualified.

NOTE The bio-decontamination agent is typically provided to the isolator through use of a generator (e.g. liquid hydrogen peroxide to vapour-phase hydrogen peroxide).

7.4.4.2 Concentration and distribution of the bio-decontamination agent can be determined by use of chemical indicators or other validated methods.

7.4.5 Bio-decontamination parameters

7.4.5.1 The internal surfaces of the isolator shall be exposed to the bio-decontamination agent. Critical parameters shall be identified during validation and then monitored during routine processing. These shall include, but are not limited to:

a) internal gas concentration;

b) isolator temperature;

c) internal humidity and pressure;

d) consumption of bio-decontamination agent;

e) room temperature and humidity;

f) air flow;

g) process phase times.

Ideally, all of the bio-decontamination agent enters through the inlet duct and exits through the exhaust filters.

7.4.5.2 Fans or other methods can be used to distribute the agent throughout the isolator.

7.4.5.3 An alarm system shall be activated to alert the operator when a parameter is out of specification.

7.4.6 Aeration and residue limits

7.4.6.1 Once the exposure period is complete, the bio-decontamination agent shall be removed from the isolator system using mechanical methods or by flushing the isolator system with fresh, (HEPA)-filtered air. The aeration time shall be validated and be based on the residue limits. Permeation into material could be possible and should be considered when establishing the aeration time.

7.4.6.2 Residues of the bio-decontaminating agent shall be removed to an acceptable level after bio-decontamination.

7.4.7 Spore log reduction

During validation, the bio-decontamination process shall be challenged with biological indicators (BIs) and/or inoculated carriers. The BIs and/or inoculated carriers shall contain a known spore population and the organism used shall have a defined resistance to the bio-decontamination agent. The user shall establish a specified spore log reduction value. A sufficient number of BIs and/or inoculated carriers shall be used to prove statistical reproducibility and adequate distribution of the agent. The target of a three- to six-log spore reduction shall be applied to bio-decontamination processes of non-product contact surfaces. For product contact surfaces, a six-log spore reduction shall be achieved.

7.4.8 Surface bio-decontamination of goods

7.4.8.1 Surface bio-decontamination of goods shall be performed to minimize the likelihood of biocontamination entering the isolator and compromising the internal environmental integrity. It shall be demonstrated that the bio-decontamination agent does not adversely affect the packaging and that the goods are unaffected by the process. The bio-decontamination process shall not be used as a sterilisation process for supplies or product.

7.4.8.2 In specific applications, parts of equipment can be bio-decontaminated *in situ*.

7.4.9 Surface bio-decontamination of container with sterile product

For containers with sterile product, it shall be confirmed that the bio-decontamination process does not affect the contents. It shall be demonstrated that there is no penetration of the bio-decontamination agent into these containers.

8 Validation

8.1 General

8.1.1 The validation of isolator systems shall include design, installation, operational and performance qualification.

8.1.2 Written protocol(s) shall be established, and shall specify how qualification and validation are to be conducted. Protocol(s) shall be reviewed and approved and shall specify critical steps and acceptance criteria. Qualification of equipment design, installation, operation and performance qualification shall be performed in accordance with the approved protocol(s). Any deviation from the protocol(s) shall be documented, investigated and resolved.

This protocol can be part of an overall validation master plan for the process.

NOTE See definitions in ISO/TS 11139.

8.2 Design qualification

Isolator systems shall be designed for their intended use based on user requirement specifications. The appropriateness of the system design, process design, and the design of all facilities, equipment, and materials used shall be confirmed at the first stage of validation to meet the requirement for the intended use.

Design qualification should be emphasized in validation activities as specified (e.g. in ISO 9001:2001).

8.3 Installation qualification

8.3.1 General

Installation qualification shall be performed to demonstrate that the isolator system with its ancillary items (equipment) has been supplied and installed in accordance with its specification. This shall include all equipment used to run the isolator system and its surrounding environment.

8.3.2 Installation

8.3.2.1 The installation qualification shall include, but not be limited to, the following:

a) compliance with design specification;

b) completeness of equipment and devices;

c) filter elements;

d) material of construction;

e) condition of inner surfaces;

f) piping system;

g) material of gloves;

h) operators manual;

i) sufficient lighting;

j) certificates of the supplier for measurement devices;

k) compliance with the mock-up model;

l) automated systems;

m) completeness of drawings;

n) energy supply in cases of power failure.

8.3.2.2 It shall be verified that

a) the location of the equipment conforms to its specification;

b) the equipment is installed in accordance with installation instructions;

c) the services to the equipment conform to their specification.

8.3.2.3 The calibration of all measuring instruments critical to the process (including any test instruments) used for monitoring, controlling, indicating or recording shall be confirmed. Alternatively, calibration can be confirmed at the commencement of operational qualification.

8.3.2.4 Computerized control systems and associated software, when installed, shall be qualified to demonstrate conformance to ISO/IEC 90003 or other relevant guidelines for the manufacture of the product.

8.4 Operational qualification

8.4.1 Operational qualification shall be conducted after installation qualification.

8.4.2 The operation of each component of the system that is critical to product quality shall be assessed to demonstrate that the equipment operates within predetermined limits when used in accordance with its operational procedures. The evidence obtained shall be documented.

8.4.3 The operating procedures for the isolator system shall be verified to meet established requirements. These operating procedures shall include, but not be limited to, the following:

a) step-by-step operating instructions;

b) differential air pressure;

c) air flow rate;

d) air flow pattern;

e) distribution of bio-decontamination agent (e.g. visual fog test);

f) temperature;

g) relative humidity;

h) bio-decontamination procedures;

i) environmental monitoring (viable and non-viable particles);

j) maintenance including calibration and cleaning procedures;

k) residues of bio-decontamination agent;

l) component transfer systems;

m) integrity of installed HEPA, ULPA (ultra low penetration air filter), membrane filters;

n) integrity/leak rate of the isolator;

o) integrity of gloves, sleeves, suits;

p) method by which a failure to attain the operating parameters can be identified, and the actions to be taken.

8.4.4 The consequences of failure in the results from measuring instruments fitted to the isolator system (control, indication, and recording) shall be determined.

8.5 Performance qualification

8.5.1 General

8.5.1.1 After operational qualification, the entire system shall be subjected to performance qualification. Evidence shall be obtained and documented 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.

8.5.1.2 During performance qualification, procedures shall be established and validated for cleaning/CIP, bio-decontamination and aseptic processing.

8.5.1.3 Other points that should be addressed include:

a) minimum and maximum loading configurations;

b) hole-size detectability study;

c) alert/action limits established for air exchange, pressure, particles, viables, etc;

d) exposure level to the bio-decontamination agent inside the room where the isolator system is located qualified during bio-decontamination cycles.

8.5.2 Cleaning

8.5.2.1 Cleaning processes for the isolator system shall be specified and validated to achieve a known, quantified, reproducible reduction of worst-case levels of representative foreign matter from worst-case sites. The cleaning method(s), frequency, equipment, agent(s) and materials used shall be documented.

8.5.2.2 A validated drying procedure shall be used prior to bio-decontamination where the effectiveness of the bio-decontaminating agent could be affected by the presence of moisture. A maximum time limit between cleaning and bio-decontamination shall be specified.

8.5.3 Bio-decontamination

8.5.3.1 The validation process for cycle development shall include a temperature study, vapour distribution study, biological challenge and aeration. The bio-decontamination process shall be specified and validated to achieve a reproducible specified log reduction of a microbiological spore challenge organism of known resistance to the bio-decontamination agent used. Reproducibility shall be confirmed in three consecutive, acceptable validation studies. The spore challenge locations during validation shall be representative of all locations into which the agent might have difficulty penetrating, or be where a critical processing parameter (e.g. temperature) might be difficult to attain. Validation shall include mapping of those parameters that are critical to the bio-decontamination process. Aeration and reduction of the agent to acceptable levels shall be demonstrated.

8.5.3.2 Chemical and microbiological tests shall be performed to validate the bio-decontamination processes for wrapped goods and containers with sterile product. This should be performed to demonstrate that the process does not affect the wrapped goods or that the agent does not penetrate the containers. It shall be demonstrated that the growth-promoting characteristics of the nutrient medium/media employed are not affected by the bio-decontamination agent.

8.5.3.3 All components, materials and equipment parts shall be sterile/decontaminated before being transferred or conveyed into a bio-decontaminated isolator.