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Republic of Ireland

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I.S. EN ISO 13408-1 (2011) (English): Aseptic processing of health care products - Part 1: General requirements [Authority: The European Union Per Directive 90/385/EEC]

ISO INSIDE



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NSAI
Standards

Irish Standard
I.S. EN ISO 13408-1:2011

Aseptic processing of health care products - Part 1: General requirements (ISO 13408-1:2008)

I.S. EN ISO 13408-1:2011

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English Version

Aseptic processing of health care products - Part 1: General requirements (ISO 13408-1:2008)

Traitement aseptique des produits de santé - Partie 1:
Exigences générales (ISO 13408-1:2008)

Aseptische Herstellung von Produkten für die
Gesundheitsfürsorge - Teil 1: Allgemeine Anforderungen
(ISO 13408-1:2008)

This European Standard was approved by CEN on 10 June 2011.

CEN members are bound to comply with the CEN/CENELEC Internal Regulations which stipulate the conditions for giving this European Standard the status of a national standard without any alteration. Up-to-date lists and bibliographical references concerning such national standards may be obtained on application to the CEN-CENELEC Management Centre or to any CEN member.

This European Standard exists in three official versions (English, French, German). A version in any other language made by translation under the responsibility of a CEN member into its own language and notified to the CEN-CENELEC Management Centre has the same status as the official versions.

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Foreword

The text of ISO 13408-1:2008 has been prepared by Technical Committee ISO/TC 198 "Sterilization of health care products" of the International Organization for Standardization (ISO) and has been taken over as EN ISO 13408-1:2011 by Technical Committee CEN/TC 204 "Sterilization of medical devices" the secretariat of which is held by BSI.

This European Standard shall be given the status of a national standard, either by publication of an identical text or by endorsement, at the latest by December 2011, and conflicting national standards shall be withdrawn at the latest by December 2011.

Attention is drawn to the possibility that some of the elements of this document may be the subject of patent rights. CEN [and/or CENELEC] shall not be held responsible for identifying any or all such patent rights.

This document supersedes EN 13824:2004.

This document has been prepared under a mandate given to CEN by the European Commission and the European Free Trade Association, and supports essential requirements of EU Directives.

For relationship with EU Directives, see informative Annexes ZA, ZB, or ZC, which are integral parts of this document.

According to the CEN/CENELEC Internal Regulations, the national standards organizations of the following countries are bound to implement this European Standard: Austria, Belgium, Bulgaria, Croatia, Cyprus, Czech Republic, Denmark, Estonia, Finland, France, Germany, Greece, Hungary, Iceland, Ireland, Italy, Latvia, Lithuania, Luxembourg, Malta, Netherlands, Norway, Poland, Portugal, Romania, Slovakia, Slovenia, Spain, Sweden, Switzerland and the United Kingdom.

Endorsement notice

The text of ISO 13408-1:2008 has been approved by CEN as a EN ISO 13408-1:2011 without any modification.

Annex ZA (informative)

Relationship between this European Standard and the Essential Requirements of EU Directive 90/385/EEC on Active Implantable Medical Devices

This European Standard has been prepared under a mandate given to CEN by the European Commission and the European Free Trade Association to provide a means of conforming to Essential Requirements of the New Approach Directive 90/385/EEC on active implantable medical devices.

Once this standard is cited in the Official Journal of the European Union under that Directive and has been implemented as a national standard in at least one Member State, compliance with the clauses of this standard given in Table ZA.1 confers, within the limits of the scope of this standard, a presumption of conformity with the corresponding Essential Requirements of that Directive and associated EFTA regulations.

Table ZA.1 — Correspondence between this European Standard and Directive 90/385/EEC

Clauses of this EN	Essential Requirements (ERs) of Directive 90/385/EEC	Qualifying remarks/Notes
4,5,6,7,8,9,10,11,12	7	This relevant Essential Requirement is only partly addressed in this European Standard

WARNING — Other requirements and other EU Directives may be applicable to the product(s) falling within the scope of this Standard.

Annex ZB (informative)

Relationship between this European Standard and the Essential Requirements of EU Directive 93/42/EEC on Medical Devices

This European Standard has been prepared under a mandate given to CEN by the European Commission and the European Free Trade Association to provide a means of conforming to Essential Requirements of the New Approach Directive 93/42/EEC on medical devices.

Once this standard is cited in the Official Journal of the European Union under that Directive and has been implemented as a national standard in at least one Member State, compliance with the clauses of this standard given in Table ZB.1 confers, within the limits of the scope of this standard, a presumption of conformity with the corresponding Essential Requirements of that Directive and associated EFTA regulations.

Table ZB.1 — Correspondence between this European Standard and Directive 93/42/EEC

Clauses of this EN	Essential Requirements (ERs) of Directive 93/42/EEC	Qualifying remarks/Notes
4,5,6,7,8,9,10,11,12	8.3	This relevant Essential Requirement is only partly addressed in this European Standard
4,5,6,7,8,9,10,11,12	8.4	

WARNING — Other requirements and other EU Directives may be applicable to the product(s) falling within the scope of this Standard.

Annex ZC (informative)

Relationship between this European Standard and the Essential Requirements of EU Directive 98/79/EC on *in vitro* diagnostic medical devices

This European Standard has been prepared under a mandate given to CEN by the European Commission and the European Free Trade Association to provide a means of conforming to Essential Requirements of the New Approach Directive 98/79/EC on *in vitro* diagnostic medical devices.

Once this standard is cited in the Official Journal of the European Union under that Directive and has been implemented as a national standard in at least one Member State, compliance with the clauses of this standard given in Table ZC.1 confers, within the limits of the scope of this standard, a presumption of conformity with the corresponding Essential Requirements of that Directive and associated EFTA regulations.

Table ZC.1 — Correspondence between this European Standard and Directive 98/79/EC

Clauses of this EN	Essential Requirements (ERs) of Directive 98/79/EC	Qualifying remarks/Notes
4,5,6,7,8,9,10,11,12	B.2.3	This relevant Essential Requirement is only partly addressed in this European Standard
4,5,6,7,8,9,10,11,12	B.2.4	

WARNING — Other requirements and other EU Directives may be applicable to the product(s) falling within the scope of this Standard.

I.S. EN ISO 13408-1:2011
**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 20857¹⁾, *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**depyrogenation**

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.

5 Aseptic process definition

5.1 General

5.1.1 Aseptic processing is an activity composed of many unit operations that need to be effectively combined to maintain sterility.

The purpose of the aseptic process definition is to obtain a comprehensive understanding of the integration of the different elements required. Typical elements are given in Annex B.

5.1.2 A justification for the use of aseptic processing shall be documented.

NOTE The preferred option is terminal sterilization in the final container.

5.1.3 Based on the aseptic processing definition an assessment of aseptic processing risks shall be conducted. Methods and procedures to control these risks shall be described and implemented (see 5.2). Residual risks shall be justified.

5.1.4 The aseptic process definition shall be reviewed after stated intervals or whenever a change occurred that might impact the product or following a significant event (e.g. batch non-sterility).

5.1.5 The aseptic process definition shall consider the complete process and give a rationale describing how each element involved in processing contributes to the attainment and maintenance of a sterile product.

NOTE For requirements for aseptically manufactured medical devices to be designated "sterile", see also ISO 15223 and national or regional requirements given in, for example, EN 556-2 or ANSI/AAMI ST67:2003.

5.2 Risk management

5.2.1 General

5.2.1.1 A risk management process shall be carried out, applying ISO 14971 and/or ICH Q9.

Risks associated with the aseptic process shall be identified, assessed and controlled in order to establish acceptance criteria for all elements of the aseptic process definition.

Compliance with the requirements as defined in Clause 6 *et seq.* and/or regulatory documents can be used to demonstrate acceptability of the implemented risk control.

NOTE While this part of ISO 13408 is primarily concerned with microbiological contamination issues, there are other contamination risks that are relevant (e.g. endotoxin, particulate and chemical contamination).

5.2.1.2 The risk management strategy shall take into account the nature of the product and its intended clinical use. Microbiological risk management should follow the following four stages:

- a) identification of contamination risks;
- b) assessment of contamination risks;
- c) monitoring and detection of contamination;
- d) prevention of contamination.

The measures taken to control the risks shall be proportionate to perceived risks.

Specific risks shall be taken into account and the aseptic process shall be designed with due consideration of all identified factors (see Table C.1 for guidance).

5.2.2 Identification of microbiological contamination risks

Each unit operation shall be assessed for risks that might compromise the quality of the product. Factors to be considered shall include:

- a) origins of contamination:
 - 1) contamination sources;
- b) routes of contamination:
 - 1) inappropriate aseptic technique;
 - 2) ability of microorganisms to cross a segregation barrier;
 - 3) microorganisms being transported across a processing zone;
- c) proliferation of contamination:
 - 1) conditions conducive to microbial proliferation;
- d) contamination detection and removal:
 - 1) detection of microbial contamination;
 - 2) adequate microbial removal.

NOTE Examples of high risk procedures include handling by personnel, of sterile product or equipment and exposure of product or critical surfaces to the environment. The extent of the risk depends on the level of segregation between personnel and the item and the degree of control over the microbiological quality of the environment.

5.2.3 Assessment of contamination risks

Any identified contamination risks shall be assessed regarding the potential effect on product quality. This assessment should include the evaluation of relevant process or monitoring data. Measures to minimize risks shall be prioritized based on the risk assessment.

NOTE Established procedures such as Failure Mode and Effect Analysis (FMEA) or Hazard Analysis of Critical Control Points (HACCP) can be applied in order to identify risks.

5.2.4 Monitoring and detection of contamination

5.2.4.1 There shall be procedures for monitoring aseptic processing.

5.2.4.2 The procedures for monitoring the process shall not be limited to the isolation and identification of microbial contamination. Monitoring of processes shall also include particulates and endotoxins where relevant claims are made. Other contamination risks not specifically associated with aseptic processing are not addressed in this part of ISO 13408.

NOTE Particle monitoring allows real-time detection of potential process deviations.

5.2.4.3 Monitoring of the bioburden and endotoxin load of starting materials shall be conducted as relevant for the product with regard to the nature of the material and its potential for microbiological contamination. Alert and action levels shall be set with regard to the risk of microbial proliferation and with due consideration of the control methods applied in the process.

5.2.4.4 The aseptic process shall be monitored in order to allow comprehensive management of microbiological quality. Monitoring shall address:

- a) microbiological quality of the product at defined stages during the manufacturing process (see 6.8);
- b) microbiological quality of the manufacturing environment including air and surfaces of rooms (see 6.8.3.1), equipment surfaces (see 6.8.3.1) and tools (see 6.8.1.7);
- c) microbiological status of the gloves and gowns of personnel at defined intervals (see 6.8).

NOTE 1 Observation of activities is also useful for the purposes of identification of potential sources for the introduction of contaminants.

NOTE 2 Monitoring of bioburden against established limits is a requirement in certain jurisdictions.

5.2.4.5 The rationale of the monitoring methods employed shall be documented.

NOTE Pharmacopoeial procedures such as "Microbiological examination of non-sterile products: Microbial enumeration tests" shown in the Ph.Eur., JP and USP might be applicable.

5.2.4.6 The applicability of the monitoring methods and the reliability of the results obtained using those methods with respect to recognition of risks shall be assessed.

NOTE In general, the available microbiological monitoring methods are not sufficiently sensitive to detect all microbial contaminants.

5.2.4.7 Data gathered from monitoring shall be evaluated so that appropriate action can be taken. The response to a monitoring result should be correlated to the identified risk as determined in the risk management process.

5.2.5 Prevention of contamination

5.2.5.1 Once risks have been identified corrective and preventive action shall be applied to minimize or eliminate these risks.

NOTE Such measures can include design changes, additional training or procedural modifications.

5.2.5.2 Appropriate measurements shall be undertaken to demonstrate the effectiveness of the preventive measures.

6 Manufacturing environment

6.1 General

6.1.1 The manufacturing environment shall be designed and built in accordance with ISO 14644-4.

6.1.2 The objective(s) of the control programme for the manufacturing environment shall be defined.

NOTE Aseptic processing is aimed at preventing product contamination. Where highly potent or cytotoxic health care products are to be processed, protection of personnel and the environment is considered an ancillary element of aseptic processing design.

6.1.3 The control programme for the manufacturing environment shall address:

- a) APA layout and design including:
 - 1) physical attributes of the rooms;
 - 2) segregation for all cleanliness zones;

- b) APA heating, venting and air conditioning (HVAC) system including:
 - 1) airflow velocities, number of air changes per hour and differential pressures;
 - 2) airflow pattern for critical processing (and direct support zones where required);
 - 3) temperature and relative humidity;
- c) appropriate monitoring parameters and set control levels for particulates and microorganisms;
- d) introduction and exhaust of utilities;
- e) introduction and removal of materials, components, product and waste;
- f) cleaning and disinfection procedures;
- g) provisions and procedures including gowning practices for entering and leaving of personnel;
- h) access for service and maintenance;
- i) behaviour and activities of personnel in the APA;
- j) provisions for corrective measures within the APA;
- k) personnel flow;
- l) pest control.

6.2 Manufacturing environment design

6.2.1 General

6.2.1.1 The APA shall be designed and constructed in accordance with ISO 14644-1, ISO 14644-4 and ISO 14644-7.

6.2.1.2 The facility design shall be compatible with processes or product types processed therein.

6.2.1.3 A design review shall be carried out and recorded for each APA. It shall demonstrate that the design is in compliance with the aseptic process definition or equivalent. Records of design reviews shall be retained (see 4.1.4).

6.2.1.4 Before significant modifications to a facility are implemented, a design review including risk assessment shall be undertaken.

6.2.2 Construction features

6.2.2.1 Ceilings, walls, wall systems and floors shall be designed and constructed in a way that facilitates cleaning and disinfection and minimizes the shedding or accumulation of particles or microorganisms. Materials shall be chosen which are resistant to the repeated application of cleaning agents and to the disinfectants used. The edges of the floors of cleanrooms shall be covered and sealed at the junction to the walls.

6.2.2.2 Ceilings shall be sealed to prevent ingress of particles from the space above. Filters, filter frames and housings, diffusers, lamps or any other penetration points shall be sealed and fitted flush with the ceiling. False ceilings and wall elements shall be sealed to prevent contamination from the surrounding areas.

6.2.2.3 Windows shall be integrated into the walls of the cleanroom to allow observation of the aseptic operations from the outside of the cleanroom in order to minimize the need for access to the clean zones for any reason other than direct participation in the aseptic operations. Where glass is inserted in walls and doors it shall be non-opening with flush mounting on surfaces in the APA.

6.2.2.4 Where communication systems are provided in the APA they shall be designed to facilitate cleaning.

6.2.2.5 Where barriers are used to guide airflow, the material used shall be durable and resistant to the cleaning agents and disinfectants used.

6.2.2.6 The design of the APA shall be such as to minimize horizontal surfaces and to allow for the adequate cleaning and disinfection of ceilings, floors, walls and other surfaces.

6.2.2.7 Pipes, ducts and other utilities shall be installed so that they do not create recesses, unsealed openings or surfaces which are difficult to clean.

Pipes, tubing and cables shall be routed in external service areas or ducts wherever possible. Power take-off points, switchboards, taps and connections shall be designed and installed to facilitate regular cleaning and to avoid the build-up of contamination in or behind blanking covers. Where protective housings or covers cannot be avoided (for example in switchboards of equipment), these shall be sealed in a way to prevent contamination of APA and shall only be opened when the APA is not in use.

6.2.2.8 Sinks and open drains shall not be located in critical processing zones (see 6.3.2) and direct support zones (see 6.3.3). Where drains are fitted to process equipment, appropriate backflow prevention shall be used. In other areas, sinks and drains shall be suitable for disinfection, and air breaks shall be fitted between the machine or sink and the drains to prevent back contamination. Floor drains in indirect support zones (see 6.3.4) shall be suitable for disinfection, fitted with traps or water seals and sealed when not in use.

6.3 Layout

6.3.1 General

6.3.1.1 Aseptic manufacture of sterile products shall be carried out in an APA. Operations involving component preparation, product preparation and filling shall be carried out in separate areas within the APA.

NOTE Segregation (or separation) within the APA is achieved by the sweeping action of the air (airflows), pressure differentials, physical barriers or a combination thereof; see ISO 14644-4.

Appropriate layouts shall be applied when sensitizing agents, cytotoxic or other hazardous materials are processed within the APA.

6.3.1.2 The layout of equipment in the APA shall facilitate operator and maintenance personnel access while eliminating or minimizing exposure of open containers or product to the environment.

NOTE Wherever possible, utility systems and equipment are laid out to allow maintenance activities to be performed from outside the APA.

6.3.1.3 Where reference to classes listed in the ISO 14644 series is made, these classes refer to the operational state.

6.3.2 Critical processing zone

6.3.2.1 The critical processing zone shall be segregated and operated in a way that ISO 14644-1:1999, Class 5 conditions are maintained under normal operational conditions.

NOTE 1 This part of ISO 13408 refers to the classification according to ISO 14644-1. For other regional classification systems, see Annex D.

NOTE 2 Examples of activities usually performed in a critical processing zone include:

- a) aseptic assembly of filling equipment;
- b) aseptic connections;

- c) aseptic compounding and mixing;
- d) filling of product, containers and stoppers;
- e) staging and conveying of sterilized primary packaging materials;
- f) aseptic filling, stoppering, transfer of open or partially stoppered vials, including interventions;
- g) environmental monitoring.

6.3.2.2 Where isolators or similar separative devices are used for segregation of critical processing zones, ISO 13408-6 and ISO 14644-7 shall apply.

6.3.3 Direct support zones

For a critical processing zone, a direct support zone with at least an ISO 14644-1:1999, Class 7 environment shall be provided to prevent contamination of the critical processing zone.

In the case of an isolator or similar separative device, a risk assessment shall determine the necessary surrounding environmental class. 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 (see ISO 13408-6).

NOTE Examples of activities usually performed in the direct support zones include:

- a) transport and preparation of packaged materials for introduction into the critical processing zone;
- b) removal of closed product from the critical processing zone;
- c) preparation of operators for interventions in the critical processing zone (e.g. disinfection of gloves, staging of tools).

6.3.4 Indirect support zones

Indirect support zones within the APA shall be segregated and shall protect direct support clean zones. The required grade of cleanliness depends on the separation mechanism chosen.

NOTE 1 A clean zone corresponding to ISO 14644-1:1999, Class 8 is usually provided.

NOTE 2 Examples of activities usually performed in an indirect support zone include:

- a) preparation of product solutions to be filtered;
- b) assembly of cleaned equipment to be sterilized;
- c) cleaning of equipment.

6.3.5 Material airlocks, transfer hatches, and product exit openings

6.3.5.1 Airlocks and transfer hatches shall be of a suitable size to allow transfer of material without crowding, and shall be equipped with interlocking doors to prevent simultaneous opening.

6.3.5.2 Ingress or egress of materials transported into or leaving the APA shall be achieved either by separation in time or by separate material airlocks with appropriate cleaning or decontamination in between.

6.3.5.3 The environmental quality of the air of the airlock at rest shall correspond to the cleanest classification to which it connects.

6.3.5.4 Product exit openings shall be kept as small as practicable. The opening shall not compromise the cleanliness or segregation of the critical processing zone.

6.3.6 Personnel airlocks

6.3.6.1 Personnel and materials shall enter through separate airlocks.

6.3.6.2 Gowning rooms shall be designed with a clear separation into a clean side entering into the cleanroom and a less clean side accessible from the lower classification environment. The clean side shall be the same classification at rest as the area into which it leads.

NOTE A swing-over bench is usually supplied as a minimum to separate clean and less clean parts of the airlock and to facilitate the gowning procedure.

Separation of the personnel entering the direct support zone from those leaving should be achieved either by separation in time or by providing separate entry and exit routes as determined by risk assessment.

Personnel airlocks should be fitted with interlocking doors to prevent doors to the clean and less-clean areas opening at the same time. Where interlocking is not implemented, doors shall be equipped with audio-visual indicators and recorder systems. Emergency exits shall be provided with a means to show that they have been opened.

6.3.6.3 Adequate space shall be provided to put on (don, see 8.3.1.2) and remove (doff) the appropriate cleanroom garment without contamination.

6.3.6.4 Space and facilities shall be available for sterile garment storage, soiled garment disposal, hand washing and hand disinfection. Hand washing facilities should only be provided in ISO 14644-1:1999, Class 8 areas or other areas of lower control.

The proper gowning practice shall be visually displayed.

Gowning areas with access to the direct support zone shall be equipped with a mirror to allow the operator to confirm that the gowning has been completed properly.

6.3.7 Ancillary areas

Ancillary areas (such as cleaning, service and utilities), and toilet and refreshment areas shall be separated from the APA to avoid any compromise to segregation.

6.4 Material and personnel flow

6.4.1 General

6.4.1.1 Material and personnel flow procedures shall be specified. These shall describe the flow of personnel and handling and processing of materials, components and equipment delivered to the APA in order to:

- a) maintain the integrity of critical processing zones;
- b) minimize the entry of contamination from outside the APA, and retain any such contamination so that it does not reach the critical processing zone;
- c) prevent cross contamination within the APA, ensure segregation of clean and dirty items, and ensure segregation of sterilized and non-sterilized components.

6.4.1.2 Access to the APA shall be restricted to trained and qualified personnel (as described in Clause 8) who are properly gowned (as described in 8.3.2).

6.4.2 Introduction of materials and components to the APA

6.4.2.1 Access and transport of materials, components and equipment into and from the airlocks shall be controlled to maintain segregation of the cleanroom under all specified operational conditions.

6.4.2.2 Contiguous conveyors shall not go between different classification zones.

6.4.2.3 Materials taken into the critical processing zone shall be sterilized except in justified cases. If sterilization is not possible (e.g. particle counter), the materials and/or equipment shall be biodecontaminated. Such material might be included in the monitoring programme.

Where possible, dedicated equipment should be left in the APA to minimize the risk of introducing contamination.

6.4.2.4 Each of the sterilization processes used to sterilize components or materials used in the APA shall be validated in accordance with ISO 11135-1, ISO 11137-1, ISO 11137-2, ISO 14160, ISO 14937, ISO 17665-1 or ISO 20857.

6.4.2.5 Devices and procedures employed within an airlock to biodecontaminate the materials entering the APA, free of microorganisms, shall be validated.

6.4.2.6 The bioburden of raw materials, intermediates and other components and equipment that are to be sterilized and introduced into the APA shall be determined at a defined and justified frequency based on the risk assessment.

6.4.2.7 The compounding of bulk solutions and suspensions shall be controlled in order to prevent potential increase in microbiological levels and possibly endotoxins that can occur up to the time that the bulk solutions are sterile filtered.

Solutions shall be compounded in adequately protected tanks. A maximum allowable holding time for the solutions prior to filtration should be established.

6.5 HVAC system

6.5.1 General

Cleanrooms in the APA shall be ventilated and segregated to allow the specified cleanliness conditions to be maintained under operational conditions. Air entering cleanrooms shall be passed through HEPA filters to achieve the specified grade of cleanliness (see 6.2).

6.5.2 Air handling

6.5.2.1 Within the APA, an HEPA-filtered air supply shall maintain a positive pressure relative to surrounding areas of lower grade under all operational conditions.

For the critical processing zone, a unidirectional airflow of sufficient velocity to provide adequate protection shall operate other than in isolators. See 5.4 of ISO 13408-6:2005.

6.5.2.2 The number of air changes per hour and differential pressures, including limits and measuring position, shall be defined. The specified parameters shall be controlled and recorded to demonstrate the maintenance of the specified conditions during the process.

6.5.3 Airflow patterns

6.5.3.1 Within the critical processing zone and direct support zone, an effectively flushing airflow pattern shall be specified. Effectiveness shall be demonstrated, verified and documented as demonstrated by air visualization studies for specified operational conditions to ensure that airflows do not present a contamination risk (e.g. distribute particles from a particle-generating person, operation or machine to a zone of higher product risk).

6.5.3.2 Where unidirectional airflow is specified, assurance of unidirectional flow shall be assessed by adequate means at a predetermined interval for each HEPA filter and airflow patterns shall be re-established whenever a configuration change has been introduced.

NOTE Significant reductions in velocity can increase the possibility of contamination and changes in velocity can affect the unidirectional pattern of the airflow.

6.5.3.3 Care shall be taken to minimize disturbance of the unidirectional flow as turbulence can interfere with the sweeping action of the air.

6.5.4 Temperature and relative humidity

6.5.4.1 Temperature and relative humidity of the APA shall be maintained within a range comfortable to the personnel working therein and compatible to the properties of the product being manufactured. These requirements shall be met in the presence of a full complement of operational personnel and with all equipment in operation.

6.5.4.2 Temperature, humidity levels and pressure differentials shall be monitored, recorded and alarmed where necessary.

6.5.5 HEPA (including ULPA) filters

6.5.5.1 General

Filters shall be tested in accordance with ISO 14644-3.

6.5.5.2 HEPA filter certification

6.5.5.2.1 HEPA filters used to maintain the environmental conditions within the APA shall be evaluated by a defined aerosol challenge test within the filter manufacturer's facility.

6.5.5.2.2 Receipt of HEPA filters shall be accompanied by a supplier's certificate that indicates the filter has an efficiency of not less than 99,97 % for the retention of 0,3 μm or larger particles.

6.5.5.3 Installed filter leakage test

6.5.5.3.1 When installed in the APA, HEPA filters shall be subject to filter leakage testing by a defined method (e.g. aerosol challenge test).

6.5.5.3.2 The integrity of HEPA filters for the critical processing zone and direct support zone shall be confirmed.

NOTE Generally, this is performed every six months.

6.5.5.4 HEPA filter failure

6.5.5.4.1 Where it is possible that the integrity of the filter could have been compromised, there shall be documented procedures for the testing of the filters.

6.5.5.4.2 In the event of a filter failure, a documented investigation shall be conducted to identify the potential cause of the failure and any remedial action that has been taken shall be documented. A documented management review of investigation reports shall be conducted in accordance with defined procedures.

6.5.5.4.3 The percentage of the filter surface face area that can be repaired shall be specified.

6.6 Cleanroom qualification

Cleanrooms shall be qualified to demonstrate that they meet the requirements specified in ISO 14644-1, ISO 14644-2, ISO 14644-3, ISO 14644-4, ISO 14644-5 and ISO 14644-7 and applicable regulatory guidelines and shall be compatible with the manufacturing environmental contamination control programme at rest and under operational conditions. This shall be demonstrated in a formal qualification programme.

6.7 Utility services and ancillary equipment

6.7.1 General

6.7.1.1 Utility services provided for the APA shall be designed, located and installed such that the cleanroom is not compromised by contamination from such services.

6.7.1.2 Manufacturing, storage and distribution systems for process related utilities such as purified water, water for injection(s), compressed air (and/or other gases), clean steam, and cleaning-in-place/sterilization-in-place shall be validated.

6.7.2 Water and wastewater

6.7.2.1 No water taps, basins or sinks shall be provided in ISO 14644-1:1999, Class 7 or better areas. Where water is needed for functioning of equipment (e.g. cooling water) this shall be contained in a closed system so that contamination of the APA is prevented. The integrity of the closed water cooling system shall be confirmed at a defined frequency.

6.7.2.2 Water used in the process in ancillary areas (e.g. for washing of primary packaging material) shall be of suitable quality to prevent contamination being introduced to the process. The water used in the process shall comply with the requirements given in Annex E.

6.7.3 Gases

All compressed gases (excluding combustible gases) that enter the aseptic facility shall be dry and oil-free. Those that come into direct contact with sterile products, container/closures or critical surfaces shall be filter sterilized. Integrity of the sterilizing filters shall be assured before use of the filter and at regular defined intervals, preferably by in-line testing.

6.7.4 Vacuum utilities

6.7.4.1 If portable vacuum cleaning equipment is used it shall be fitted with an exhaust filter of at least the same efficacy as that filtering the air used for venting the area.

6.7.4.2 If a fixed vacuum source is used it shall be designed to prevent backflow.

6.8 Environmental and personnel monitoring programmes

6.8.1 General

6.8.1.1 The APA shall be monitored for viable and particulate contamination in accordance with a defined, documented programme that describes the routine particulate and microbiological monitoring of processing and manufacturing areas, and that includes a corrective action plan when specified action levels are exceeded.

NOTE See Annex F for information on different zones and areas.

6.8.1.2 Specifications should be set in compliance with appropriate particulate control standards following ISO 14644-1, ISO 14698-1 and ISO 14698-2 and/or relevant GMP requirements and shall take into account the risk assessment and the results of validation studies.

6.8.1.3 The defined documented sampling plan shall describe at least:

- a) sites monitored;
- b) frequency of monitoring;
- c) conditions for monitoring (at rest and/or in operation);
- d) method of monitoring;
- e) time and duration of sampling;
- f) alert and action levels.

6.8.1.4 The frequency of monitoring for the different zones shall be specified.

- a) For new facilities, the frequency shall be based on risk assessment.
- b) In other cases, the frequency shall be based on historical environmental monitoring data and with consideration of regulatory requirements.

6.8.1.5 The critical processing zone shall be monitored during each operational shift.

Monitoring approaches shall not compromise the sterility of a product.

NOTE Surface sampling is typically done at the end of the operation.

6.8.1.6 Direct and indirect support zones may be monitored less frequently than the critical processing zone. The frequency of monitoring for such zones shall be specified. The frequency should be sufficient for the recognition of trends.

6.8.1.7 Due to the limitations of fixed site sampling plans, the routine sampling plan shall include a provision for periodic surveillance monitoring at additional sites during and/or after operations.

NOTE An example of such an additional sampling site is the surface of tools used for intervention in the critical processing zone. Sites selected typically relate to activities that present possible contamination risks to the product.

6.8.1.8 Additional monitoring shall be performed following initial start-up of operations or following periods of extended shutdown or modifications to the facility.

6.8.2 Sampling for particulate monitoring

The particulate monitoring programme for areas or equipment in the aseptic processing facility where product quality or testing accuracy can be affected by particulates shall be in accordance with ISO 14644-2.

NOTE 1 It is accepted that it might not always be possible to demonstrate conformity with particulate standards at the point of product exposure when aseptic processing is underway due to the generation of particles or droplets from the process itself.

NOTE 2 In certain jurisdictions continuous or frequent sampling of particles is required for the critical processing zone and is recommended for the direct support zone.

6.8.3 Sampling for microbiological environmental monitoring

6.8.3.1 The sampling plan for microbiological monitoring shall contain (in addition to 6.8.1.3) the designation of sites monitored by active and passive air monitoring and sites for surface monitoring, including equipment surfaces.

6.8.3.2 Sampling sites shall be selected based on a contamination risk assessment specific to a particular aseptic processing operation. Sites shall be derived from, and be consistent with those used during validation activities and shall represent the highest microbiological risk to the product. Rationale for sites chosen shall be documented.

6.8.3.3 Air samples shall be collected in operation. Product contact surfaces shall be monitored only after completion of the filling operation to prevent the risk of contamination of the product.

6.8.4 Monitoring of personnel

6.8.4.1 Personnel trained and qualified to work in the APA shall be subject to a routine microbiological monitoring programme. Monitoring data shall be used to identify trends and evaluate the need for retraining.

Gloved fingerprints of personnel present in the direct support zone and/or critical processing zone shall be monitored daily. At defined intervals samples from the gowns shall also be taken (e.g. both forearms, chest, hood). After a garment has been tested for microbial contamination it shall not be worn in the APA until it has been cleaned and sterilized.

NOTE The frequency of sampling of gowns and gloves is based on the nature of the activities performed.

6.8.4.2 Personnel found to frequently exceed established microbiological levels shall be investigated and removed from work in the APA. Procedures shall be established for retraining and requalification.

6.8.5 Monitoring procedures

6.8.5.1 The APA shall be routinely monitored for the presence of microorganisms by use of quantitative air sampling methods. Semi-quantitative sampling methods should be used in addition, e.g. settle plates, swabs and contact plates, as appropriate. For active sampling, calibrated equipment shall be used. The rationale for the choice of sampling methodology shall be documented.

6.8.5.2 Growth media used shall be shown to allow recovery of bacteria, yeast, moulds which can occur in the manufacturing environment and/or in product. The justification for the media selected and the microorganisms used to establish their growth-promoting capacity shall be documented.

NOTE Qualified media, e.g. the pharmacopoeial media shown in "Microbiological examination of non-sterile products: Microbial enumeration tests" can be used.

6.8.5.3 The microbiological environmental monitoring programme shall include characterization of the recovered microorganisms (isolates) to facilitate a continued assessment of the risk to the product.

NOTE All isolates from the critical processing zone are identified to the species level where feasible. The depth of routine characterization or identification of isolates from other zones will depend on the location of the sampling site within the APA.

Differentiation of microbiological isolates shall be part of failure investigation in case of exceeded action levels.

6.8.6 Evaluation of monitoring data

6.8.6.1 Alert and action levels

Alert and action levels shall be developed for all sampling sites in the APA. For the critical processing zone, each microorganism detected shall be investigated. Alert levels and action levels shall be reviewed at defined, regular intervals. Alert levels in the APA shall be derived from and be consistent with results obtained from data trend analysis.

NOTE 1 Action levels in support zones are typically based on regulatory guidance.

NOTE 2 For new facilities, microbiological monitoring data from historical databases, process simulations, cleanroom qualification, and sanitization studies are frequently used in developing monitoring levels.

Appropriate investigation followed by corrective and preventive action shall be taken when action levels are exceeded. Repeated alert level results may be treated as being equivalent to an exceeded action level.

6.8.6.2 Review of data and trend analysis

6.8.6.2.1 The results of each individual sample of environmental monitoring within the critical processing zone during the period of manufacture shall be reviewed against the alert and action levels established for the APA prior to batch release. The impact of any excursions on the product's quality shall be assessed.

NOTE Averaging of results without due consideration of individual high values can mask unacceptable localized conditions.

6.8.6.2.2 Environmental data (both counts and the type of microbial isolates) shall be analysed for trends on a routine basis. A trend report giving an overview of all environmental observations and trends shall be issued in fixed intervals. Trend reports should include data generated by location, shift, room, operator or other parameters. When indicated by individual excursions and/or trend data, an investigation shall be initiated.

NOTE 1 It is important not to ignore correlations between sampling sites as single site trends may not provide a complete representation of the environment being monitored.

NOTE 2 Examples of trends leading to an investigation include:

- a) a trend towards higher numbers of microorganisms at a sampling site;
- b) repeated occurrence of microorganisms not often encountered.

6.8.6.3 Investigations and reports

6.8.6.3.1 Investigations carried out using documented procedures shall be initiated following events that indicate a possible loss of environmental control such as:

- a) excursions above action levels;
- b) excursions above alert levels indicating a possible adverse trend;
- c) increased incidence of microbial counts below the action level and above historical levels;
- d) the occurrence or persistence of unusual circumstances (e.g. extended mechanical breakdowns);
- e) audit observations indicating a possible increase in contamination risk;
- f) a documented adverse trend.

NOTE 1 Elements for consideration in course of the investigation include, e.g.:

- 1) extent of the problem;
- 2) data to be collected (e.g. surveillance monitoring at additional positions);
- 3) extent of review of environmental control data;
- 4) potential impact on product (e.g. need for quarantine of product);
- 5) follow-up testing;
- 6) notification of affected responsible personnel.

NOTE 2 Additional testing can be required for, e.g.:

- the identification of source(s) of the contamination;
- the determination of possible impact of a deviation on product quality;
- a demonstration that any corrective actions were successful and the area is once again under control.

6.8.6.3.2 The investigation shall be documented in a report. The report shall be reviewed and approved by qualified personnel and distributed to the responsible key personnel.

6.8.6.3.3 Where appropriate, the report shall contain recommendations for corrective actions and disposition of product.

7 Equipment

7.1 Qualification

7.1.1 General

Equipment used in the aseptic processing or associated testing, such as component washers, sterilizers, filter assemblies, sterilization filters, closure placement equipment, sealing machinery and lyophilizers shall be qualified to assure its suitability for the intended purpose.

NOTE This part of ISO 13408 deals only with features specific to aseptic processing. Equipment qualification is a wider concept and additional considerations are needed for technical qualification.

7.1.2 User requirements

A user requirements document shall be generated defining the required equipment functionality and performance. It shall be reviewed and approved by the user. Considerations (in addition to other technical or safety questions) shall include, where appropriate:

- a) surface finish quality;
- b) specification for capability of being cleaned;
- c) specification for capability of being sterilized;
- d) ease of access for aseptic assembly;
- e) avoidance of recesses in or underneath the equipment;
- f) suitable arrangement of utility piping, tubing, or cables for aseptic operation;
- g) ease of access of internal workings without putting the APA at risk, including ability to service the equipment from outside, wherever possible;
- h) ease of mechanical and electrical adjustments from outside the critical processing zone wherever possible, or ease of access with minimal disturbance of the critical processing zone;
- i) compatibility of equipment handling with operation in an isolator, where applicable;
- j) prevention of contamination from computers and keyboards;
- k) fitting of equipment with an exhaust with filters such that the exhaust is of at least the same air quality grade as that of the area into which it is discharged;
- l) cleaning-in-place or sterilization-in-place of equipment.

7.1.3 Design qualification

7.1.3.1 Equipment shall be designed for use in the specified clean zone and shall meet the functional and safety requirements relevant for its intended use.

7.1.3.2 Documented evidence shall be collected to demonstrate suitability of the equipment for the intended product or process.

7.1.4 Installation qualification

7.1.4.1 Installation qualification shall be carried out in accordance with a documented procedure, which shall cross-reference appropriate equipment and "as installed" specifications. Documented evidence shall be collected to verify that the equipment is supplied and installed suitably for operation in the APA. Instruments shall also be calibrated before operational qualification.

7.1.4.2 Operating instructions shall be available.

7.1.4.3 Computerized control systems and associated software, when installed, shall be qualified before or concurrent with the equipment qualification.

7.1.5 Operational qualification

Documented evidence shall be collected to demonstrate that the equipment can be operated in the APA so that specified cleanroom conditions are maintained. For equipment operated in the critical processing zone, ISO 14644-1:1999, Class 5 conditions or better shall be maintained under all routinely-encountered operating conditions.

Operational qualification shall demonstrate that the installed equipment is capable of delivering the specified process within the defined operating range.

NOTE Specific items that are typically addressed during operational qualification for equipment used in aseptic processing include, e.g.:

- a) integrity of barriers;
- b) verification of airflow pattern and air quality;
- c) verification of alarm systems.

7.1.6 Performance qualification

7.1.6.1 Data generated during installation qualification and operational qualification shall be reviewed for compliance with 7.1.4 and 7.1.5.

7.1.6.2 Requirements shall be established for performance qualification. Performance qualification shall include a demonstration that the equipment operates to consistently yield sterile product.

7.1.6.3 Data shall be generated to demonstrate the attainment of defined physical and/or chemical conditions within specified tolerances throughout the process.

7.1.6.4 Documented evidence shall be collected to demonstrate that the equipment will maintain consistent segregation and function with minimal intervention when operated under worst case challenge conditions.

7.1.7 Requalification

7.1.7.1 An evaluation of the need to perform requalification of processes carried out with specified equipment shall be performed at defined intervals or as required as a result of investigations of deviations or complaints.

7.1.7.2 Monitoring and in-process data shall be reviewed periodically against specified acceptance criteria in accordance with documented procedures. Records shall be retained of reviews of revalidation data, and of corrective action taken in the event of the specified acceptance criteria not being met.

7.1.7.3 The extent to which requalification is carried out shall be justified.

7.1.7.4 Requalification report(s) shall be documented and retained.

7.2 Maintenance of equipment

7.2.1 Scheduled preventive maintenance

7.2.1.1 Utilities, services and equipment shall be part of the preventive maintenance programme.

7.2.1.2 Preventive maintenance including calibration of instruments shall be planned, performed and documented in accordance with documented procedures.

7.2.1.3 Tools and other maintenance aids shall be:

- a) of suitable design;
- b) capable of being cleaned;
- c) capable of being disinfected or sterilized;
- d) appropriately stored to prevent contamination.

7.2.1.4 Maintenance procedures shall be established and documented with due consideration of APA requirements.

7.2.1.5 Where integrity of the APA cannot be maintained during maintenance, the area shall be taken out of service and shall not be re-used until it has been subjected to a defined cleaning and disinfection procedure before the area has been requalified.

7.2.2 Unplanned maintenance

7.2.2.1 During aseptic operations any unplanned maintenance in the critical processing zone and direct support zone shall be performed using aseptic techniques and only to the extent that it has been simulated during process simulation. If the unplanned maintenance has not been qualified, the process shall be stopped and any exposed units of product shall be removed from the process and disposed of appropriately.

7.2.2.3 Where integrity of the APA cannot be maintained during maintenance the area shall be taken out of service and not be re-used until it has been subjected to a defined cleaning and disinfection procedure before the area has been requalified.

7.2.2.2 Restart of the process after unplanned maintenance shall follow established procedures assuring that the specified process conditions have been re-established.

8 Personnel

8.1 General

8.1.1 Documented procedures for personnel training and assessment of personnel performance shall be established and implemented. Management shall be responsible for defining criteria to assess personnel performance. These criteria shall include, at a minimum, process simulation participation, gowning qualification and compliance with procedures.

8.1.2 Defined procedures shall be in place to assure that personnel do not compromise aseptic processing environmental conditions. The effectiveness of the documented procedures shall be evaluated at intervals defined by the manufacturer.

8.1.3 Management shall be responsible for implementing an appropriate training programme to ensure that personnel (including supervisors, quality assurance staff and maintenance staff) are appropriately qualified before entering or being assigned work in the APA, as defined in 8.2.

8.2 Training for APA qualification

8.2.1 All personnel entering the APA including those who require only temporary access shall be qualified based on successful completion of defined training. Training in the various disciplines and activities should be in proportion to the individual's duties and directed at the appropriate level of knowledge.

8.2.2 All personnel working in the APA shall be trained in:

- a) fundamentals of microbiology related to aseptic processing;
- b) design and necessary functionality of the facility contamination control concept including awareness of segregation, barriers, monitors and alarms;
- c) microbiological risk assessment and risk prevention;
- d) personal hygiene (e.g. hand washing and disinfection procedures, and the requirement to report any adverse health conditions);
- e) rules concerning the wearing of cosmetics, wristwatches and jewellery;
- f) manufacture of sterile products within the APA;
- g) aseptic technique;
- h) gowning procedures;
- i) cleanroom practices;
- j) emergency procedures to protect product quality (e.g. failure of HVAC system, loss of power, etc).

NOTE General issues of good manufacturing practice and health and safety aspects are not within the scope of this part of ISO 13408.

8.2.3 Training in cleanroom practices shall include an overview of operator effect on the APA and the manufacturing process. Specifically, this training ensures operators have the requisite knowledge in good aseptic technique and practices necessary to avoid:

- a) any contact with critical surfaces including sterilized materials and components;
- b) unnecessary contact with walls, floors and cleaned surfaces;
- c) unnecessary and/or rapid movements which can generate particles or create turbulence;
- d) unnecessary talking;
- e) reaching across open containers and exposed product and components;
- f) blocking airflow over critical surfaces.

8.2.4 Gowning qualification shall include observation of technique and microbiological monitoring. This monitoring shall include multiple locations on the gown. Verification of results shall be documented and communicated to the personnel and management.

8.2.5 Gowning qualification shall be repeated at a frequency defined by the manufacturer, based on the nature of the operations performed. The rationale shall be documented.

8.2.6 Access of non-APA personnel to the APA shall be minimized and, when required, non-APA personnel shall be accompanied at all times by a person who has been qualified. Requirements shall be specified for access to the APA for persons who have a legal or contractual right of access (e.g. competent authorities, notified bodies, contractors).

Other visitors shall not have access to the critical processing zone and direct support zone.

8.2.7 At least once per year, all personnel that directly participate in setting up aseptic manufacturing equipment, filling or manufacture of sterile products or maintenance work in the critical processing zones shall take part in a process simulation that meets the requirements of this part of ISO 13408.

8.2.8 New personnel who will work in the critical processing zone shall take part in at least one successful process simulation or justified equivalent aseptic operation, which may be performed in a training environment, before they are permitted to participate in processes carried out in critical processing zones.

8.2.9 All personnel shall be retrained, in accordance with documented procedures, on both job functions and relevant quality systems elements at a defined frequency and if there is an indication of necessity.

8.2.10 Training shall be documented and its effectiveness shall be assessed as appropriate (e.g. by oral or written tests, successful participation in practical exercises or in process simulation). Records of training and evaluation shall be maintained.

8.3 Gowning procedures

8.3.1 General

8.3.1.1 Gowning requirements shall be established consistent with the aseptic processing steps, facility contamination control assessment and the segregation requirements for the APA. Gowns to be used in the APA shall have a documented specification.

8.3.1.2 The gowning cascade shall include:

- a) removal of personal outer clothing;
- b) donning factory uniform;
- c) donning indirect support zone clothing;
- d) donning critical processing zone and direct support zone clothing.

NOTE It is possible to go from b) to d) using a dedicated changing room.

Personnel shall not wear direct or indirect support clothing outside the APA.

8.3.1.3 The maximum number of people that can be in the gowning airlock simultaneously shall be defined.

8.3.2 Gowning for entering the APA

8.3.2.1 Documented procedures shall be implemented to ensure that personnel do not compromise the aseptic processing environment. The procedures shall address:

- a) removal of outside garments, wristwatches, jewellery, cosmetics and shoes;
- b) hand washing and/or hand disinfection;
- c) specification of the complete set of cleanroom garments;

- d) stepping over barriers in compliance with the segregation concept;
- e) sequence of putting on the cleanroom garments;
- f) techniques of gowning and de-gowning;
- g) washing and validated sterilization procedures for gowns.

The permissible number of washing/cleaning and sterilization cycles for the gowns shall be defined and a tracking system implemented to confirm the permissible number of washing/cleaning and sterilization cycles. Criteria shall be established for acceptability of gown integrity.

8.3.2.2 Hair, including beards and moustaches, should be covered. A one-piece suit or two-piece trouser suit, gathered at the wrists and with high neck and appropriate shoes or overshoes should be worn. These should not shed fibres.

8.3.2.3 Sterilized garments for critical processing zone and direct support zone shall fully cover the body. There shall be no exposed areas of the face. The garments shall retain particles while allowing passage of moisture vapour for wearing comfort. The fabric shall minimize particle shedding. Fresh garments shall be worn each time a person enters these zones.

NOTE 1 Sterile garments for critical processing zone and direct support zone are frequently composed of a one-piece suit, hood, overboots, gloves, face-mask and goggles.

NOTE 2 Some cleanroom operations use arm covers, extra high boots and double gloves to minimize the likelihood of gaps or tears occurring during movement.

NOTE 3 Typically, cleanroom gowns are washed in a dedicated facility, individually packed in sterilizable bags and sterilized by steam or irradiation.

8.3.2.4 Garments worn in the APA shall fit the individual operator.

NOTE For example, a large gown on a small individual could create a bellows-like effect and, in the process of normal operations, the gown could bellow outwardly emitting microorganisms and particulates into the room. Conversely, a small gown might not provide adequate coverage of hair and skin.

8.3.2.5 Employees shall wear gloves in critical processing and direct support zones.

NOTE Two pairs of gloves are frequently used; the first pair of gloves can be used as gowning gloves.

8.3.2.6 Before entering the clean zones, the correct fit and integrity of the gowns and gloves shall be verified by at least looking in a mirror.

8.3.2.7 Care should be taken to ensure that at the areas where clothing meet (such as the lower leg, wrist and neck) no gaps or exposed skin are apparent.

8.3.2.8 Personnel in ISO 14644-1:1999, Class 8 or lower classification areas shall wear garments designed to minimize particulate generation, but these garments normally need not be sterile prior to use.

8.4 General employee health

8.4.1 Personnel working in the APA shall be required to report conditions which might affect aseptic work such as fever, skin lesions, common cold, diarrhoea, etc.

8.4.2 Personnel with reported or observed health conditions affecting aseptic work shall not be permitted to enter the APA but may be assigned work in other areas.

9 Manufacture of the product

9.1 Attainment and maintenance of sterility

9.1.1 Component sterilization

9.1.1.1 Raw materials, intermediates and components introduced into the critical processing zone shall have been sterilized.

9.1.1.2 Suitable protection after sterilization shall be provided to prevent recontamination.

9.1.2 Depyrogenation

9.1.2.1 Materials used to manufacture parenteral and other products required or claimed to be free from endotoxins shall comply with a limit test for endotoxins defined and justified by the manufacturer. This applies to raw materials (including water), intermediate products (such as bulk solutions or suspensions) and other components (such as container components) used as part of the product. The levels of endotoxin shall be determined by pharmacopoeial procedures unless it is necessary, taking into account the nature of the product, for the manufacturer to define and document an alternative or modified test procedure.

NOTE Examples of pharmacopoeias include Ph.Eur., JP and USP.

9.1.2.2 Data shall be available to demonstrate a knowledge of the amount of endotoxin present on components prior to treatment in a depyrogenation process.

9.1.2.3 When a depyrogenation process is used validation studies shall be performed to demonstrate that the process will remove a greater quantity of endotoxin than might have been originally present in the component or product.

Typically, a reduction by a dry heat depyrogenation of at least three orders of magnitude of spiked endotoxin process is required.

NOTE Plastic medical devices, closures and/or containers can be depyrogenated by rinse processes, and/or high temperature moulding and/or extrusion processes prior to filling. Rubber compound stoppers can be rendered pyrogen-free by multiple cycles of washing and rinsing prior to final steam sterilization.

9.1.3 Product sterilization

9.1.3.1 Where the product is manufactured using an aseptic technique, the materials used in its manufacture (including raw materials incorporated directly in the product, bulk suspensions prepared in advance and container components) shall be sterilized where possible using validated methods of sterilization appropriate to the specific material. The chosen method of sterilization shall be justified.

9.1.3.2 Where the product is manufactured using sterilization based on sterile filtration then the requirements of ISO 13408-2 shall apply.

9.1.3.3 Where it is not possible to sterilize some materials (e.g. live tissues or some live vaccines, the procedures to achieve product of the required quality shall be specified).

9.2 Duration of the manufacturing process

The total time for each unit operation of an aseptic process shall be minimized and limited to a defined maximum. Examples include:

- a) holding time for formulated bulk prior to filtration, where applicable;
- b) holding time for sterilized components prior to and during filling/assembly;

- c) filling or aseptic assembly;
- d) holding sterile product prior to filling;
- e) component washing and sterilization;
- f) maximum exposure time of sterilized containers and closures in the critical processing zone (including filling) prior to closure.

9.3 Aseptic manufacturing procedures

9.3.1 Procedures shall be in place describing the operation of all critical equipment.

9.3.2 Aseptic manufacturing procedures shall be described in detail in documented operating procedures. The procedures shall specify the sequence of steps to be performed, their execution, their time course and any permitted interventions.

9.4 Cleaning and disinfection of facilities

9.4.1 General

9.4.1.1 A cleaning and disinfection programme for the APA shall be specified.

9.4.1.2 Justified procedures shall be in place to evaluate, approve and control the use of cleaning agents and disinfectants.

Cleaning agents and disinfectants used on the same surface shall be mutually compatible.

9.4.1.3 The application of cleaning and disinfection procedures shall be documented and records retained.

9.4.1.4 The removal of disinfectant and cleaning agent residues from critical surfaces shall be validated.

NOTE Residuals from cleaning agents might need to be removed prior to disinfection.

9.4.1.5 Aseptic processing areas shall be cleaned and disinfected at a frequency that provides appropriate environmental control based on the evaluation of environmental data trends and the assessment of product contamination due to the frequency and nature of aseptic processing.

9.4.1.6 Disinfectant and cleaning agent containers and other cleaning equipment to be used in the APA shall be reserved exclusively for this area.

9.4.1.7 The manufacturers' instructions shall be followed with respect to storage and use of cleaning agents and disinfectants unless alternative procedures are justified.

9.4.1.8 Safety regulations shall be considered when selecting cleaning agents and disinfectants and disinfection procedures.

9.4.1.9 Disinfectants and cleaning agents used in the critical processing zone and direct support zones shall be sterile.

9.4.2 Cleaning

The documented cleaning plan shall address at least:

- a) approved agents for cleaning, their working dilution, approved storage time and methods for sterilization, where applicable;
- b) procedures for cleaning;

- c) cleaning aids used, their maintenance and, where applicable, sterilization and storage;
- d) time and frequency of cleaning;
- e) responsibilities.

9.4.3 Disinfection

9.4.3.1 The documented disinfection plan shall address at least:

- a) approved agents for disinfection, their working dilution, approved storage time and conditions, methods for sterilization for ISO 14644-1:1999, Class 5 and Class 7 APAs; a sporicidal agent shall be used if environmental monitoring indicates the necessity;
- b) procedures for disinfection, disinfectant application, required time of action and employee safety precautions;
- c) disinfection aids used, their maintenance and, where applicable, sterilization and storage;
- d) post-disinfection cleaning where required;
- e) time and frequency of disinfection;
- f) responsibilities.

9.4.3.2 Disinfectant containers shall be labelled with an expiration date.

9.4.3.3 Containers for working dilution of disinfectants shall be cleaned thoroughly and sterilized before use for critical processing zone and direct support zone. The use of these containers shall be restricted to one working day.

9.4.3.4 Interchanging or rotating disinfectants should be considered.

NOTE When variations in species or species ratio of microorganisms are observed, interchanging or rotating disinfectants can be considered in order to avoid the development of microbial resistance to the disinfectants.

9.4.4 Equipment used for cleaning/disinfection in APA

9.4.4.1 Equipment used for cleaning/disinfection in the APA shall be of suitable design and approved for use. Equipment in ISO 14644-1:1999, Class 7 or better shall be sterilized before use.

9.4.4.2 The intended use of equipment for cleaning or disinfection in the APA shall be considered and an appropriate evaluation shall be performed. The following characteristics shall be considered for APA use:

- a) particle generation (both wet and dry);
- b) sterilization compatibility;
- c) packaging to ensure sterile transfer into the APA area.

9.4.5 Monitoring of cleaning and disinfection effectiveness

The continued effectiveness of cleaning and disinfection shall be assessed and documented (see 6.8.6).

9.4.6 Effectiveness of disinfection procedures

9.4.6.1 The effectiveness and frequency of application of the disinfection procedure(s) necessary shall be determined.

NOTE Validation of disinfectant effectiveness is usually done in laboratory studies demonstrating the capacity of the agents to inactivate inoculated test microorganisms in suspension and in simulated use conditions. Manufacturer's validation reports, if suitably verified, or validation reports of independent testing institutions, can be accepted if it is confirmed to be relevant to the individual manufacturer situation.

9.4.6.2 Evaluation of the efficacy of disinfection procedures shall be related to the types and numbers of microorganisms recovered from surfaces before and after cleaning.

9.5 Cleaning, disinfection and sterilization of equipment

9.5.1 General

9.5.1.1 A cleaning, disinfection and sterilization programme for the equipment shall be established.

9.5.1.2 Cleaning, disinfection and sterilization shall be documented and records retained.

9.5.1.3 Levels of residuals of cleaning agents shall be controlled at defined and justified maximum levels.

9.5.2 Cleaning of equipment

9.5.2.1 Cleaning procedures for critical surfaces shall be established, validated and documented and shall ensure removal of residues to defined levels.

NOTE Residues can interfere with subsequent disinfection and sterilization.

9.5.2.2 Cleaning procedures shall address:

- a) location where cleaning is to be performed;
- b) procedures for disassembly, cleaning and reassembly;
- c) approved cleaning agent(s) used including their concentration, volume applied, cleanliness grade or specification, pre-treatment (e.g. sterilization) and approved storage time and conditions;
- d) tools to be used (e.g. wipes) including their cleanliness grade or specification, pre-treatment (e.g. sterilization) and storage conditions;
- e) measures to protect cleaned equipment or parts thereof from recontamination;
- f) specification of cleanliness (e.g. permitted residue limits) to be reached;
- g) control measures taken to assure that cleanliness specifications are met.

9.5.2.3 Where cleaning-in-place is used, ISO 13408-4 shall apply.

9.5.3 Disinfection of equipment

9.5.3.1 The effectiveness of the disinfection procedures shall be determined.

9.5.3.2 Disinfection shall follow approved methods which address at least:

- a) procedures for disinfection, disinfectant application, required contact time, post-disinfection cleaning (if required) and employee safety precautions;
- b) approved agents for disinfection, concentration (working dilution), methods for sterilization of the agents, where applicable, approved storage time (expiry dating) and applicable storage conditions;
- c) schedule and responsibility for disinfection.

9.5.4 Sterilization of critical surfaces

9.5.4.1 Critical surfaces of equipment shall be sterile.

NOTE SIP is preferred over disassembly, sterilization and aseptic reassembly.

9.5.4.2 Sterilization procedures shall be validated.

9.5.4.3 Sterilization procedures shall address at least:

- a) detailed procedure for disassembly, pre-treatment, sterilization and reassembly, where applicable;
- b) type of sterilization process and sterilization conditions to be reached;
- c) documented control measures taken to assure that process specifications are met throughout the equipment and all critical surfaces are reached;
- d) procedures to protect sterilized equipment or parts thereof from recontamination;
- e) storage time and conditions of sterilized components where applicable;
- f) procedure and frequency of revalidation measures for the sterilization process.

9.5.4.4 Where sterilization-in-place is used, ISO 13408-5 shall apply.

9.5.5 Endotoxin control on critical surfaces

9.5.5.1 Manufacturers shall document the justification for whether it is necessary to control or reduce the endotoxin level for a particular product or product component.

9.5.5.2 When a process is used to reduce the endotoxin level on critical surfaces, that process shall be validated to demonstrate a defined reduction in endotoxin level.

9.5.5.3 Adequate cleaning, drying and storage procedures shall be approved to control the defined endotoxin level.

10 Process simulation

10.1 General

10.1.1 Process simulation shall cover all parts of the aseptic process and include all aseptic manipulations. It is possible to divide the process into unit operations but all parts of the process shall be simulated. Filter bacterial retentive capacity shall be validated in accordance with ISO 13408-2.

NOTE Process simulation is not intended to validate product sterilization (e.g. the capacity of the sterilizing filter).

10.1.2 For sterile liquids, process simulation shall be conducted using microbiological growth media in lieu of product as the principal method available to assure that the aseptic process is functioning as intended.

For sterile aseptically produced semi-solids, powders, solid materials (including medical devices), microspheres, liposomes and other formulations, evaluation by use of traditional liquid media filling may not be possible. In such cases surrogate procedures that represent the operations as closely as possible shall be developed and justified. These procedures may include processing of a sterile surrogate as normal with subsequent immersion in sterile media or some other means of simulation. Sterility of the surrogate shall be determined after it has been subjected to the total aseptic process.

10.2 Media selection and growth support

10.2.1 The microbiological growth media selected for process simulation runs shall be capable of growing a designated group of reference microorganisms and supporting microbiological recovery of low numbers of these microorganisms.

NOTE Process simulation is usually conducted with soybean casein digest medium. Media fills with anaerobic media can be required if obligate anaerobic organisms are isolated from environmental or product samples.

10.2.2 Where surrogate materials such as buffers are used in parts of the process simulation, the surrogate material shall not inhibit the growth of the reference microorganisms.

10.2.3 Verification of growth promotion of media used in specific simulation runs shall be conducted following incubation of the filled units and shall use an appropriate number of units from the run. Growth promotion tests shall be conducted with the organisms and methods specified in the applicable pharmacopoeias. The growth promotion inoculum shall be less than 100 cfu (colony forming units) per filled unit.

NOTE 1 Examples of pharmacopoeias include Ph.Eur, JP and USP.

NOTE 2 For complex process simulations, it can be necessary to ascertain that the samples of media taken for growth promotion testing are representative of the entire process to ensure that no parts of the process alter the growth-promoting properties of the media.

10.3 Simulation procedures

10.3.1 Process simulations shall be conducted under conditions that simulate routine manufacturing procedures and shall, as far as is reasonably practicable, include permissible worst case conditions.

Simulations shall include:

- a) maximum permitted holding times and interventions representative of the routine process at the maximum accepted frequency per number of filled units (e.g. weight adjustments, container/closure or product re-supply, sampling or environmental monitoring);
- b) frequently occurring unscheduled interventions in representative number and with the highest degree of intrusion acceptable (e.g. corrections for container breakage or tip-over, corrections for leakage of fluid, corrections for stopper jams, correction of line stoppage).

A list of permitted interventions shall be prepared and retained.

10.3.2 If multiple sizes of the same container/closure configuration are filled aseptically, representative sizes may be used for initial validation (i.e. bracketing).

NOTE 1 Following initial validation each configuration can be used in a process simulation at a defined frequency.

NOTE 2 Containers with the widest diameter openings and operation at the lowest line speed can represent a worst case due to longest exposure, whereas small containers can represent a worst case due to lack of container stability in the line operations and the need for increased manual intervention.

10.3.3 Process simulation shall be performed in conjunction with a comprehensive environmental monitoring programme.

10.3.4 The volume filled per container shall be sufficient to wet all surfaces of the containers when swirled or inverted, and provide sufficient head space to ensure capability of microbial growth and to ensure that turbidity can be detected at examination.

10.3.5 The container shall be sufficiently transparent to allow evaluation of turbidity of the contents. If this is not possible the examination shall be by transfer of the entire contents to a transparent vessel.

10.3.6 For products manufactured routinely under an inert atmosphere, the inert gas shall be substituted with air in the process simulation unless anaerobic simulation is intended.

10.3.7 Units (either individually or grouped) from process simulation should be identified chronologically or otherwise to assist in the investigation should one become necessary.

For lyophilized products process simulation, ISO 13408-3 applies.

10.3.8 Process simulation runs shall be conducted over the maximum permitted filling time. Where this is not possible, simulation runs shall be of sufficient duration to cover representative manipulations, interventions and shift changes performed in actual processing.

Where the actual aseptic process is interrupted (e.g. during the night and continued the next day) such breaks should also be simulated. Environmental monitoring shall be conducted to ensure that there has been no deterioration of the filling environment.

10.4 Incubation and inspection of media filled units

10.4.1 Media filled containers shall be agitated, swirled or inverted before incubation to ensure contact of the media with all interior surfaces in the container.

10.4.2 Units that are leaking, broken or otherwise damaged to the extent that there is no question of their not being rejected during routine documented visual inspection procedures shall be recorded and removed. Cosmetic defects, non-destructive weight checks and all other units shall be identified and incubated with the other units.

If documentation clearly describes the disposition of containers exposed during interventions and these are normally discarded, then there is no need to incubate such containers produced during process simulation tests.

10.4.3 Media fill evaluation units shall be incubated for not less than 14 days. Incubation temperatures shall be within the range of 20 °C to 35 °C. The use of a specific temperature or temperature range shall be justified and documented.

NOTE If two temperatures are used for incubation, the units are typically incubated for at least 7 days at each temperature (starting with the lower temperature).

10.4.4 After completion of the incubation period the media filled containers shall be inspected for the presence of microbial growth using a defined procedure.

NOTE Inspection of the units at an earlier time period can be useful to gain a preliminary indication of the results.

10.4.5 Microorganisms isolated from contaminated units shall be identified to species level or to a level required to assist in the determination of the likely source of the contaminant.

NOTE Genotypic identification methods can be of use in assisting in determining the likely sources of contaminants if applied to test and environmental isolates.

10.5 Initial performance qualification

10.5.1 General

Initial performance qualification shall be conducted for each aseptic processing operation for each line and for each unique product configuration that has not been represented in a previous performance qualification.

10.5.2 Numbers to be filled

10.5.2.1 A sufficient number of units shall be processed (filled) to simulate effectively all activities that are representative of the manufacturing process.

10.5.2.2 The minimum number of simulations and the number of units filled per simulation are summarized in Table 1.

NOTE It might be necessary to fill more than the minimum number of containers per media fill run in order to accommodate process variables and interventions routinely encountered during production.

10.5.3 Acceptance criteria

10.5.3.1 The aim of any process simulation shall be to achieve zero contaminated units.

NOTE As the aim is to fill sterile product and not to fill product with a low number of contaminated units, the filling of a larger number of vials does not result in a higher number of contaminated units that can be accepted.

10.5.3.2 Any contaminated unit shall result in an investigation to determine the cause (if possible).

For acceptance criteria, see Table 1.

10.6 Periodic performance requalification

10.6.1 Scheduling requirements

10.6.1.1 Scheduled process simulation requalification shall be conducted twice annually (approximately every six months) for each aseptic process and filling line. A single filling configuration shall be chosen for each requalification run. The line qualification shall include the activities and interventions representative of each shift and shift changeover.

10.6.1.2 Aseptic filling lines and product/container configurations used less frequently than every six months shall be requalified with an acceptable process simulation test before production is resumed.

10.6.1.3 Requalification of the process or line prior to the scheduled six-month interval should be performed when investigation identifies the need, e.g. in case of major changes in personnel, anomalies in environmental monitoring results or finished product sterility test results.

NOTE Change control might require requalification.

10.6.2 Numbers to be filled

The minimum number of runs and the number of units filled per simulation are summarized in Table 2.

NOTE It can be necessary to fill more than the minimum number of units per media fill run in order to accommodate process variables and interventions routinely encountered during production.

10.6.3 Acceptance criteria

10.6.3.1 The aim of the process simulation shall be zero contaminated units.

10.6.3.2 Each process simulation resulting in contaminated units shall be investigated.

10.6.3.3 Acceptance criteria are shown in Table 2.

10.6.3.4 Where contaminated units are found, corrective measures shall be taken before the performance qualification is restarted.

10.7 Repeat of initial performance qualification

An aseptic process or filling line shall be subject to a repeat of the initial qualification studies when:

- a) requalification of the line has failed;
- b) production lines have not been in operation for an extended period of time, e.g. one year;
- c) there has been a change that has potential to affect the aseptic process.

10.8 Documentation of process simulations

10.8.1 All process simulation runs shall be fully documented. All runs shall include a reconciliation of units processed. Information included with, or cross referenced in, the records for each process simulation run should be, e.g.:

- a) date and time of process simulation;
- b) identification of processing area or room used;
- c) container/closure type and size;
- d) volume filled per container;
- e) processing speed;
- f) type of media filled;
- g) number of units filled;
- h) number of units rejected at inspection and the reason for the rejection;
- i) number of units incubated;
- j) number of units positive;
- k) incubation time(s) and temperature(s);
- l) procedures used to simulate any steps of a normal production fill, which might include, for example, mock lyophilization or substitution of vial headspace gas;
- m) microbiological monitoring data obtained during the media fill set-up and run;
- n) list of personnel per shift who participated in the process simulation;
- o) growth promotion results;
- p) identification of the microorganisms from any positive units;
- q) management review;
- r) product(s) covered by the process simulation;
- s) investigation of runs with a positive unit or failed runs.

10.8.2 Where investigations conclude or suggest a cause of the failure, corrective measures shall be implemented.

The effectiveness of the corrective measures should be investigated, where possible, and verified separately before conducting additional runs.

10.9 Disposition of filled product

10.9.1 All product that has been produced on a line subsequent to the process simulation shall be quarantined until a successful resolution of the process simulation has occurred.

10.9.2 In case of a failed process simulation there shall be a prompt review of all appropriate records relating to aseptic production since the last successful process simulation. The outcome of the review shall include justification for the disposition of batches of product affected.

Table 1 — Media fills — Initial performance qualification

Minimum number of simulations	Number of units filled per simulation	Contaminated units in any of the three simulations	Simulation runs affected by contaminated units	Action
3	< 5 000	≥ 1	≥ 1	Investigation, corrective measures, restart validation
3	5 000 to 10 000	1	1	Investigation, consideration of repeat of one media fill
		> 1	> 1	Investigation, corrective measures, restart validation
3	> 10 000	1	1	Investigation
		> 1	> 1	Investigation, corrective measures, restart validation

Table 2 — Media fills — Periodic performance requalification

Minimum number of simulations	Number of units filled per simulation	Contaminated units	Action
Two per year ^a	< 5 000	1	Investigation, revalidation
	5 000 to 10 000	1	Investigation, consideration of repeat media fill
		> 1	Investigation, corrective measures, revalidation
	> 10 000	1	Investigation
		> 1	Investigation, corrective measures, revalidation

^a The simulations shall cover all line configurations and all shifts.

11 Test for sterility

11.1 General

Where sterility testing is required for aseptically-filled products, this testing shall be conducted for each batch. The pharmacopoeial sterility tests are used when the method is applicable. Where there is no specific method in the pharmacopoeia that is applicable to a particular product the manufacturer shall specify the method to be used.

NOTE 1 Examples of pharmacopoeias include Ph.Eur., JP and USP.

NOTE 2 In certain jurisdictions approval of non-pharmacopoeial sterility tests is required by the relevant competent authorities.

11.2 Investigation of positive units from tests for sterility

11.2.1 Positive units from a test for sterility shall be evaluated and an investigation shall be initiated to determine the source of contamination, including whether the growth occurred due to contamination during the test.

11.2.2 A correlation assessment shall be conducted between types of microorganisms found in the manufacturing environment and the sterility testing room and those isolated from positive units using tests for sterility.

NOTE Further guidance on the investigation of organisms isolated from positive units using tests for sterility can be found in the pharmacopoeias.

Annex A
(informative)

Example of a flow chart

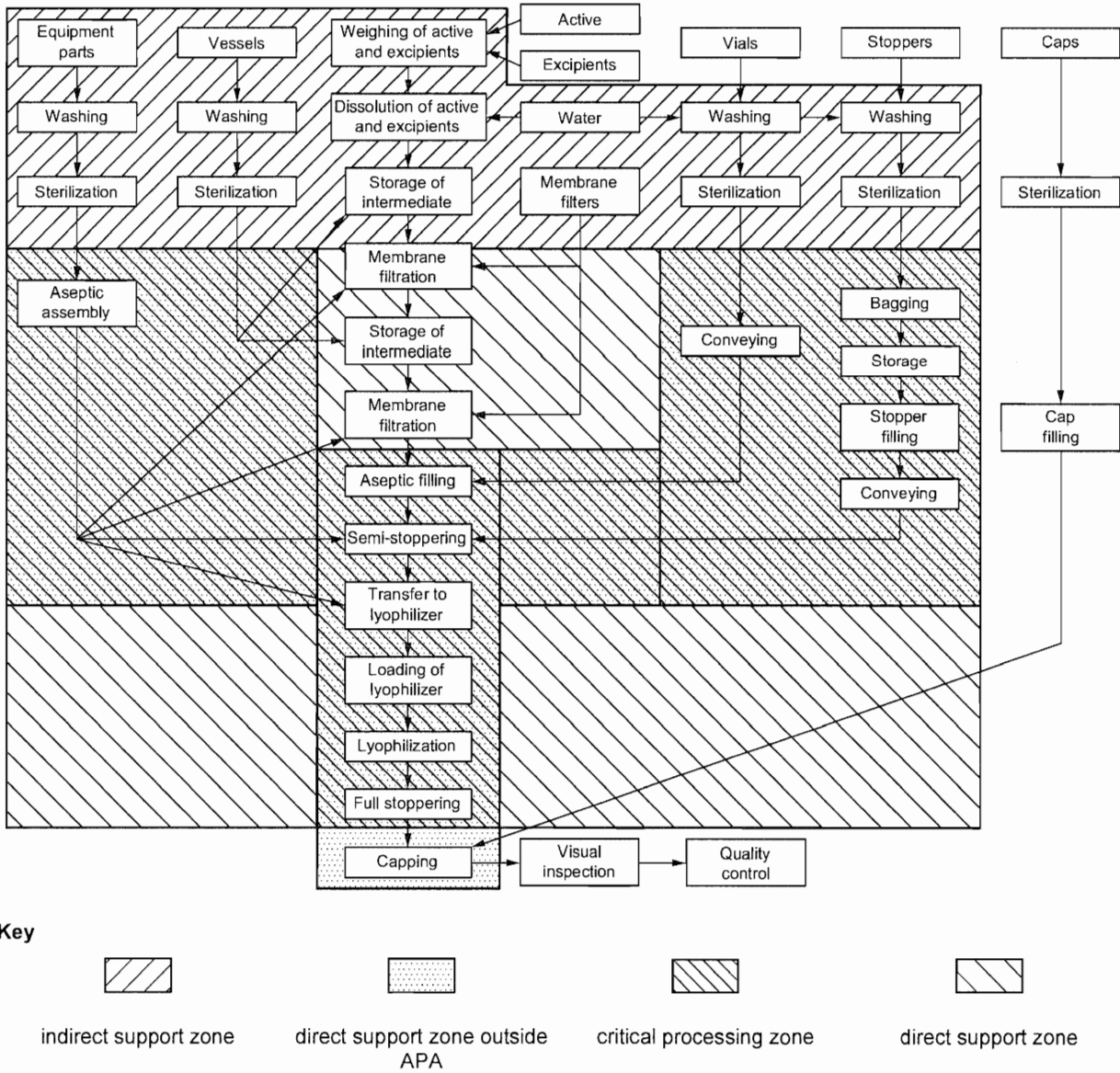


Figure A.1 — Example of an aseptic process divided into unit operations

Annex B (informative)

Typical elements of an aseptic process definition

The following list contains typical elements that should be compiled to establish and document an aseptic process definition:

- a) justification (for not using terminal sterilization);
- b) applicable regulatory requirements and guidance;
- c) applicable quality management systems;
- d) facilities design;
- e) equipment design;
- f) product and delivery system;
- g) processes and technologies implemented;
 - 1) product and component preparation;
 - 2) product, component and equipment sterilization/depyrogenation;
 - 3) aseptic process containment, i.e., RABS (restricted access barrier system), isolators or cleanrooms;
 - 4) personnel protection systems'/methods' effect on aseptic processing;
 - 5) product manufacturing methods;
 - 6) closure/packaging integrity assurance;
- h) environmental control and monitoring programme;
- i) master validation plan (e.g., process simulations, validation of unit operations);
- j) change control process;
- k) product release process.

In preparing an aseptic process definition, products might be grouped together based on their characteristics and presentation.

NOTE It is useful to organize the aseptic process by unit operations, see example of a flow chart in Annex A.

Annex C (informative)

Examples of specific risks

Table C.1 is given for guidance only. It includes examples of specific risks that might be of relevance in the risk management strategy.

Table C.1 — Examples of specific risks including examples of control measures^a

Aspect	Examples	Examples of specific microbiological risks	Examples of control measures ^a
Ingredients	<ul style="list-style-type: none"> • Biological origin • Natural product • Synthetic origin • Ingredient with biocidal activity 	<ul style="list-style-type: none"> • High numbers of yeast, mould and bacteria • Mycoplasma • Viruses • Endotoxin level • Prions 	<ul style="list-style-type: none"> • Choice of approved suppliers • Supplier audits • Supplier certificates • Control of incoming materials • Control of pre-filtration bioburden (yeasts, moulds and bacteria) • Ultrafiltration (endotoxins)
Nature of the product	<ul style="list-style-type: none"> • Solution (preserved or unpreserved) • Suspension • Crystallized powder • Lyophilized powder • Cream or ointment • Solid device • Combination product Formulations with biocidal activity 	<ul style="list-style-type: none"> • Ability to support microbial growth • Bioburden increase • Endotoxin contamination • Contamination during manufacture 	<ul style="list-style-type: none"> • Perform growth studies on product (if water based, non preserved) • Single dose formulation • Water activity determination • Holding time limitations of non sterile bulk • Refrigeration of non sterile bulk • In process bioburden monitoring
Product presentation/design	<ul style="list-style-type: none"> • Ampoules • Vials • Pre-filled syringes • Form-fill-seal • Multi-dose containers 	<ul style="list-style-type: none"> • Contamination during manufacture 	<ul style="list-style-type: none"> • 100 % leak test • Container closure integrity test • Use of RABS or isolators • Dual filters, final filter close to point of fill • Environmental programme including continuous particle monitoring
Technical complexity of the manufacturing process	<ul style="list-style-type: none"> • Multi-stage manufacturing • Manual assembly steps • Complicated delivery device 	<ul style="list-style-type: none"> • Contamination during manufacture 	<ul style="list-style-type: none"> • Use of RABS or isolators • Pressurize sterile bulk tanks during holding time • CIP/SIP of all sterile product contact parts • Robotic assembly versus manual • Automatic transport and loading/unloading of freeze dried products
Intended clinical use of the product	<ul style="list-style-type: none"> • Topical use • Parenteral use • Eye care • Single dose/Multiple use • Implantable • Multidose preservative free presentations 	<ul style="list-style-type: none"> • Potential impact of product 	<ul style="list-style-type: none"> • Patient convenience devices • Nurse convenience devices (e.g. for reconstitution of vials) • In-use time studies • New preservative systems

^a These are examples only; alternative measures may be available and may be more effective for a specific application.

Annex D (informative)

Comparison of classification of cleanrooms

In this part of ISO 13408 reference has been made to ISO 14644-1 classification only. This annex gives information on other regional and/or national classification systems.

Table D.1 — Classification systems

ISO 14644-1 (particles > 0,5 µm/m ³)	Classification according to			
	ISO 13408-1	Traditional ^a (particles ≥ 0,5 µm/ft ³)	EU GMP Guide Annex 1 ^b (in operation)	EU GMP Guide Annex 1 ^b (at rest)
5 (3 520)	Critical processing zone	100	Grade A	Grade A and B
6 (35 200)	Not defined	1 000	Not defined	Not defined
7 (352 000)	Direct support zone	10 000	Grade B	Grade C
8 (3 520 000)	Indirect support zone ^c	100 000 ^c	Grade C	Grade D
			Grade D	undefined

^a FDA Guidance for aseptic processing, September 2004.

^b EU GMP Guide, Annex 1:2003 (drafted revision 2005) refers to ISO 14644 but limits for non-viable particles are defined differently.

^c Activities performed in these zones are split in the EU GMP Guide, Annex 1 into Grade C and D.

Annex E (informative)

Specification for water used in the process

E.1 Source water

E.1.1 Potable water or water brought to potable water specification shall be the source water for the manufacture of purified water qualities used in aseptic manufacturing. Other use of source water shall be restricted to cleaning purposes outside of the APA, and for washing of hands in gowning rooms.

E.1.2 A specification shall be established and documented for source water. Due account shall be taken of local legislation relating to the quality of source water in setting this specification.

E.2 Treated source water

E.2.1 If source water is given additional treatment to reduce further the bioburden, then strict separation shall be maintained between such water and untreated source water.

NOTE 1 Suitable additional treatments can include ozonation or chlorination as an initial step.

NOTE 2 Treated source water can also be used in certain circumstances such as spray coolant in such autoclaves where the coolant cannot be sterilized (e.g. by recirculating throughout the autoclave).

E.2.2 Treated source water for spray cooling during autoclave cycles shall be monitored frequently for microbial content and for activity of added substance(s).

E.3 Purified water

E.3.1 Purified water can be used in initial rinsing of components, equipment, closures, etc. Purified water can be used as an ingredient in certain non-parenteral products, e.g. contact lens solutions.

NOTE Purified water might be defined in national and regional pharmacopoeias.

E.3.2 The microbial content shall be monitored and controlled to a limit appropriate to the intended use of the water as may be required by applicable regulatory or pharmacopoeia specifications.

NOTE Suitable test methods can be found in the pharmacopoeias.

E.3.3 Purified water distributed in fixed systems shall be circulated or kept in motion to minimize the formation of biofilm inside pipes and tanks. The system shall be sanitized according to a specified and documented frequency.

E.3.4 The water distribution system shall be designed to avoid areas where water does not flow freely and shall not allow water to stagnate.

E.3.5 If bacteria-retentive filters are used in the system they shall be sterilized, integrity tested, and shall be changed according to a defined frequency and procedure. Filters of other porosities, e.g. particulate retentive filters, if used, shall be changed at a defined frequency.

E.3.6 Tanks and distribution systems for purified water should be constructed from suitable materials for the intended use.

E.4 Water for injections

E.4.1 Water for injection (WFI) shall be used for formulation of injectable products and other health care products as required by national regulations and in final rinsing of components, equipment, closures, etc. for the manufacture of such products.

E.4.2 The feed-water to the WFI equipment shall be pretreated appropriately. Attention should be paid to bioburden and/or endotoxin levels in the feedwater.

The composition of the incoming source water should determine the choice of subsequent pretreatment steps. If chlorine is present, the use of a carbon bed should be considered. If colloids, organic substances or silicates in the source can penetrate the ion exchangers, additional steps like single or double pass reverse osmosis units can be employed as additional steps. It is recommended that the feed water be circulated in order to minimize the formation of biofilm.

E.4.3 WFI in distribution systems shall be maintained at $> 70\text{ }^{\circ}\text{C}$ and circulated within a loop. Where temperatures are $< 70\text{ }^{\circ}\text{C}$ a validated periodic sanitization cycle shall be used. The system shall be designed to avoid areas where water does not flow freely, and shall not allow water to stagnate. The temperature should minimally be monitored and recorded at the end of the return loop.

E.4.4 The WFI distribution system shall be made of stainless steel suitable for the intended use. Its suitability shall be documented in the design qualification. Guidelines, e.g. ISPE Baseline, may be consulted for design aspects of finish, welding, slope, etc.

E.4.5 Frequent monitoring of conductivity, TOC, bioburden and endotoxins shall be undertaken. Specified and documented monitoring shall be performed on all use points where water can be drawn from the system.

NOTE Suitable test methods can be found in the pharmacopeias.

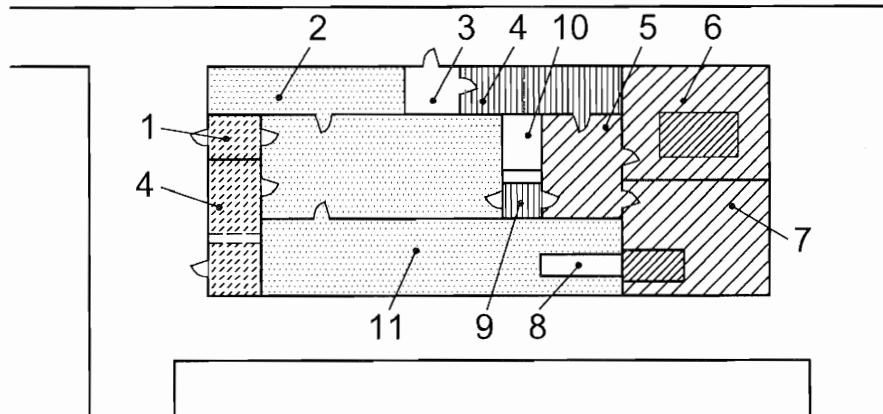
E.4.6 Disinfection or sanitization of the WFI system shall be undertaken according to a defined procedure and frequency, and after a system breach or after a system integrity failure. If chemicals are used in the cleaning/disinfection/sanitization process their removal from the system shall be validated and confirmed.

WFI systems recirculating continuously at $> 70\text{ }^{\circ}\text{C}$ may not require periodic disinfection unless a system breach or integrity failure has occurred. However, provisions are recommended for heating up to, e.g., $95\text{ }^{\circ}\text{C}$ under certain circumstances.

Annex F
(informative)

Aseptic processing area

Figure F.1 illustrates an example of an aseptic processing area.



Key



critical processing zone direct support zone direct support zone at rest indirect support zone indirect support zone at rest non-classified areas

- | | |
|------------------------------------|-----------------------------------|
| 1 material airlock | 7 aseptic processing room 2 |
| 2 preparation of product solutions | 8 vial washer, sterilizing tunnel |
| 3 airlock | 9 material airlock |
| 4 changing room | 10 autoclave |
| 5 cooling area | 11 final washing |
| 6 aseptic processing room 1 | |

Figure F.1 — Aseptic processing area

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