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Third 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

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The procedures used to develop this document and those intended for its further maintenance are described in the ISO/IEC Directives, Part 1. In particular, the different approval criteria needed for the different types of ISO documents should be noted. This document was drafted in accordance with the editorial rules of the ISO/IEC Directives, Part 2 (see www.iso.org/directives).

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

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

The main changes are as follows:

— a complete restructuring of the document;

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

— revision of the normative references;

— alignment of definitions with ISO 11139:2018;

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

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

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

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

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

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

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

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

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

Introduction

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

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

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

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

Examples of applications in which aseptic processing is used include:

— aseptic handling and filling of solutions, suspensions, semisolids and powders;

— aseptic handling, transfer and packaging of solid products including solid medical devices;

— aseptic handling, transfer and packaging of combination products;

— aseptic handling of tissues or biological production systems (e.g. vaccines).

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

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

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

— process design;

— risk assessment;

— contamination control strategy (CCS).

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

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

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

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

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

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

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

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

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

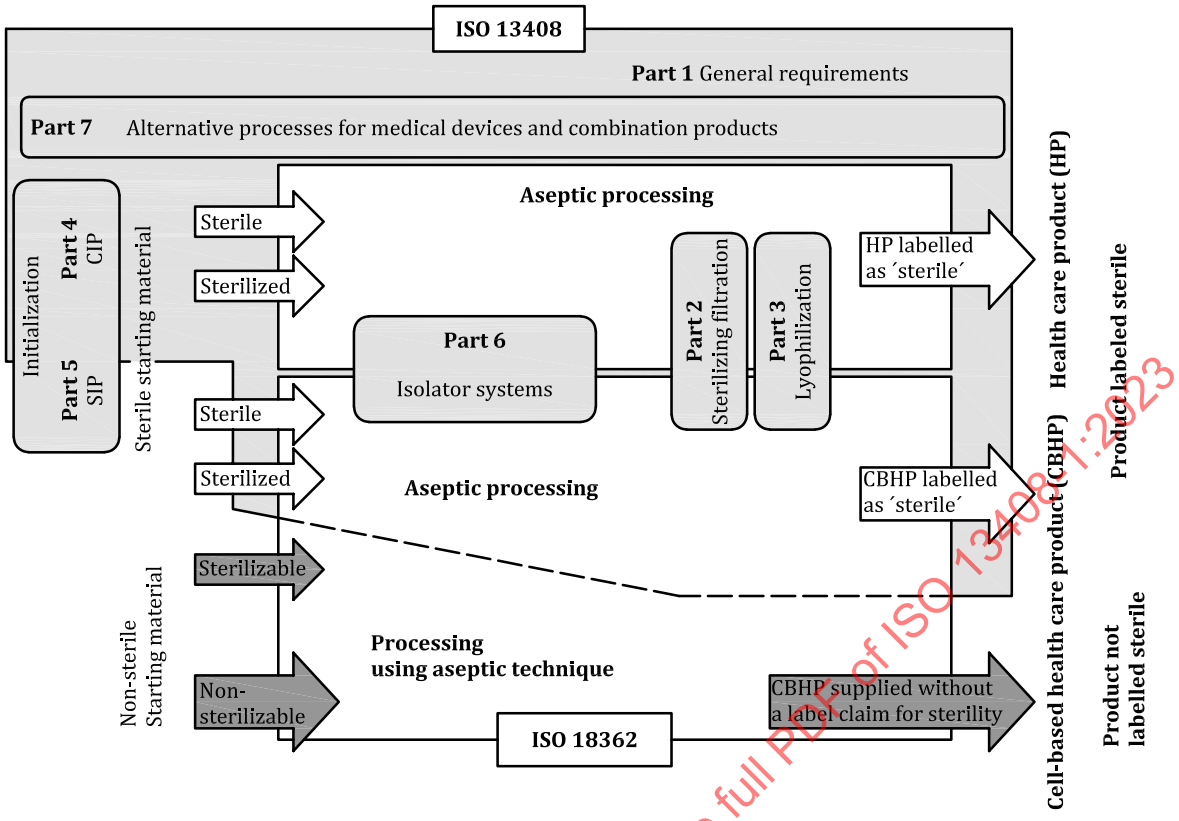


Figure 1 — Relationship between the ISO 13408 series and ISO 18362

Aseptic processing of health care products —

Part 1:
General requirements

1 Scope

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

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

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

2 Normative references

The following documents are referred to in the text in such a way that some or all of their content constitutes requirements of this document. For dated references, only the edition cited applies. For undated references, the latest edition of the referenced document (including any amendments) applies.

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

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

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

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

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

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

3 Terms and definitions

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

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

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

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

3.1
action level
value from monitoring that necessitates immediate intervention

[SOURCE: ISO 11139:2018, 3.5]

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

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

[SOURCE: ISO 11139:2018, 3.10]

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

[SOURCE: ISO 11139:2018, 3.11]

3.5
aseptic processing
handling of sterile product, containers and/or devices in a controlled environment in which the air supply, materials, equipment and personnel are regulated to maintain sterility

[SOURCE: ISO 11139:2018, 3.14]

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

[SOURCE: ISO 11139:2018, 3.15]

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

Note 1 to entry: For the purposes of aseptic processing, the bioburden of concern is that on or in the product including all factors affecting it such as raw materials, intermediates, other components and equipment.

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

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

[SOURCE: ISO 11139:2018, 3.27]

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

[SOURCE: ISO 11139:2018, 3.46]

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

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

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

[SOURCE: ISO 11139:2018, 3.50]

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

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

[SOURCE: ISO 11139:2018, 3.54]

3.13
correction
action to eliminate a detected nonconformity

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

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

[SOURCE: ISO 9000:2015, 3.12.3]

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

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

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

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

[SOURCE: ISO 9000:2015, 3.12.2]

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

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

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

[SOURCE: ISO 11139:2018, 3.67]

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

[SOURCE: ISO 11139:2018, 3.68]

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

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

[SOURCE: ISO 11139:2018, 3.77]

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

[SOURCE: ISO 11139:2018, 3.220.1]

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

[SOURCE: ISO 11139:2018, 3.81]

3.21
disinfectant
chemical or combination of chemicals used for disinfection

[SOURCE: ISO 11139:2018, 3.82]

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

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

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

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

[SOURCE: ISO 11139:2018, 3.101]

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

[SOURCE: ISO 11139:2018, 3.127]

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

[SOURCE: ISO 11139:2018, 3.132]

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

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

[SOURCE: ISO 11139:2018, 3.142]

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

[SOURCE: ISO 11139:2018, 3.220.2]

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

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

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

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

[SOURCE: ISO 11139:2018, 3.220.3]

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

[SOURCE: ISO 11139:2018, 3.192]

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

[SOURCE: ISO 11139:2018, 3.220.4]

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

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

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

[SOURCE: ISO 9000:2015, 3.12.1]

3.33
process analytical technology
PAT
system for designing, analyzing, and controlling manufacturing through timely measurements (i.e. during processing) of critical quality and performance attributes of raw and in-process materials and processes with the goal of ensuring final product quality

[SOURCE: ICH Q8, 3]

3.34
process simulation
exercise that mimics the manufacturing process or portions of the process in order to demonstrate the capability of that process

[SOURCE: ISO 11139:2018, 3.212]

3.35
protective packaging
configuration of materials designed to prevent damage to the sterile barrier system and its contents from the time of their assembly until the point of use

[SOURCE: ISO 11139:2018, 3.219]

3.36
qualification
activities undertaken to demonstrate that utilities, equipment, and methods or modes are suitable for their intended use and perform properly

Note 1 to entry: Qualification of equipment and/or processes generally includes *installation qualification* (3.27), *operational qualification* (3.29) and *performance qualification* (3.31).

[SOURCE: ISO 11139:2018, 3.220]

3.37
quality by design
QbD
systematic approach to development that begins with predefined objectives and emphasizes product and process understanding and process control, based on sound science and quality risk management

[SOURCE: ICH Q8, 4]

3.38
restricted access barrier system
RABS
system that provides a segregated, but not sealed, controlled environment using physical barriers and air overspill and which is capable of being subject to reproducible interior bio-decontamination

Note 1 to entry: Operators are separated from the controlled environment using an absolute physical barrier, but can access the controlled environment by opening the physical barrier (e.g. a door).

3.39
risk assessment
overall process comprising a risk analysis and a risk evaluation

[SOURCE: ISO/IEC Guide 51:2014, 3.11]

3.40
risk control
process in which decisions are made and measures implemented by which risks are reduced to, or maintained within, specified levels

[SOURCE: ISO/IEC Guide 63:2019, 3.12]

3.41
risk evaluation
process of comparing the estimated risk against given risk criteria to determine the acceptability of the risk

[SOURCE: ISO/IEC Guide 63:2019, 3.14]

3.42
risk management
systematic application of management policies, procedures and practices to the tasks of analysing, evaluating, controlling and monitoring risk

[SOURCE: ISO/IEC Guide 63:2019, 3.15]

3.43
separative device
equipment utilizing constructional and dynamic means to create assured levels of separation between the inside and outside of a defined volume

Note 1 to entry: Some industry-specific examples of separative devices are clean air hoods, containment enclosures, glove boxes, isolators and mini-environments.

[SOURCE: ISO 11139:2018, 3.250]

3.44
shift
scheduled period of work or production staffed by a single defined group of workers

[SOURCE: ISO 11139:2018, 3.253]

3.45
sterile
free from viable microorganisms

[SOURCE: ISO 11139:2018, 3.271]

3.46
sterile barrier system
SBS
minimum package that minimizes the risk of ingress of microorganisms and allows aseptic presentation of the sterile contents at the point of use

[SOURCE: ISO 11139:2018, 3.272]

3.47
sterilization
validated process used to render a product free from viable microorganisms

Note 1 to entry: In a sterilization process, the nature of microbial inactivation is exponential and thus the survival of a microorganism on an individual item can be expressed in terms of probability. While this probability can be reduced to a very low number, it can never be reduced to zero.

Note 2 to entry: Note 1 to entry is not applicable to sterilizing filtration.

[SOURCE: ISO 11139:2018, 3.277, modified — Note 2 to entry added.]

3.48
terminal sterilization
process whereby a product is sterilized within its sterile barrier system

[SOURCE: ISO 11139:2018, 3.295]

3.49
unidirectional airflow
air stream which has a defined direction

[SOURCE: ISO 11139:2018, 3.308]

3.50
unit operation
defined part of a manufacturing process

Note 1 to entry: See example of a flowchart in Annex E.

[SOURCE: ISO 11139:2018, 3.309, modified — Note 1 to entry added.]

3.51
validation
confirmation process, through the provision of objective evidence, that the requirements for a specific intended use or application have been fulfilled

[SOURCE: ISO 11139:2018, 3.313, modified — Notes to entry deleted.]

4 General

4.1 Aseptic processing activities are undertaken in accordance with quality risk management (QRM) principles to manage microbiological contamination risks to product quality. To ensure the consistent implementation of the requirements specified in this document, the necessary processes shall be established, implemented and maintained. Processes of particular importance in relation to aseptic processing include, but are not limited to:

— control of documentation, including records,

— assignment of management responsibility,

— provision of adequate resources, including competent human resources and infrastructure,

— control of the product provided by external parties,

— judicious decision-making during product lifecycle, including modernizing and improving aseptic processes to further reduce risks to product quality,

— establishment of aseptic processing and maintenance of a state of microbiological control,

— investment in aseptic process understanding and monitoring of process performance,

— identification and traceability of the product throughout the process, and

— control of a non-conforming product including related corrective and preventive actions.

NOTE Quality management is a management function that directs and controls an organisation in relation to quality. The essential concepts of good manufacturing practice (GMP), quality control and quality assurance are interconnected within the context of quality management. Their significance in aseptic processing of medicines and CBHPs is described in national and regional codes of GMP. For medical devices, ISO 13485 covers all stages of the product lifecycle in the context of quality management systems for regulatory purposes. National and/or regional regulatory requirements for the provision of health care products can require the implementation of a full quality management system and the assessment of that system by a recognized conformity assessment body.

4.2 A process shall be specified for the calibration of all equipment, including instrumentation for test purposes, used in meeting the requirements of this document.

5 Principles of aseptic processing

5.1 General

5.1.1 Aseptic processing is an activity composed of individual unit operations that shall be effectively combined to maintain sterility. These operations shall be documented and justified.

5.1.2 The use of advanced aseptic processing systems shall be considered as part of the risk management process.

NOTE 1 The aseptic processing encompasses all set-up activities conducted in the aseptic processing area (APA) in preparation for product manufacture and all production steps following sterilization of product and components until sealing of the final container or package.

NOTE 2 Further guidance on unit operations and typical elements of aseptic processes can be found in Annex A.

5.1.3 At each stage of the design, development qualification and operation of aseptic processing, risks shall be assessed, controlled and where appropriate, monitored. Risk assessments shall be documented.

5.1.4 A contamination control strategy (CCS) shall be developed, which describes how the identified risks are monitored and controlled to minimise the risk of product contamination.

5.1.5 The effectiveness of risk control measures shall be assessed.

5.1.6 A risk-based approach shall be used in the design of processes, layouts, activities and testing regimes.

Figure 2 illustrates the activities that are key to development and operation of aseptic processing.

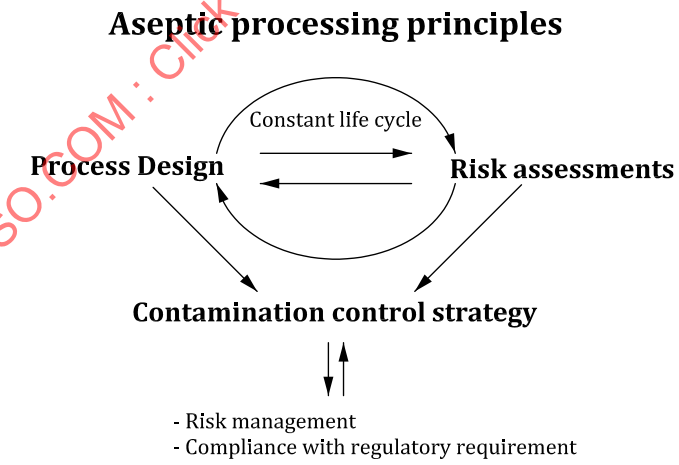


Figure 2 — Key activities in the development and operation of an aseptic process and their relationships

5.2 Use of an aseptic process

The requirement for a product to be supplied sterile shall be identified as an input to process design and development.

The ability of the product to withstand a terminal sterilization process that delivers a specified sterility assurance level (SAL) shall be assessed.

Where possible, a sterile product shall be sterilized in its final container by a validated terminal sterilization process. If a product is not able to withstand the processing conditions for terminal sterilization, then aseptic processing provides an acceptable alternative for manufacture of sterile product.

The rationale for selection of aseptic processing for a product shall be documented. The rationale shall include the strategies investigated to overcome the detrimental effects on a product of a terminal sterilization process and technical reasons to support the selection of aseptic processing for that product. The rationale shall include, but is not limited to, discussion of:

a) The feasibility of changing materials or formulation to enable the product to withstand the processing conditions for a terminal sterilization process.

b) The feasibility of redesigning or modifying the product or sterile barrier system (SBS) to enable the product to withstand the processing conditions for terminal sterilization.

c) The feasibility of changing the presentation of the product to a sterilization process to reduce the extent of processing conditions for terminal sterilization.

d) The feasibility of reducing and controlling the product and packaging bioburden to allow the use of sterilizing conditions that have a less detrimental effect.

e) The feasibility of changing the process parameters of a sterilization process to reduce detrimental effects on the product.

f) The feasibility of establishing a terminal sterilization process with less severe processing conditions than an overkill process, e.g. use of the bioburden-based, or combined bioburden-biological indicator approaches to the process definition.

g) The feasibility of considering different terminal sterilization modalities to mitigate detrimental effects associated with a particular terminal sterilization modality.

h) Where applicable, evidence that product packaging, which cannot be terminally sterilized, provides enhanced application and/or therapeutic advantages.

i) For a product with a short shelf-life, whether terminal sterilization adversely affects product stability and further reduces shelf-life.

j) Where applicable, the volume administered per dose, noting that where possible, a large volume parenteral product shall be terminally sterilized.

k) A comprehensive evaluation of the benefit-risk ratio in relation to aseptic processing versus terminal sterilization.

The rationale to select aseptic processing shall still be documented when a product:

— contains a material or substance that is clearly recognized as incompatible with terminal sterilization; or

— is recognized as being manufactured traditionally by aseptic processing, for example, some ophthalmic preparations,

NOTE 1 Guidance can be found in ISO/TS 19930:2017, Clause 7, Reference [35] and Reference [46].

NOTE 2 National or regional requirements can apply to aseptically processed medical devices that are designated ‘sterile’, for example, EN 556-2 and ANSI/AAMI ST67:2019.

5.3 Core elements

Core elements that shall be considered during the process design, CCS and risk assessment are:

a) environment and air handling (including facility and premises);

b) materials and components (including surfaces);

c) handling and processing (including personnel);

d) equipment (e.g. barrier systems, filling and sealing equipment, automation, robotics) and utilities;

e) the product;

f) flow management;

g) cleaning and disinfection.

NOTE There can be other elements to consider depending on either the product or the process, or both.

5.4 Aseptic processing zones

5.4.1 General

Aseptic processing zones shall be specified for the aseptic processing activities.

NOTE 1 Further guidance on aseptic processing zones is given in Annex C.

NOTE 2 Further guidance on classification of cleanrooms is given in Annex D.

5.4.2 Critical processing zone

The critical processing zone shall be segregated and operated in a way that ISO 14644-1:2015, Class 5 conditions are maintained.

NOTE 1 This document refers to the classifications of air cleanliness by particle concentration according to ISO 14644-1, which are referred to as, for example, ISO Class 5, ISO Class 8 etc.

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

a) aseptic assembly of filling equipment;

b) aseptic connections;

c) aseptic compounding and mixing;

d) staging and conveying of sterilized primary packaging materials;

e) aseptic filling, stoppering, transfer of open or partially stoppered containers, including interventions;

f) environmental monitoring.

Where separative devices are used for segregation of critical processing zones, either ISO 13408-6 or ISO 14644-7, or both shall apply.

5.4.3 Direct support zones

For a critical processing zone, a direct support zone with at least an ISO 14644-1:2015, ISO Class 7 environment shall be provided to prevent contamination of the critical processing zone.

In the case of an isolator system or similar separative device, the necessary surrounding environmental class shall be determined according to 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) preparation of operators for interventions in the critical processing zone (e.g. disinfection of gloves, staging of tools).

5.4.4 Indirect support zones

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

NOTE 1 A clean zone corresponding to ISO 14644-1:2015, ISO 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 Process design, development and risk management

6.1 General

6.1.1 The inputs, including product attributes, for designing the aseptic process shall be documented.

A formal, risk-based design and development process shall be used to develop the aseptic process.

The design, development and risk management process shall:

— consider all core elements of an aseptic process (see 5.3);

— include a documented analysis of contamination risk.

6.1.2 The design output shall include:

— specification for each element of the aseptic process with verifiable performance criteria for which objective evidence can be generated during design qualification;

— process parameters for the aseptic process;

— materials and product handling processes (see 6.5) including transfer systems (see 6.12) disinfection, sterilization, depyrogenation and maintenance of sterility measures as applicable;

— the necessary manufacturing environment (see 6.6) including clean room clothing systems (see 6.8.3) and containment zones (see 6.12);

— risk controls identified in the risk analysis including critical control points (see 6.4);

— the basis for the development of the CCS (see 7.1);

— the strategy for design qualification using a risk-based approach for each process element.

NOTE 1 A risk-based approach assumes risks exist within a design. It identifies, assesses and ranks risks (in order of highest to lowest priority), implements strategies to preferably eliminate or at least reduce risk to an acceptable level (in order of risk priority) and adopts ongoing monitoring of risk to identify fluctuations in risk level.

NOTE 2 This is also known as a Quality-by-Design (QbD) approach. The approach proactively considers the impact of the process and equipment design on the quality attributes of product during the design phase.

6.1.3 New technologies should be considered and evaluated regularly for their potential to reduce product and process risks.

Process analytical technologies (PATs) are characterized by three elements that are interrelated: continuity, automatic control and monitoring. PATs include, but are not limited to:

— thermometry and pressure measurement of a continuous sterilizer;

— continuous monitoring of particulates in the environment;

— continuous monitoring of airborne microorganisms in the environment;

— automatic integrity testing of filters.

In manufacturing processes with high continuity, microbial contamination can be detected earlier by performing frequent or continuous measurements.

Real-time testing can provide improved product quality assurance and should be considered. Real-time testing can provide a rationale for faster release of product.

Where real-time testing is implemented, the following requirements apply:

— real-time testing shall be planned and documented;

— PATs shall be established within the manufacturing process;

— calibration and control requirements for PAT devices involved in real-time testing shall be justified.

NOTE 1 See EU GMP, ANNEX 17[39].

NOTE 2 Increased assurance of sterility provides greater confidence in patient safety; however, it is not possible to measure sterility as it is not possible to detect a microorganism that is not present. An advanced aseptic processing system that encompasses robust risk-based process design, microbiological contamination control and risk management can justify consideration of discussion with a regulatory body in relation to the feasibility of release of product based on process controls without the inclusion of a test for sterility. For example, an automated process conducted within an isolator system where there is no routine operator intervention in the critical processing area and where there is continuous monitoring of critical control parameters, non-viable particles (NVPs) and viable particulates for each product batch, with the capability to identify an out-of-specification result promptly, can provide an opportunity to consider release of finished product without the inclusion of a test for sterility, as the technologies used provide a greater assurance of sterility and therefore patient safety than conventional cleanroom aseptic processing.

6.1.4 Quality assurance and through that, patient safety, is increased if the following elements are applied together and controlled within a robust quality risk management framework:

— QbD principles;

— PAT including real-time testing (which provides assurance of final product quality based on information collected during the manufacturing process);

— in-depth product knowledge;

— thorough understanding of manufacturing processes.

6.2 Process design

The process design input shall include a complete description of the product to be manufactured including special handling and safety precautions, as applicable.

NOTE The most important aspect in determining the strategy and design of an aseptic process is a complete understanding of the product to be manufactured.

EXAMPLE Highly sensitizing materials, high potency materials, viruses or radiopharmaceuticals.

The manufacturing process from raw materials and components through to final aseptic packaging shall be determined. The handling and processing steps in the manufacturing process shall be established. The use of manual or automated handling shall be evaluated based on a documented risk assessment.

The total time for each unit operation of aseptic processing shall be limited to a defined maximum, and where possible, this time shall be minimized. Examples include but are not limited to:

a) holding time for formulated bulk prior to sterilizing filtration (where applicable);

b) holding time for sterilized components prior to use;

c) filling or aseptic assembly;

d) holding time for sterile bulk prior to filling;

e) component washing and sterilization;

f) exposure time of sterilized containers and closures in the critical processing zone (including filling) prior to closure.

6.3 Risk assessment

Risk assessment tools appropriate for the element to be assessed shall be selected.

Criteria for risk acceptability shall be established prior to conducting risk assessments.

NOTE 1 ISO 14971 or ICH Q9 [41] provide guidance on design of risk assessment.

NOTE 2 Risk is the combination of the probability of occurrence and the severity of harm. The goal of aseptic processing is to manufacture product free from microbial contamination as product contamination has the potential to cause harm. In the scope of this document the severity of the harm to the patient is therefore considered high by default.

For simplicity and ease, an aseptic process can be sub-divided into its individual blocks or operations (e.g. product transfer, filling, lyophilisation), with each block being risk-assessed separately. The risk assessments can be aggregated to evaluate the risk profile of the entire aseptic operations.

NOTE 3 More details can be found in Annex B.

6.4 Identification of critical control points and process parameters

Critical control points shall be identified, and where applicable, limit values specified, during the design process and the risk assessment. The critical control points shall be documented as an output of the design process.

NOTE Critical control points are aspects of the aseptic process that present a hazard of defined risk to successful completion of the process. They are often located where microbiological contamination of product can occur, e.g. exposure of product or primary packaging components to the environment or to personnel interventions, or both. A critical control point has a limit value applied to it to control the hazard. Monitoring is undertaken to ensure that the limit value is not breached.

The process design shall identify how to monitor critical control points and enable analysis of data (see 8.3.2).

The critical process parameters (CPPs) and quality characteristics of a process shall be understood and evaluated in each manufacturing step to ensure product sterility. The influence of each parameter on quality characteristics shall be evaluated to determine the CPPs related to sterility.

6.5 Handling and processing

Automated processes shall be implemented where feasible, due to the advantages these systems offer, for example, greater reliability, reducing risk of human error, operator safety and improved product quality.

Product handling processes shall be designed to minimise the release of particulates and to ensure that first air is not contaminated before it contacts exposed product.

NOTE First air is air that exits the supply high efficiency particulate air (HEPA) or ultra-low penetration air (ULPA) filters. First air typically is distributed by air diffuser screens, and first makes contact with a surface without contacting any other surface en-route.

6.6 Environment and air handling

The manufacturing environment shall be designed according to ISO 14644-4, installed and certified to consistently meet ISO 14644-1 cleanroom and clean zone requirements, and meet stringent microbiological contamination controls unless otherwise justified.

Environmental controls and monitoring programs shall be established to ensure an aseptic processing environment.

NOTE 1 ISO 14644-2 and ISO 14644-3 can be applied.

NOTE 2 Further guidance on classification of cleanrooms is given in Annex D.

The design process for the manufacturing environment shall consider:

a) APA layout including:
   1) physical attributes of the enclosure(s);
   2) segregation for all cleanliness zones;
   3) flow of personnel and materials (e.g. raw materials, components, waste);
   4) segregation of operations (e.g. component preparation, product preparation, filling).
b) APA air handling requirements including:
   1) airflow velocities;
   2) differential pressures (where appropriate);
   3) airflow pattern(s) (including airflow direction);
   4) temperature and humidity.
c) monitoring for particulates and microorganisms;
d) introduction and exhaust of utilities;
e) introduction and removal of materials;
f) cleaning and disinfection;
g) clothing and gowning of personnel;
h) service and maintenance access.

NOTE 3 Personnel are considered to be the greatest source of contamination within an aseptic processing environment. The use of barrier systems that exclude personnel, such as isolators and RABS, is an effective means to reduce contamination risk. Isolator systems can be located in lower grade background environments (see 5.4.3 and ISO 13408-6).

6.7 Materials

6.7.1 Surfaces within an aseptic processing environment shall:

a) be smooth and impervious (including fittings, e.g. switches, power sockets);

b) be durable, robust and minimize particle shedding;

c) be readily accessible and easy to clean with minimal ledges or recesses;

d) withstand exposure to cleaning and disinfecting agents.

6.7.2 The design shall use construction materials that protect personnel from exposure to hazardous materials (e.g. radiation) when applicable.

NOTE Barrier systems, for example isolator systems, can be used to protect personnel from hazardous substances.

6.8 Personnel

6.8.1 General

Personnel are considered to be the greatest source of contamination within an aseptic processing environment.

6.8.2 Training

Operators shall be trained and possess the knowledge and skills required to perform their function competently. Training objectives and outcome assessments shall be documented prior to training program initiation. Areas of training can include:

a) GMP;

b) basic microbiology and aseptic techniques;

c) specific operating procedures;

d) specific handling requirements;

e) equipment operation;

f) hygiene practices;

g) contamination control;

h) clothing-related requirements.

Training shall be documented. Refresher training shall be provided at specified intervals or in case of a change in the process.

Successful participation in the training program shall conclude in operator qualification. Documentation shall be provided and requalification carried out at specified intervals.

NOTE 1 The use of personnel monitoring, automatic data capture and analytics to identify deteriorating performance trends can reduce risk of operator error.

NOTE 2 The integration of simulated scenarios or virtual reality can be useful tools in operator training.

NOTE 3 Carrying out a newly developed aseptic process or aseptic process operation can require an additional training program.

NOTE 4 Typically, qualification of operators includes successful annual participation in at least one aseptic processing simulation.

If adverse events occur, additional or more frequent requalification of process-associated personnel can be required.

6.8.3 Health

Personnel who are assigned to work in a cleanroom or controlled environment shall report to management any health issues that have the potential to affect product quality or contaminate the environment where the aseptic process is performed. These include, but are not limited to:

a) fever;

b) coughing;

c) respiratory illness;

d) gastrointestinal distress;

e) eczema;

f) rash;

g) sunburn;

h) nasal and eye infections.

Management shall decide if the person exhibiting or experiencing a health issue is suitable to participate in the aseptic process or enter the controlled environment.

6.8.4 Interventions

Operator interventions shall be identified and documented as critical control points (see 6.4 and 8.2.2).

NOTE The risks associated with both the number and type of manual operator interventions can be minimized through automation.

Operator interventions and the related risks and controls shall be elements of operator training and qualification programs.

6.8.5 Service personnel

Service personnel shall be trained to understand the basic requirements of GMP and good hygiene procedures required for aseptic processing. Competency qualification is applicable to all personnel entering the critical processing zone or the adjacent cleanroom when they are under routine manufacturing operations, including “at rest” status.

NOTE This does not apply to shut down conditions.

6.8.6 Cleanroom clothing systems

The cleanroom clothing system shall be designed to minimize the risk of contamination based on an evaluation of the specific interventions to be performed in the aseptic environment, considering the presence of barrier systems and the classification of the aseptic processing environment(s).

The cleanroom clothing system shall be described in detail in a cleanroom clothing system specification including all the necessary garments, accessories and packaging as well as the need for sterilization, if applicable.

The cleanroom clothing system specification shall be complemented with a detailed description of the donning and doffing process steps including any required disinfections.

NOTE 1 The process for de-gowning can be important to protect operators and the environment from contamination with potential or known hazards, e.g. chemical and biological hazards.

The usability of cleanroom clothing systems for the donning and doffing process steps including the aseptic presentation of packaged sterile garments, if applicable, and required disinfection steps shall be assessed.

The cleanroom clothing system qualification shall include:

— the cleanroom clothing system design, including the materials and the usability;

— the aseptic donning and doffing steps as applicable including the required change rooms;

— disinfections and aseptic removal of SBSs;

— all personnel working in critical zones.

NOTE 2 Further guidance on how sterile cleanroom clothing system qualification can be implemented is given in Annex G.

A separate qualification program shall be established for the washing, cleaning and, if applicable, re-sterilization processes for reusable garments to make sure that:

a) the minimum performance characteristics of garments are maintained;

b) the process follows the established instructions;

c) the process is repeatable;

d) identified risks are under control and risk controls are effective.

The description of cleanroom clothing systems, donning and doffing process steps and the related risks, controls and qualification and re-qualification requirements shall be documented in the CCS (see Clause 7).

6.9 Aseptic processing equipment

6.9.1 General

Aseptic processing equipment shall be fit for its intended purpose. It shall be designed, manufactured and qualified to ensure maintenance of aseptic processing conditions.

Equipment or parts of equipment in the critical processing zone shall be:

— capable of being sterilized and aseptically assembled, or surface disinfected prior to the start of aseptic processing (product contact parts shall be sterile);

— easy to assemble, with the minimal number of connections.

Equipment shall be designed to minimize or eliminate human interventions during aseptic processing, and wherever possible, provide a physical barrier separating the aseptic processing operator from the sterile product and components.

Equipment calibration requirements shall be documented. Equipment design shall minimise maintenance requirements and the need for in-process adjustments.

6.9.2 Automated processes and robotics

Automatic processing machines, including robots, shall be capable of being cleaned and disinfected or sterilized where applicable. They shall be designed to minimise or preferably prevent particle release. Automatic processing machines shall have sufficient security measures to prevent inadvertent or unauthorised alteration of the intended process and these shall be documented. The operation of programmable automatic processing machines shall be verified against the process design specification. Design specifications shall consider service and maintenance accessibility.

NOTE Further guidance on closed systems and robotics is given in Annex F.

6.9.3 Single use systems and connecting devices

Single use systems for aseptic processing shall be suitable to meet product processing requirements and maintain sterility under actual conditions of use and be evaluated through the duration of use.

Determining the best solution for a given application depends on a number of factors such as the material being processed, tubing selected, flow requirements, process conditions, storage and transport, and space availability for an appropriate assembly environment, SIP system, and tube welding equipment. During the design of single use systems, consideration shall be given to system storage prior to use, shelf-life and variations in component size.

Single use systems shall be compatible with the product. Where a single use system is intended to act as a closed system or container, its integrity shall be validated, including the integrity of any sterile connections and tubing. Verification of the integrity of individual components of a single use system shall be conducted, including consideration of, but not limited to:

— leaks at ports;

— pin holes.

As a minimum, systems shall undergo visual inspection for loss of integrity prior to, during and post use.

6.9.4 Auxiliary equipment and utilities

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 the manufacturing environment and shall only be opened when product is not being produced.

Auxiliary equipment shall be cleaned and disinfected before it is brought into the manufacturing environment.

NOTE A best practice is to leave the auxiliary equipment stored in the area rather than moving it into and out of that area. Covering the equipment while stored prevents contamination and possible additional cleaning.

Sinks and drains shall not be located in critical processing zones and direct support zones. Where drains are fitted to process equipment, appropriate backflow prevention shall be used. In indirect support zones, 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 shall be suitable for disinfection, fitted with traps or water seals and sealed when not in use.

Where closed system washdown is required (for example in cytotoxics manufacture) segregation and disposal of contaminated wastewater shall be considered and addressed.

6.10 Components

All components that are a part of the finished product shall have written specifications containing acceptance criteria including bioburden or sterility, endotoxin and packaging as necessary. All components shall be handled and stored in a manner that prevents deterioration, contamination or inaccurate identification.

6.11 Product related safety requirements

Product that presents a hazard to personnel, other product, or to the manufacturing environment, shall be subject to an effective and documented aseptic contamination control containment strategy.

Also see 6.2 and 6.3. The process design and risk assessment shall, at a minimum, consider the following:

a) type of hazard (e.g. radiological, corrosive, carcinogenic, infectious agent, aerosols from filling process, powder from lyophilisation, liquid spillage);

b) exposure route (e.g. inhalation, skin contact);

c) exposure dose;

d) handling and manipulation;

e) packaging;

f) inadvertent release (i.e. spill management).

Strategies shall be developed that consider either residual hazardous product deactivation or removal, or both from the APA on completion of the process.

6.12 Aseptic final packaging process

Containers and closures shall be sterile and, where applicable, non-pyrogenic. Sealing aids such as silicone shall be sterile and compatible with the product.

The suitability of the container-closure system to maintain the integrity of its microbial barrier, and as a result, sterility of product, throughout shelf-life, shall be demonstrated and documented.

EXAMPLE Examples of container-closure integrity testing methodologies include immersion tests, microbiological challenge tests, bubble tests, vacuum tests, dye penetration tests, electrical conductivity tests, trace gas leakage tests.

6.13 Flow management

6.13.1 Containment

Containment zones shall be established based on the hazards of the aseptic processing operation. Where operator protection is a principal concern, primary and secondary containment zones designed to protect the product and operator from contamination can be beneficial.

Containment design shall consider residual product containment and potential personnel exposure through the entire process, including area clean down and equipment maintenance (i.e. contaminated filter replacement).

Transfer systems, including manual systems, shall be designed to protect the aseptic processing zone(s) from contamination ingress and in the case of processing hazardous product, prevent contamination egress. Items being transferred from a lower grade zone to a higher grade zone shall be bio-decontaminated to a level of cleanliness that is at least equivalent to that of the environment the items are entering.

6.13.2 Cross contamination

Separation strategies such as physical barriers, aerodynamic barriers, spatial zoning and time shall be employed to minimize the risk of product cross-contamination as well as microbiological contamination. Airflows and pressure cascades shall be designed to remove airborne contamination or move it from a higher classification area to a lower classification area. Where personnel protection is a principal concern, airflows and pressure cascades can be designed to prevent the egress of contamination to a lower classification area.

Process-specific cleaning and disinfection strategies shall be documented.

The aseptic process design shall consider the presence of product, component and cleaning and disinfectant residues both during and after the aseptic operation and shall include strategies to control residues, where present, to acceptable levels.

6.13.3 Item introduction

Items shall only be introduced to the APA in accordance with planned arrangements. Items entering the controlled environment shall possess a level of cleanliness appropriate for the controlled environment. Protocols for item introduction shall be validated. Protocol design shall consider, at a minimum, the following:

a) item arrangement and loading pattern (i.e. to eliminate surface occlusion);

b) surface bio-decontamination (i.e. manual vs automated);

c) environment segregation;

d) cleaning and disinfectant residues;

e) transfer system ergonomics;

f) item packaging, including appropriate integrity verification for the intended manufacturing process and controlled environment.

Where items are packaged as sterile, an integrity verification strategy shall be implemented to ensure maintenance of sterility from the sterilization processing up to the point of use, including the method and frequency of testing or examination, with suitable acceptance criteria (including requirements in 7.4).

Multi-layer packaging can be used as a means to provide an environmental barrier or environmental segregation during item introduction. The use of multi-layer packaging can remove the need to carry out surface bio-decontamination during the transfer process, but shall be specified and subject to validation.

6.13.4 Egress

Items (i.e. product, equipment and materials) shall only be removed from the classified areas in accordance with planned arrangements. Egress protocols shall be validated to confirm the air cleanliness of the classified area is not adversely affected.

6.13.5 Waste management

Waste materials shall be separated from components and product to prevent cross-contamination or inadvertent use. Waste materials shall exit the aseptic processing zone via a different route to finished product, or shall be physically separated from finished product and clearly identified as waste if the same exit route is used.

Waste materials shall be managed to minimise clutter within the APA.

Solid and liquid waste from cleaning operations shall be contained when processing hazardous materials.

6.14 Manufacturing process duration

The process design shall consider the intended duration of product manufacture (i.e. the number of units to be produced in a batch). Manual processes shall consider the impact of operator fatigue on process repeatability.

Periods of product exposure to the environment shall be minimised. The following factors can have an impact on the manufacturing process duration and should be considered during the process design:

a) processing time;

b) critical zone dimensions;

c) area of open product and container exposure;

d) set-up time and positioning of items;

e) periods between decontamination;

f) manual vs automated processes;

g) number of planned interventions;

h) probability of unplanned interventions.

7 Contamination control strategy (CCS)

7.1 General

A CCS shall be implemented. As a minimum, the strategy shall consider the output of the risk assessments (see 6.1) and address at least the following:

a) cleaning and disinfection programs;

b) sterilization programs, including required SBSs for maintenance of sterility as applicable and the control of endotoxin and depyrogenation processes;

c) maintenance and calibration programs;

d) environmental monitoring program;

e) containment of potent or toxic substances;

f) control of raw materials and components (sourcing and incoming quality programs);

g) personnel training and qualification programs;

h) cleanroom clothing systems and gowning procedures.

7.2 Cleaning and disinfection programs

7.2.1 General

The following items shall be addressed and documented:

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

b) Procedures shall be in place to evaluate, approve and control the use of cleaning agents and disinfectants.

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

d) Retention of records to demonstrate application of cleaning and disinfection procedures.

e) The removal of disinfectant and cleaning agent residues from critical surfaces (differentiating between product-contact and non-product contact surfaces) shall be validated.

NOTE Residuals from cleaning agents can interfere with disinfection.

f) APAs shall be cleaned and disinfected to provide appropriate environmental control based on the evaluation of environmental data trends, the assessment of product contamination and the frequency and nature of the aseptic process.

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

h) The manufacturer's instructions shall be followed with respect to storage and use of cleaning agents and disinfectants unless alternative procedures are justified and validated.

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

j) Identification and tagging of equipment shall be done to facilitate cleaning traceability.

k) Containers for cleaning agents and disinfectants shall be labelled, at a minimum, with the substance name and its expiration date.

7.2.2 Cleaning

The documented cleaning plan shall address at least:

a) approved agents for cleaning, their working dilution, approved storage conditions and methods for sterilization, where applicable;

b) procedures for cleaning, based on validated methods, where applicable (refer to 7.2.5);

c) cleaning aids used, their maintenance and, where applicable, sterilization and storage;

d) time and frequency of cleaning;

e) assignment of responsibilities;

f) residues;

g) frequency and extent of cleaning validation;

h) cleaning records;

i) operator training and frequency of assessment.

7.2.3 Disinfection

The documented disinfection plan shall address at least:

a) approved and validated disinfectants, their working dilution, anticipated temperature of use, approved storage conditions and time, and methods for sterilization, where applicable;

NOTE The United States Federal Insecticide, Fungicide and Rodenticide Act (FIFRA) and the European Biocidal Products Regulation (BPR) are examples of applicable disinfectant registration and approval regulations.

b) procedures for disinfection, disinfectant application, required contact time of action and employee safety precautions, based on validated methods, where applicable;

c) disinfection aids used, their maintenance and, where applicable, sterilization and storage;

d) residues and where required, post-disinfection cleaning;

e) time and frequency of disinfection;

f) assignment of responsibilities;

g) frequency and extent of disinfection validation;

h) disinfection records;

i) the use of more than one disinfectant on a rotational basis including the use of a sporicidal agent, except when a sporicidal agent is solely used (e.g. an automated disinfection process in an isolator system);

j) operator training and frequency of assessment.

7.2.4 Equipment used for cleaning and disinfection in APA

Equipment used for cleaning and disinfection in the APA shall be of suitable design and approved for use. Where appropriate, the equipment shall be dedicated to the manufacturing area or critical processing zone.

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.

7.2.5 Cleaning process validation

Validation of cleaning processes shall be carried out based on a QRM approach and shall be documented.

NOTE 1 Determination of whether a cleaning process needs to be validated is based on the complexity and criticality of the cleaning process. For example, a validation of the floor mopping process in an ISO 14644-1:2015, ISO Class 8 general purpose corridor is not required.

The cleaning validation shall address at least:

a) acceptance criteria for removal of chemical and particulate contamination;

b) limits of detection and analysis;

c) validation applicability;

NOTE 2 The validation requirements of a cleaning process can be different depending on the situation. For example, cleaning a piece of equipment between processing of different batches of the same product, versus cleaning the same piece of equipment prior to processing a different product.

d) process variability (for example vigorous vs. non-vigorous manual cleaning);

e) repeatability.

7.2.6 Disinfection process validation

The need for and the extent of a validation of disinfection processes shall be determined based on a documented risk assessment.

The disinfection validation shall address at least:

a) anticipated microbial contamination;

b) target microorganisms (e.g. spores, viruses, bacteria, fungi), surface soiling and required level of disinfection;

c) application dose, temperature of use and contact time;

NOTE Temperature of use means, for example, room temperature, refrigerated conditions or elevated temperatures.

d) distribution and coverage;

e) neutralisation and elimination;

f) process variability;

g) repeatability.

7.2.7 Cleaning and disinfection of equipment

A cleaning and disinfection programme for the equipment shall be established and documented. All records generated shall be retained. The programme shall address at least:

a) Levels of residuals of agents to be controlled. These shall be at specified and justified maximum levels.

b) Cleaning and disinfecting procedures for critical surfaces. These shall be established, validated and documented and shall ensure removal of residues to specified levels.

NOTE 1 Residues can interfere with subsequent disinfection and sterilization.

c) The effectiveness of the cleaning and disinfection procedures.

NOTE 2 Guidance on cleaning-in-place can be found in ISO 13408-4.

7.2.8 Cleaning and disinfection procedures

Cleaning or disinfecting procedures shall address:

a) location where cleaning or disinfection is to be performed;

b) procedures for disassembly, cleaning and reassembly;

c) approved agent(s) and tools used, including concentration, volume applied, cleanliness grade or specification, pre-treatment (e.g. sterilization) and approved storage time and conditions;

d) measures to protect cleaned equipment or parts thereof from re-contamination;

e) specification of cleanliness (e.g. permitted residue limits) to be reached;

f) control measures taken to assure that cleanliness specifications are met;

g) schedule and responsibility for cleaning and or disinfection;

h) order or sequence of cleaning or disinfection.

7.3 Sterilization

7.3.1 General

Raw materials, intermediates and components introduced into the critical processing zone shall be sterilized by a suitable and validated sterilization process. The selected sterilization process shall be justified.

Critical equipment surfaces, including indirect product contact surfaces, and components (e.g. raw materials incorporated directly into a product and bulk suspensions prepared in advance) that contact aseptically-processed product or its sterilized container and closures shall be sterilized by a suitable and validated sterilization process. The selected sterilization process shall be justified.

7.3.2 Sterilization processes

Sterilization processes shall be:

a) validated, controlled and monitored to demonstrate efficacy of the processes;

b) requalified periodically at established intervals.

NOTE Further guidance and requirements on requalification of sterilization processes can be found in ISO 11135, the ISO 11137 series, the ISO 17665 series, ISO 20857, ISO 14160, ISO 14937 or ISO 13408-5.

7.3.3 Sterilization equipment

Sterilization equipment shall be:

a) qualified to ensure its suitability for the intended purpose;

b) subject to regular preventative maintenance to ensure it remains fit for purpose.

NOTE The ISO standards identified in the 7.3.2 NOTE include requirements and guidance for qualification and maintenance of sterilizing equipment.

7.3.4 Sterilization procedures

Sterilization procedures shall include at a minimum:

a) procedures for disassembly, pre-treatment, sterilization and reassembly, where applicable;

NOTE 1 SIP is preferred for equipment over disassembly, sterilization and aseptic reassembly.

b) the type of sterilization process, process parameters and their tolerances, and the required SAL to be achieved;

c) control measures to ensure that the validated and specified sterilization process has been delivered and that the sterilization process specification has been met;

NOTE 2 Routine tests for sterility are not performed on sterilized items that are used in an aseptic process, in an attempt to verify sterility. Proper verification of sterility can be accomplished by, for example, a review of sterilization validation data and batch sterilization cycle parameters.

d) procedures to protect sterilized items from recontamination using SBSs or covers as appropriate (see 7.4);

e) storage conditions and time limits for sterilized items (where applicable) to prevent recontamination.

Sterilized items shall be clearly differentiated from non-sterilized items.

Where a product is sterilized by a sterilizing filtration process, the requirements of ISO 13408-2 shall apply.

Sterilization records shall be reviewed as part of the batch release process for an aseptically-processed product. A non-conforming sterilization process shall be investigated formally.

Sterilization sub-contractors (e.g. for containers, container closures) shall be subject to the same sterilization standards requirements as those identified for on-site sterilization processing.

7.3.5 Post aseptic lethal treatments

Post aseptic lethal treatments refer to a terminal sterilization process including a specified SAL, employed after aseptic processing. Where post aseptic processing lethal treatments are utilized for products following aseptic processing, the approaches used in standard sterilization processes to demonstrate desired lethality are followed. Processing conditions are determined by the specifics of the product in conjunction with controls or risks throughout the aseptic process.

7.3.6 Endotoxin control

The justification for whether it is necessary to control or reduce the endotoxin level for a particular product or product component shall be documented.

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

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

Materials used to manufacture a parenteral product or other product required or claimed to be non-pyrogenic shall comply with a specified limit test for endotoxin. The specified limit shall be justified. This shall apply to raw materials (including process water), intermediate product (such as bulk solution or suspension) and other components (such as container components) used in product manufacture.

7.3.7 Depyrogenation process

Depyrogenation processes shall be:

— validated, controlled and monitored to demonstrate the required efficacy of the process;

— requalified periodically at established intervals.

NOTE 1 Plastic medical devices (e.g. single-use bags), 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 non-pyrogenic by multiple cycles of washing and rinsing prior to final sterilization.

NOTE 2 ISO 20857 includes requirements and guidance for dry heat depyrogenation processes.

Depyrogenation equipment shall be:

— qualified to ensure its suitability for the intended purpose;

— subject to regular preventative maintenance to ensure it remains fit for purpose.

NOTE 3 ISO 20857 includes requirements and guidance for qualification and maintenance of dry heat depyrogenation equipment.

The specified endotoxin $\log_{10}$ reduction for a depyrogenation process shall be determined taking into consideration the product and manufacturing process capability, e.g. input sources, levels of endotoxin, efficiency of the depyrogenation process(es) and specified endotoxin limit for finished product.

NOTE 4 Historically, the efficiency of a depyrogenation process has been assessed by a requirement to demonstrate at least a 3 $\log_{10}$ reduction in spiked endotoxin challenge. Adoption of risk management and QbD principles can mean that a single, standard endotoxin reduction criterion (i.e. a minimum 3 $\log_{10}$ reduction) is no longer valid for all depyrogenation processes. For example, glass vials moulded at high temperatures and packaged promptly can have low endotoxin content per unit volume prior to washing in water for injection, with a requirement to demonstrate a 3 $\log_{10}$ reduction in endotoxin content possibly seen as excessive. Conversely, some processes can be expected to have high endotoxin content and so can require a greater than 3 $\log_{10}$ reduction in endotoxin content to ensure the endotoxin content of the finished product is at a safe level.

The level of endotoxin shall be determined by an internationally harmonised pharmacopoeial bacterial endotoxin test or other recognized standard unless it is necessary, taking into account the nature of the product, for a manufacturer to identify and document an alternative or modified test procedure.

NOTE 5 The bacterial endotoxin test methods in the Ph. Eur,[50] JP[46] and USP[51] are internationally harmonised. Guidance can also be found in ISO 11737-3.

Where applicable, depyrogenation records shall be reviewed as part of the batch release process for an aseptically-processed product. A non-conforming depyrogenation process shall be investigated formally.

Depyrogenation sub-contractors (e.g. for container closures) shall be subject to the same manufacturing quality systems requirements as those identified for on-site depyrogenation processing.

7.4 Maintenance of sterility

7.4.1 Unless sterilized items can be transferred directly from the sterilizer into the critical zone under ISO Class 5 unidirectional airflow conditions (or similar), risk control measures shall be implemented to reduce the risk of recontamination.

To protect sterilized items from recontamination, they shall be sealed or enclosed in one or more SBS(s) before sterilization.

Multiple entry SBSs with more than one sterile packaging layer can be used to reduce the risk of contaminating the aseptic environment by removing layers of packaging during transfer from a lower to a higher-grade zone. Appropriate aseptic techniques, transfer processes (e.g. no touch transfer, rapid transfer ports) or disinfection steps shall be applied during transfer to minimize the risk of contamination. The effectiveness of the risk control measures shall be demonstrated.

Sealed or closed SBSs are preferred for maintenance of sterility, however, covering the sterilized items after sterilization to reduce the risk of contamination may be considered for short term exposures in the appropriate environments.

NOTE Covers can also be used before sterilization to minimize the risk of contamination after cleaning and before sterilization or packaging for sterilization.

If SBSs are used, the following shall apply:

a) A terminally sterilized SBS with its protective packaging, if included, shall be designed to minimize the risk of loss of integrity so that it maintains sterility through exposure to expected conditions and hazards during the specified processing, storage, and handling until that SBS is opened at the point of use or until the expiry date.

b) The design of the SBS shall allow for removal of the sterilized item(s) whilst minimising contamination risk to the sterile item(s) and the aseptic processing environment.

c) Packaging materials shall be selected and qualified to minimize risks of particulate, microbiological or chemical contamination of sterilized items or aseptic processes.

d) Porous materials, if used, shall provide an adequate microbial barrier to microorganisms.

e) An SBS shall be compatible with the specified sterilization process as applicable, including cycle parameters, for the item(s) sealed or enclosed within it. The SBS shall allow effective sterilization of an item(s) sealed or enclosed within it, to withstand the conditions of the sterilization process and maintain the microbial barrier after sterilization and during any subsequent storage or handling of the sterilized item(s). Any detrimental effects of the sterilization process shall not affect functionality or performance of the SBS.

7.4.2 Seal or closure processes for SBSs shall be validated. The seal strength and width shall be specified. Seals shall meet the established specification. Validation shall include peel-open characteristics for peel-able seals. Either seal integrity or closure integrity, or both shall be demonstrated.

Test methods for packaging shall be documented including:

a) a rationale for their selection;

b) their acceptance criteria;

c) their validation with test method repeatability and reproducibility;

d) test method sensitivity for integrity tests.

Integrity of the SBS over the specified shelf life shall be demonstrated for the sterilized item. Tests for sterility are not appropriate to support shelf life claims.

NOTE ISO 11607-1 and ISO 11607-2 provide guidance on validation of SBSs for terminally-sterilized medical devices, including compatibility with sterilization processes. The general elements of these standards can be applicable to SBSs for sterilized raw materials, intermediates or components entering the aseptic processing environment. Key aspects to evaluate include SBS integrity, microbial barrier and physical properties.

7.4.3 If covers are used, the following shall apply:

a) The materials used shall be qualified for use in an aseptic processing environment minimizing the risks of particle generation, microbiological and chemical contamination.

b) Porous materials shall have an adequate microbial barrier to minimize the risk of ingress of potential contaminants.

c) The shelf life of covers shall be specified based on stability data of key properties as delineated in the user requirement specification considering the exposure to intended sterilization processes.

d) The covers shall be designed to:

   1) allow covers to be placed easily and minimise operator movements;

   2) remain in place during storage and transport;

   3) allow for easy removal.

Unless covers are transferred directly into the aseptic processing environment after sterilization, sterilized covers shall be packaged in an SBS that is validated and allows for aseptic presentation. Multiple-entry packaging may be used to reduce the risk of contamination when bringing the sterile covers into the aseptic processing environment.

NOTE For control of a specific microbiological state of items introduced into the APA that purposefully contain viable matter that cannot be sterilized, see ISO 18362.

7.5 Maintenance and calibration programs

7.5.1 Service personnel

The CCS shall include a control program defining access for service personnel to perform maintenance and calibration activities in the manufacturing environment. During APA design and layout of equipment, operator and service personnel access shall be considered.

NOTE Typically, utility systems and equipment are installed in a manner to allow maintenance activities to be performed outside the classified area(s).

An appropriate training program shall be implemented to ensure that service personnel are appropriately qualified before entering, or being assigned to work in, the APA. This training can include, but is not limited to:

a) reference to hygiene;

b) cleanroom practices;

c) contamination control;

d) aseptic techniques;

e) potential safety implications to the patient of a loss of product sterility;

f) basic elements of microbiology.

At least once per year, all personnel that perform either maintenance or calibration work, or both in active critical processing zones during operations or "at rest" conditions shall take part in a process simulation trial that meets the requirements of this document (see 8.2.3). There shall be written procedures outlining the process by which outside staff who have not received such training (e.g. building or maintenance contractors) need to be brought into the APA.

7.5.2 Planned maintenance activities

The CCS shall include scheduled preventive maintenance activities. Preventive maintenance including calibration of instruments shall be planned, performed and documented in accordance with pre-defined written procedures with due consideration of APA requirements.

A preventive maintenance program shall include utilities, services and equipment. Transfer systems, gaskets, and seals are among the other parts that shall be covered by the maintenance program. All equipment such as sterilizers, air handling and filtration systems, water treatment, generation, storage and distribution systems shall be subject to preventive maintenance and their return to use shall be approved.

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.

NOTE Typically, dedicated equipment is left in the APA to minimize the risk of introducing contamination.

If the integrity of the APA cannot be guaranteed during maintenance activities, the APA shall be taken out of service until it has been subjected to specified cleaning and disinfection processes and satisfactorily requalified. Restart of the process after planned maintenance shall follow established procedures assuring that the specified process conditions have been re-established.

7.5.3 Unplanned maintenance

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.

Where unplanned maintenance of equipment critical to the sterility of the product is to be carried out, an assessment of the potential impact to the sterility of the product shall be performed and recorded. If the unplanned maintenance has not been qualified or the assessment shows risk of loss of sterility of the product, the process shall be stopped and any exposed units of product shall be removed from the process and disposed of appropriately.

If the integrity of the APA cannot be guaranteed during maintenance activities, the APA shall be taken out of service until it has been subjected to defined cleaning and disinfection processes and satisfactory requalification. Restart of the process after unplanned maintenance shall follow established procedures assuring that the specified process conditions have been re-established.

7.5.4 Calibration of equipment

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

Instruments shall be calibrated prior to operational qualification of the process or processing system.

Calibration of measuring instruments or measuring systems shall be planned, performed at suitable intervals and documented in accordance with pre-defined written procedures. Further written procedures shall be established to ensure that these devices are maintained in a calibrated state.

The calibration program shall contain schedules, limits for accuracy and precision, and provisions for remedial action in the event that either accuracy or precision limits, or both are out of specification.

The accuracy and tolerance of all measuring instruments shall be adequate for the process to be measured. Measuring instruments not meeting established specifications shall not be used.

7.6 Environmental monitoring

7.6.1 General

The APA shall be monitored for viable and non-viable particulate contamination in accordance with a documented programme that includes an investigation and corrective action plan when specified action levels are exceeded. Risk assessments should be re-evaluated at specified intervals in order to confirm the effectiveness of the environmental monitoring program.

NOTE 1 See Annex C and Annex D for information on different zones and areas.

NOTE 2 National or international GMP requirements can apply.

NOTE 3 Guidance can be found in ISO 14644-1, ISO 14644-2, ISO 14698-1 and ISO 14698-2.

Appropriate alert and action levels shall be set for the results of monitoring. Alert and action levels shall be established based on risk assessment and results of performance qualification (PQ) tests or trend data and shall be subject to periodic review.

The documented sampling plan shall describe at least:

a) sites monitored;

b) frequency of monitoring;

c) conditions for monitoring (at either rest or in operation, or both);

d) method of monitoring;

e) time and duration of sampling;

f) alert and action levels.

The critical processing zone shall be monitored during each operational shift; more frequent or continuous sampling can be required in certain jurisdictions.

Monitoring approaches shall not compromise the sterility of a product and the maintenance of aseptic conditions.

NOTE 4 Surface sampling and sampling of personnel are typically done at the end of the operation or after critical interventions.

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 shall be sufficient for the recognition of trends.

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

NOTE 5 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 (i.e. critical control points).

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

7.6.2 Sampling for non-viable particulate monitoring

Non-viable particulate monitoring of areas or equipment in the APA, where product quality or testing accuracy can be affected by particulates, shall be performed in accordance with ISO 14644-2.

NOTE 1 In some situations it is not always possible to demonstrate conformity with particulate standards during in operation conditions, for example, at the point of product filling where the process itself generates droplets or particulates.

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.

7.6.3 Sampling for microbiological environmental monitoring

The sampling plan for microbiological monitoring shall contain the designation of sites monitored by active and passive air monitoring and sites for surface monitoring, including equipment surfaces.

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.

Air samples shall be collected during operation. Product contact surfaces shall be monitored only after completion of the aseptic processing operation to prevent the risk of contamination of the product.

It may be possible to consider reducing the level (e.g. number of positions, number of times) of microbiological monitoring in the isolator system in comparison to the level of monitoring required for an aseptic processing environment of higher risk when aseptic processing occurs in a validated isolator system:

a) which prevents direct intervention of operators with open product containers or exposed product contact surfaces in the critical processing zone;

b) is bio-decontaminated using a validated process;

c) is subject to continuous monitoring of critical control parameters;

d) where monitoring data over a suitable, stated time period demonstrates zero detection of microorganisms.

For example, consideration can be given to omitting the use of settle plates provided that active air sampling is conducted. Any reduction in monitoring shall be addressed via a robust assessment of microbiological contamination risk.

NOTE National and/or regional regulations or Codes of GMP can require the use of both passive and active methods of air sampling. Reducing the level of microbiological monitoring in an isolator system can require prior approval from regulatory authorities.

7.7 Containment of highly potent or toxic substances

Suitable containment to prevent cross-contamination and to protect operators shall be considered and implemented effectively for processes that use highly potent or toxic substances.

Cleaning processes shall be validated to achieve a known quantifiable and reproducible reduction of worst-case levels of highly potent substances from worst-case sites.

For each product, the required limits to protect operators during production shall be established as well as the required cleaning or cross-contamination limits.

NOTE Further guidance can be found in ISO 10993-17.

8 Demonstration of the effectiveness

8.1 Equipment qualification and validation

8.1.1 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.

8.1.2 User requirements specification

A user requirements specification 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) capability of being cleaned;

c) 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.

8.1.3 Design qualification

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

8.1.4 Installation qualification (IQ)

Installation qualification (IQ) 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.

Operating instructions shall be available.

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

8.1.5 Operational qualification (OQ)

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

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 14644-1:2015, ISO Class 5 conditions or better shall be maintained under all routinely encountered operating conditions.

8.1.6 Performance qualification (PQ)

Data generated during IQ and operational qualification shall be reviewed for conformance with 8.1.4 and 8.1.5 before starting PQ.

Requirements shall be established for PQ and shall include a demonstration that the equipment is fit for purpose and operates consistently as intended.

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

PQ shall be conducted under conditions that mimic routine operational procedures and shall as far as is reasonably practicable, include worst case conditions.

8.1.7 Requalification

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

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 requalification data, and of corrective action taken in the event of the specified acceptance criteria not being met.

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

Requalification report(s) shall be documented and retained.

8.2 Aseptic process validation

8.2.1 General

Manufacturing processes shall be shown to be robust and ensure consistent product quality before any product is released to the market. Manufacturing processes shall undergo a prospective validation programme.

As a part of process validation, aseptic process simulation (APS) shall be conducted.

8.2.2 Establishment and management of interventions

During aseptic process development and optimization QRM and QbD principles shall be considered in relation to each aseptic intervention. Appropriate action shall be implemented to eliminate or reduce risk to the product.

Interventions shall be classed as either routine or corrective (unscheduled) interventions. There shall be an approved list of permitted routine and corrective interventions that can occur during product manufacture or during process simulation.

Procedures for conducting interventions shall be updated as necessary, to ensure consistency with actual manufacturing activities.

Specific monitoring shall occur during and after corrective (unscheduled) interventions.

8.2.3 Process simulation

8.2.3.1 General

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.

NOTE 1 Process simulation is often referred to as media fill.

Filter bacterial retentive capacity shall be validated.

NOTE 2 For more information see ISO 13408-2.

NOTE 3 Process simulation is not intended to validate sterilizing filtration of product (i.e. the capacity of the sterilizing filter to retain microorganisms).

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 products other than sterile liquids, e.g. sterile aseptically produced semi-solids, powders, solid materials (including medical devices), microspheres, liposomes, large or irregularly shaped product, rare and scarce product, or product that breaks down in the culture medium generating particles that can be confused with microbial growth, evaluation by use of traditional liquid media filling is not always possible. In such cases surrogate procedures that represent the operations as closely as possible shall be developed and justified. These procedures can 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 at the end of the process simulation.

NOTE 4 For more information see ISO 13408-7.

In developing the process simulation test plan, risk management principles shall be used. The rationale for the configuration used for process simulation shall be justified and documented.

Processes comprised of a variety of different techniques, such as open processing, aseptic (intrinsic) connections, sterile (intrinsic) connections and closed systems, shall be covered by a process simulation test plan to demonstrate successful interaction of the different systems. Activities inside of closed systems may be omitted from process simulation if qualified separately.

Single closed system-based processes can be considered non-conventional aseptic processing and do not always require process simulation.

NOTE 5 Further guidance on closed systems and robotics can be found in Annex F.

8.2.3.2 Media selection and growth support

The microbiological growth media selected for process simulation runs shall pass the growth promotion test. Growth promotion tests shall be conducted with the organisms and methods specified in the harmonised pharmacopeial chapters for tests for sterility. The growth promotion inoculum shall be less than 100 cfu (colony forming units) per filled unit.

NOTE 1 Process simulation is usually conducted with a soybean casein digest medium. Anaerobic culture media can be required if obligate anaerobic organisms are isolated from environmental or product samples. Plant-derived culture media can be used for process simulation to prevent contact of manufacturing lines with animal-derived culture media, if applicable.

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.

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.

NOTE 2 Examples of pharmacopoeias include Ph. Eur,[50] JP[46] and USP[51].

NOTE 3 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.

8.2.3.3 Simulation procedures

Process simulation shall be designed in part based on a formal process risk assessment focused on contamination control. 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 or closure or product re-supply, sampling or environmental monitoring);

b) unscheduled interventions in representative numbers 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).

If multiple configurations of the same product are aseptically processed, representative configurations may be used for initial validation (i.e. bracketing).

NOTE 1 Following initial aseptic qualification, each configuration can be used in a process simulation at a prescribed 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.

NOTE 3 Some product containers are problematic for visual inspection of filled containers to detect the presence of microbial growth. Examples include opaque containers and dark containers. It is acceptable to conduct process simulation using an alternative container to facilitate visual inspection of filled containers for microbial growth, provided that the alternative container is representative of the product filling process and does not affect the critical parameters of the process.

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

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.

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.

NOTE 4 Identification of units (e.g. chronologically or otherwise) can assist in a failure investigation if one becomes necessary.

NOTE 5 For more information on lyophilized products see ISO 13408-3.

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 shall also be simulated. Environmental monitoring shall be conducted to ensure that there has been no deterioration of the filling environment.

8.2.3.4 Incubation and inspection of media filled units

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

Units that are leaking, broken or otherwise damaged and which would be rejected during routine visual inspection, shall be recorded and removed. Cosmetic defects, non-destructive weight checks and all other units shall be identified and incubated with the other filled 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 runs.

Intact, filled process simulation 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 ranges shall be justified and documented.

NOTE 1 If two temperatures are used for incubation, the units are typically incubated for at least 7 days at each temperature.

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

NOTE 2 Inspection of the units at an earlier time period can be useful to gain a preliminary indication of process simulation results. In the case of opaque or dark containers where the inspection of contamination can be complex, a culture medium with a colour indicator can be used as an aid to help detect growth and turbidity in the aseptically filled units.

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 3 Genotypic identification of process simulation and environmental contaminants can assist in determining the possible source(s) of the contaminants.

8.2.4 Initial aseptic qualification

Initial aseptic qualification shall comprise a minimum of three consecutive, successful process simulation runs, which cover all shifts of the aseptic process.

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

8.2.5 Periodic performance requalification

8.2.5.1 General

Periodic aseptic requalification shall comprise at a minimum, one successful process simulation run for a filling configuration that includes the activities and interventions representative of the aseptic process, including shifts and shift changes.

As a default, periodic aseptic requalification shall be conducted at approximately six-month intervals, for each aseptic process, each filling line, and for each representative product configuration.

Where justified, a frequency deviating from the default shall be specifically addressed in the risk management approach for the aseptic manufacturing process.

For example, for an advanced aseptic manufacturing process conducted in a validated isolator system where each product batch is subject to continuous microbiological and non-viable particulate monitoring, it is possible to consider annual aseptic requalification. The rationale behind such a decision shall be justified and documented, taking into consideration the CCS.

NOTE 1 A manual aseptic manufacturing process in a cleanroom has a greater number of interventions, thereby resulting in an increased contamination risk to product in comparison to a robotic manufacturing process in an isolator system. Requirements concerning the frequency of aseptic requalification can be expected to be more onerous for a higher risk aseptic processing environment and process than for a lower risk environment and process.

NOTE 2 National and/or regional regulations or Codes of GMP can require aseptic requalification to be conducted twice per year regardless of the nature of the aseptic processing environment for the product and the monitoring of this environment. Reducing the frequency of aseptic requalification in an isolator system can require prior approval from regulatory authorities.

Requalification of the process or line prior to the scheduled interval shall 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 3 Change control can require requalification.

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

Aseptic filling or manufacturing lines and product container configurations used less frequently, as cited by the risk assessment, shall be requalified with an acceptable simulation test before production can be resumed.

Requalification reports shall be documented and retained. Each requalification simulated use test shall be thoroughly documented, including, e.g. deviations, non-conformances and shall have full traceability.

8.2.5.2 Numbers to be processed

A sufficient number of units shall be processed during each process simulation run to simulate effectively, the standard operations, process variables, activities and interventions, representative of the aseptic process. The rationale for the number of units shall be justified and documented.

NOTE 1 For small scale batch sizes, the number of units typically equals the production batch size.

NOTE 2 For large scale batch sizes, the number of units can be less than the production batch size.

8.2.5.3 Acceptance criteria

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

Any contaminated unit shall result in failure of the process simulation run. An investigation to determine the root cause(s) and appropriate corrective action(s), shall be conducted and documented.

Appropriate corrective measures shall be implemented before aseptic qualification is restarted.

A minimum of three consecutive, successful process simulation runs shall be performed to demonstrate that the aseptic process is in a state of satisfactory control and in a validated state.

If failure of a process simulation run is attributed to factors not relevant to the effectiveness of the aseptic process, then the failure may be documented as unrelated to the effectiveness of the process, without requiring three further consecutive, successful, process simulation runs to be conducted, e.g. power failure, loss of other services.

8.2.6 Repeat of initial aseptic qualification

An aseptic process or filling line shall be subject to a repeat of the initial aseptic 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 or more;

c) there has been a change that has potential to affect the aseptic process.

A minimum of three consecutive, successful process simulation runs shall be performed to demonstrate that the aseptic process is in a state of satisfactory control (see 8.2.4).

8.2.7 Documentation of process simulations

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 shall include, for example:

a) date and time of process simulation;

b) identification of processing area or room used;

c) container and 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 may 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;

t) routine and corrective interventions included in the process simulation.

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

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

8.2.8 Disposition of filled product

All products that have been produced on a filling line following process simulation shall be quarantined pending successful resolution of the process simulation.

NOTE This can be referred to as conditional line release.

In the event of a process simulation failure, all products processed on that line shall be quarantined pending successful resolution of the failure.

A prompt review of all appropriate records relating to aseptic production since the last successful process simulation shall be conducted. This review shall include assessment of the risk of breach(es) to sterility for all product processed on that line since the last successful process simulation.

The outcome of the review shall be documented and shall include justification for the disposition of affected product batches.

8.2.9 Aseptic process lifecycle considerations

The design of the process simulation shall take into account the entire aseptic process lifecycle.

The initial process simulation approach shall be established during the development of the aseptic process and the first process simulation shall be performed in advance of the production of the first-in-human clinical products to verify acceptable aseptic processing conditions.

As the aseptic process is scaled up and enhanced for later stages of clinical production, the process simulation approach shall be modified to address the changing aseptic process.

NOTE The aseptic process used for early clinical production is often manual and/or not optimized or scaled up for commercial production.

For commercial production, a process simulation study shall be designed and performed as part of the process validation.

8.3 Maintenance of process

8.3.1 General

To ensure an aseptic manufacturing process is being maintained in its state of control, the following items shall be considered:

a) review of the process at specified intervals (e.g. performing annual reviews);

NOTE This review is a separate activity to periodic aseptic requalification described in 8.2.5.

b) changes or developments to the process which have the potential to affect process performance (e.g. changes in equipment, facility design or key operators);

c) review of the risk assessment at specified intervals;

d) a significant event (e.g. batch non-sterility).

8.3.2 Review of the manufacturing process

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 specified acceptance criteria not being met.

A thorough review of the process shall be performed prior to re-qualification and shall include a review of the following:

a) trend analysis;

b) deviations;

c) non-conformances;

d) change controls;

e) identified critical monitoring points;

f) preventative actions.

8.3.3 Changes or developments to the manufacturing process

Any change to the aseptic process which can add risk shall generate additional risk assessment and mitigation as well as a re-evaluation of the process simulation strategy.

Aseptic processes using systems closed from the environment and that have no personnel interaction have less risk of extrinsic contamination and are encouraged. Critical contamination points, such as connection points, shall be assessed and monitored as necessary.

While still accepted, use of open type systems are discouraged based on the risks associated with extrinsic contamination from the environment and personnel. These risks shall be clearly identified, monitored, trended and assessed for continuous improvement.

A sound scientific rationale shall be used and justification shall be documented. It is recommended to involve a microbiologist or individual trained in microbiology to help provide scientific insight and rationale.

9 Product release

9.1 General

The procedure(s) for product release from aseptic processing shall be specified. The procedure(s) shall delineate the criteria, including sterility, non-pyrogenicity, and absence of mycoplasma when needed, to be met for designating conformance of the aseptic manufacturing process to the process specification(s) confirmed during aseptic process validation.

If a process does not fulfil the conformance criteria identified in the preceding paragraph, the cause shall be investigated. The investigation shall be documented.

The product shall be considered as non-conforming if one or more of the conformance criteria for the process is/are not fulfilled. Any non-conformance shall be addressed in accordance with relevant procedure(s).

9.2 Testing for sterility

When a test for sterility is required for an aseptically filled product (see 9.1), this test shall be conducted for each batch of product.

The product shall be tested using the harmonised pharmacopeial test for sterility where this method is applicable to the product to be tested. Suitability of the sterility test method for a product shall be demonstrated.

If the harmonised pharmacopeial test for sterility is not applicable to a particular product, then the manufacturer of the product shall specify the appropriate test method(s) and sampling schedule to be used. This test method shall be validated. Suitability of the test method(s) for the particular product shall be demonstrated.

NOTE 1 The harmonised test for sterility is described in the Ph. Eur,[50] JP,[46] USP[51] and BP.[34] These pharmacopoeias also allow the use of validated alternative test methods, for example, rapid microbiological methods (RMMs) or non-growth based test methods, as an alternative to the harmonised pharmacopeial test for sterility.

NOTE 2 Some products are not suited to testing as per the harmonised pharmacopeial test for sterility, for example, products with limitations in sample size or time constraints for patient administration.

NOTE 3 For single unit batch products, for example, advanced therapy medicinal products or radiopharmaceuticals, it can be that only a small quantity of product is available for testing.

NOTE 4 In certain jurisdictions, approval of a non-pharmacopeial test for sterility can be required by the relevant competent authorities.

9.3 Testing for bacterial endotoxins

When a test for bacterial endotoxins is required for an aseptically filled product (see 9.1), the test frequency, sampling plan, test method and acceptance criteria shall be specified. The test frequency is often established as being conducted for each batch of product but may be conducted less frequently based on risk assessment.

NOTE 1 The acceptance criteria can vary depending on the type of contact the product has with the patient and on national regulations.

NOTE 2 Guidance can be found in pharmacopoeia, ISO 11737-3 or ANSI/AAMI ST72.

9.4 Testing for mycoplasma

When a test for mycoplasma is required for an aseptically filled product, the test frequency, sampling plan, test method and acceptance criteria shall be specified.

9.5 Rapid and alternative microbiological methods

The implementation of rapid or alternative microbiological methods to support aseptic processing activities is encouraged. Any rapid or alternative microbiological method shall be validated. Its limitations should not exceed those of the classical or compendial method and should be able to detect the same adverse trends as the classical or compendial method.

NOTE For guidance see Annex H.

Annex A
(informative)

Aseptic processing — Typical elements

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

a) justification (for not using terminal sterilization);

b) applicable regulatory requirements and guidance;

c) applicable quality management systems;

d) facility design;

e) equipment design;

f) product and delivery system;

g) processes and technologies implemented;

   1) product and component preparation;

   2) sterilization and depyrogenation of product, component and equipment;

   3) product and component transfers into and within the APA;

   4) aseptic process containment, i.e. RABS, isolators or cleanrooms;

   5) personnel protection systems' and methods' effect on aseptic processing;

   6) product manufacturing methods;

   7) either container closure or SBS integrity assurance, or both;

h) environmental control and monitoring programme;

i) master validation plan (e.g. process simulations, validation of unit operations);

j) product release process and acceptance criteria.

In preparing an aseptic process definition, products can 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 E.

Annex B
(informative)

Risk management

B.1 General

QRM is one of the most important tools for the design and qualification of aseptic processes. An effective risk-management program aids in the careful control of the aseptic process, reducing the risk of contamination.

QRM is a systematic process for the assessment, control, communication and review of risks to product quality across the product lifecycle. Examples of the uses of quality-risk-management tools in aseptic processing include:

a) Equipment and Facility Design: QRM tools such as failure mode and effects analysis (FMEA) and fault tree analysis can be used to identify high-risk facilities and equipment. This input includes adding environmental control and monitoring systems to cleanroom design to reduce the occurrence of, or eliminate, potential failure modes.

b) Equipment and Facility Qualification: QRM tools can be used to identify critical aspects of the aseptic processing equipment or cleanrooms and clean zones to be qualified.

c) Process Validation: QRM tools can be used to identify the key inputs, key process parameters, and key outputs that need to be monitored and controlled. This allows for focused APS validation that ensures that process parameters that are critical to product sterility assurance are appropriately validated.

B.2 Quality risk-management process

B.2.1 Risk assessment

Risk assessment consists of identifying potential hazards, analysing hazards, harm, and risks associated with exposure to those hazards. Key points about the risk assessment process include:

a) Risk assessments should be performed by a team of qualified experts from disciplines such as engineering, quality assurance, validation, and manufacturing, preferably facilitated by someone familiar with the risk assessment process.

b) Three fundamental questions should be answered in the risk assessment:

   1) What can go wrong? Identify hazards that can result in potential harm to the end user as a result of a loss of sterility.

   2) How likely is it to go wrong? What is the probability of occurrence of a hazard?

   3) How severe are the consequences of the hazard occurring?

c) Estimation of the risk associated with the identified hazard (risk analysis).

d) Comparison of the identified and analyzed risk against pre-determined criteria (risk evaluation).

B.2.2 Risk control

Risk control consists of developing a plan to either reduce or accept risks, or both. The purpose of risk control is to preferably eliminate risk or reduce it to an acceptable level. The following questions should be asked during this phase:

a) What are the criteria for risk acceptability?

b) What is an acceptable level of risk?

c) What can be done to reduce or eliminate risks?

d) Do the risk control efforts introduce new risks?

e) What can be done to continue to improve the accuracy of the risk assessment?

f) How should it be done and how often?

B.2.3 Risk communication

Communication of risks between decision makers can be done formally or informally, as appropriate for the risk level of the product and process.

National or regional requirements can apply in relation to risk management communication.

B.2.4 Risk review

Risk review is a periodic review of risks as part of the ongoing quality management process. Examples of where formal or informal risk review can be performed include periodic management review, as part of a change control program or as part of annual product reviews. Figure B.1 provides an example of quality risk management process.

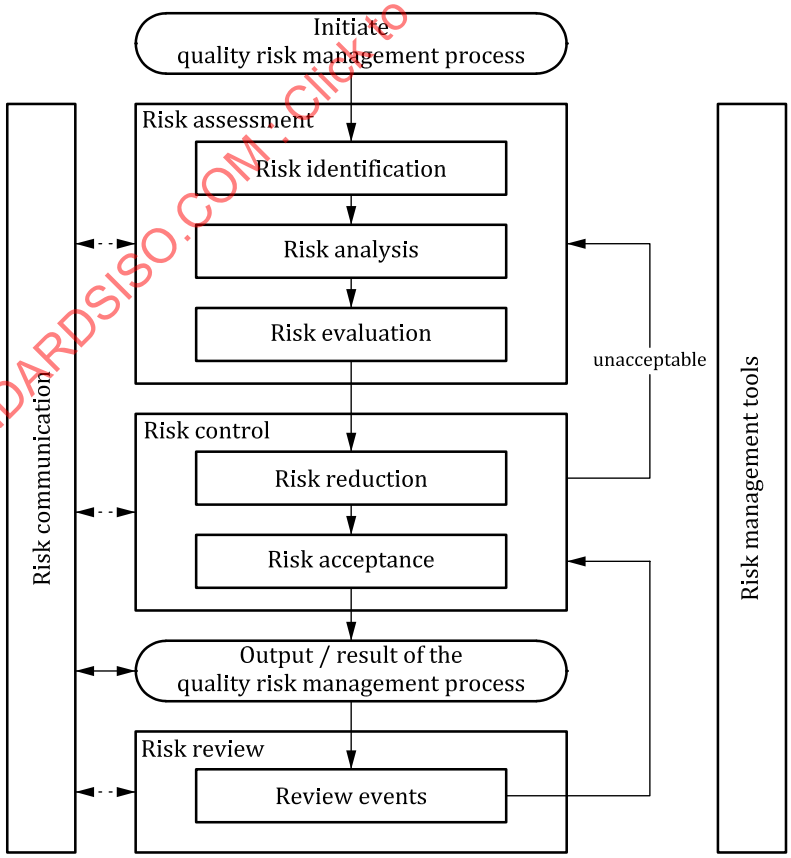


Figure B.1 — Overview of a typical quality risk management process (reference ICH Q9)

NOTE Figure B.1 is reproduced from Figure 1 in ICH guideline Q9 on quality risk management, EMA/CHMP/ICH/24235/2006[41].

B.3 Risk assessment tools

B.3.1 General

Risk assessment tools should be appropriate for the element to be assessed. The following are several frequently used risk-assessment tools used in the health care products industries. These are examples and other risk management methods can be used.

B.3.2 Failure mode and effects analysis (FMEA)

Failure mode and effects analysis (FMEA) is a team-based structured risk assessment method that can assign a numerical risk priority number based on relative perceived risk. FMEA is commonly used during the aseptic process design and development phase of a product life cycle, and throughout the product life. A FMEA is dependent on the expertise of the team members. Table B.1 and Table B.2 provide examples of FMEA for situations in aseptic processing.

Table B.1 — Sample FMEA for aseptic connection of single-use processing equipment

Failure mode	Potential effects	S	Potential causes	PO	Current controls	PD	RPN	Risk mitigation
Operator blocks first air when making aseptic connection	Contamination of product contact surface; contaminated product	5	Operator poor aseptic technique, inadequate instructions or instruments	5	ISO Class 5 environment, sterile gown and gloves, partial barrier separating operator from aseptic core	5	125	Use documented, detailed procedures; use tools that separate the operator's gloved hands and forearms from product and product contact surfaces
Key S = Severity PO = Probability of occurrence PD = Probability of detection RPN = Risk priority number								

Severity, Probability of Occurrence and Probability of Detection are scored based on a numerical scale, for example 1 to 10. The FMEA scoring system should be determined and documented prior to starting the risk assessment, along with the RPN acceptance level. The scoring system should describe the relationship of the numerical scale to the outcome or consequence. Using Probability of Detection as an example, a score of 1 can be allocated to an event that is guaranteed to be detected. A score of 5 can be allocated to an event that is as likely to be detected as not (i.e. 50/50 chance of detection) and a score of 10 can be allocated to an event that would go undetected. Users can set the range of their numerical scale to provide greater precision in their scoring, for example using a numerical scale of 1 to 50 instead of 1 to 10. However, the numerical range and its relationship to the outcome or consequence should be appropriate and realistic.

Table B.2 — Bioreactor is cleaned in place

Failure mode	Potential effects	S	Potential causes	PO	Current controls	PD	RPN	Risk mitigation
Bioreactor not cleaned properly	Residual product could contaminate next product	5	CIP process is incomplete	1	Process alarms and monitors	1	5	Current controls are adequate
		5	Chemical concentration	1	None	5	25	Periodic testing and calibration of alarms

Key

S = Severity

PO = Probability of occurrence

PD = Probability of detection

RPN = Risk priority number

An additional example of an FMEA can be found in ISO 13408-7:2012, Annex A.

B.3.3 Fault tree analysis (FTA)

FTA is a risk-assessment method that begins with a failure event and uses diagrams to determine the sequence of events required to cause the failure. FTA is used for equipment design, for determining procedural controls needed to prevent a failure event, and for determining qualification and control strategies. FTA involves the following steps:

a) identify the failure (undesired event) to study;

b) gain knowledge of the system (gather a team of experts to analyse the system);

c) construct the fault tree;

d) evaluate the fault tree,

e) develop control strategies for the identified hazards.

Figure B.2 is an example of FTA.

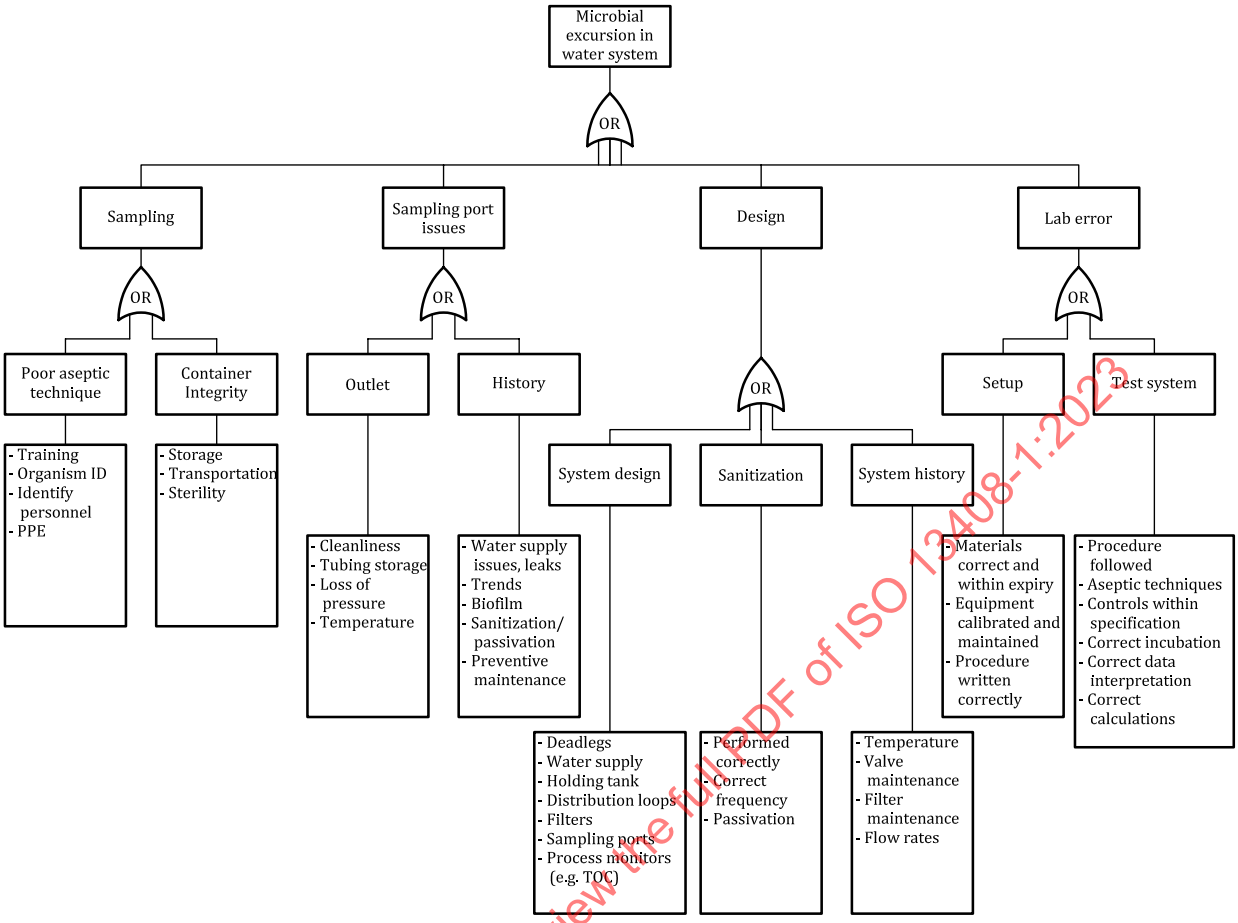


Figure B.2 — Example FTA diagram

B.3.4 Hazard and operability analysis (HAZOP)

HAZOP is a structured technique used in identifying potential hazards and/or problems with facility, utilities and cleanroom operability as well as personnel interactions, recognizing consequences arising from various causes and providing recommendations for improvements in design and operations.

HAZOP analysis is used to identify potential hazards in a system or deviations in an operation. Such hazards can include mechanical (i.e. moving systems), chemical, electrical, temperature (e.g. heat, cold). HAZOP analysis can be used in situations where hazards are difficult to quantify, such as those associated with human actions or behaviours. It is used to identify reasonable use and misuse conditions.

EXAMPLE 1 Someone adds too much or too little of a chemical to a process. Too much can cause a hazardous situation (e.g. exothermic reaction), too little and the chemical cannot produce the intended effect or result.

EXAMPLE 2 Someone interacts with a moving vial filling line before it has stopped moving or while it is still in motion. The person can incur minor or severe injuries, the line can be damaged, the product can be incorrectly processed or adulterated.

EXAMPLE 3 During a process, an operator is required to move a piece of equipment that is sharp, heavy, and complex in shape and place it into a holder. The operator can get trapped fingers, incur lifting strain, incur cuts from edges.

Further information on HAZOP can be found in IEC 61882.

B.3.5 Hazard analysis and critical control points (HACCP)

HACCP involves the identification of hazards and an evaluation of the hazard in terms of the degree of risk to the end user. Once the hazard is identified and evaluated, the team identifies critical control points. These points are where the hazard shall be controlled, or it will present a risk to the end user. HACCP is most often used once an aseptic process has been validated, for routine manufacturing. The seven principles of HACCP include:

a) conduct a hazard analysis;

b) determine the critical control points (CCPs);

c) establish critical limits;

d) establish a system to monitor control of the CCP;

e) establish the corrective action to be taken when monitoring indicates that a particular CCP is not under control;

f) establish procedures for verification to confirm that the HACCP system is working effectively;

g) establish documentation concerning all procedures and records appropriate to these principles and their application.

An HACCP assessment is used to identify and control any biological, chemical, radiological or physical property that can cause the product being produced to be adulterated. The assessment applies a critical control point to the point, step or procedure to eliminate the hazard or reduce it to an acceptable level. The critical control point has a limit value applied to the control point used to control the hazard and monitoring is put in place to ensure that the limit value is not breached. A plan identifying the corrective actions that are to be taken if a breach occurs shall be put in place to ensure no adulterated product is released from the process.

EXAMPLE Particles that can be shed from the surface of gloves, a mechanical transfer system or a robotic arm in an isolator. The downflow velocity of the laminar airflow is a critical control point to ensure that there is sufficient airflow to take any particles generated away from the product. Limit values are set for the speed of the air and monitoring is put in place to confirm that the air velocity is within the limit values. If the limit values are breached, the operator is informed, usually via an audible and/or visual alarm and a pre-established procedure followed to determine the next steps in relation to the product and airflow.

B.3.6 Simplified risk assessment

The level of assessment and choice of approach should be commensurate with the potential hazard and the complexity of the process being assessed. For example, gowning requirements for a given aseptic processing operation can be assessed in a documented risk assessment meeting that includes members of the effected functions. In this case the risk assessment document can consist of a summary of the meeting discussion and determinations.

For example, it was determined that the gowning requirements for aseptic processing operators working with an isolator system are company-provided scrubs or disposable, non-sterile gown, company provided shoes, hairnet and gloves based on the following information:

a) The isolator is housed in an ISO Class 8 environment.

b) Isolator integrity testing (leak testing of gloves and isolator) is performed daily prior to use and results are immediate. This demonstrates, on a daily basis, that the internal isolator environment is restricting external contamination.

c) Use of masks increases technician discomfort and decreases ease of communication and thus will not be required. If microbiological trending (e.g. environmental monitoring or failure investigation) indicates a potential oral contamination source, the requirement of masks will be reconsidered.

d) Isolator decontamination process is automated, validated, and process records are reviewed after exposure and before manufacturing to ensure proper decontamination of internal surfaces.

It was determined that the gowning requirements for aseptic processing operators working with an Open RABS unit are company-provided scrubs and shoes, sterilized personal protective equipment (PPE, i.e. gown, hood covering, mask, goggles, gloves and sleeves). The additional requirements compared to the isolator system are due to the following:

— The RABS is housed in an ISO Class 7 environment that usually has more stringent gowning requirements.

— There are no integrity or leak tests performed routinely but if the door is opened the process is automatically halted.

— The sterile gown, mask and sleeves are intended to eliminate skin contact with RABS surfaces and the environment, both from a microbiological perspective and a particulate perspective.

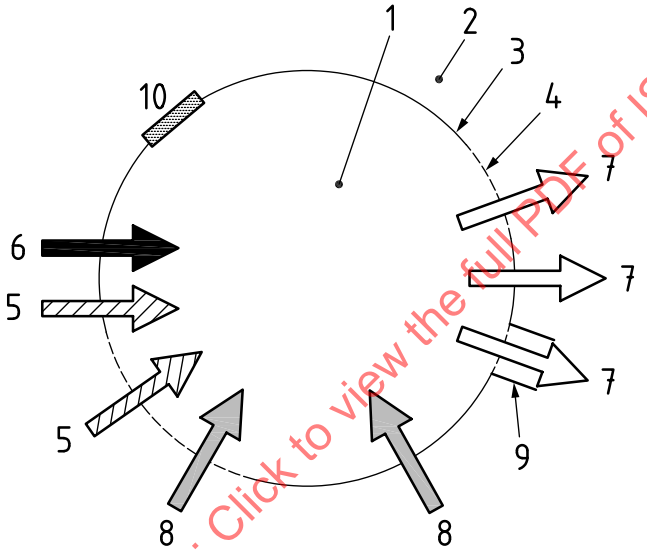
— The RABS decontamination process is manual and thus carries greater opportunity for variability from process to process.

Annex C
(informative)

Typical processing zones

C.1 General

An APA consists of a critical processing zone and other support zones. The boundaries of a critical processing zone are designated by a separative barrier or enclosure, with a direct support zone located outside of the boundary. The critical processing zone forms a system, the categorization of which is determined by the interaction of materials and personnel with and through its boundary.



Key

1		critical processing zone
2		direct support zone
3	————	physical barrier at boundary
4	– – – – – – – – – –	air flow barrier at boundary
5	⇨	ingress of material by manual bio-decontamination process
6	➡	ingress of material by automated bio-decontamination process or sterile (intrinsic) and/or aseptic connection
7	⇨	egress of material
8	⇨	movement across barrier (e.g. personnel interaction)
9	⌐	mouse hole
10	▭	HEPA or ULPA filter

Figure C.1 — Critical processing zone and support zone

Figure C.1 presents a schematic representation of the boundary segregation of the critical processing zone from the environment by considering the material flow, movement and air supply across the boundary of the critical processing zone during operation.

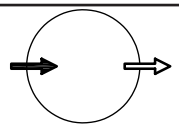
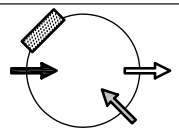
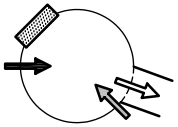
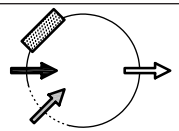
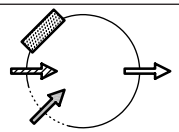
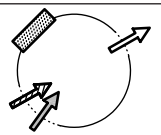
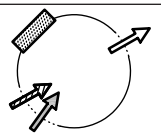
Table C.1 presents the types of APA system categorized in relation to the boundary for material flow, movement and air flow across the boundary of the critical processing zone during operation.

There are open and closed systems. Closed systems physically isolate the critical processing zone from the surrounding environment and do not allow the operator to directly access the critical processing zone. Closed systems can be operated in an ISO Class 8 or higher cleanliness support zone. Open systems either do not physically isolate the critical processing zone from the surrounding environment or allow the operator to directly access the critical processing zone. Open systems are installed in a supporting environment of ISO Class7 or higher cleanliness. A well designed and correctly operated open isolator system can be operated in an ISO Class 8 or higher cleanliness supporting environment.

NOTE Using boundary categorisation all RABS are open systems.

Table C.1 also presents a hierarchy of closure integrity which is generally proportional to contamination risk. Systems can move up and down the hierarchy depending on, e.g. the transfer system, disinfection method, operation. For example, a RABS utilising an automated disinfection and transfer system can have a lower contamination risk than an open isolator with a manual disinfection and transfer system.

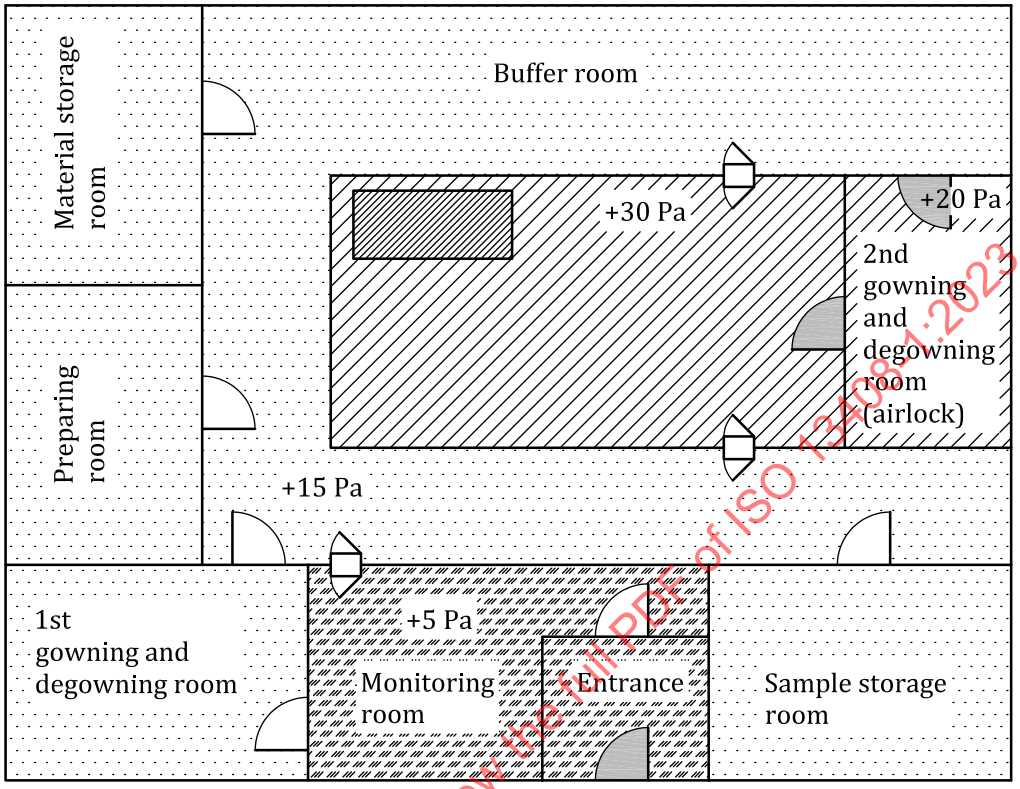
Table C.1 — APA system

System[a]		Equipment	Cleanliness in support zone	Clean up of system	Material ingress procedure across the boundary	Barrier type for motion across the boundary
Closed system		Tank, Bag	ISO Class8 or higher	Sterile or sterilization	Sterile (intrinsic) connection	Physical barrier
Closed isolator system		Isolator without mouse hole		Sterile, sterilization, or bio-decontamination	Aseptic connection, sterilization, or automated bio-decontamination	
Open isolator system		Isolator with mouse hole				Physical barrier in combination with momentary air flow barrier
Other open system		RABS	ISO Class 7 or higher	Bio-decontamination or disinfection		
		RABS			Disinfection	
		Clean bench				Air flow barrier with pressure drop
		Safety cabinet				Air flow barrier without pressure drop

[a] The keys in the system are the same as for Figure C.1.

C.2 Aseptic processing area (APA) example set-up

Figure C.2 illustrates an example of an APA configuration using a RABS or biological safety cabinet.



Key

critical processing zone (ISO Class 5, safety cabinet)

direct support zone (ISO Class 7 in operation)

indirect support zone (ISO Class 8 in operation)

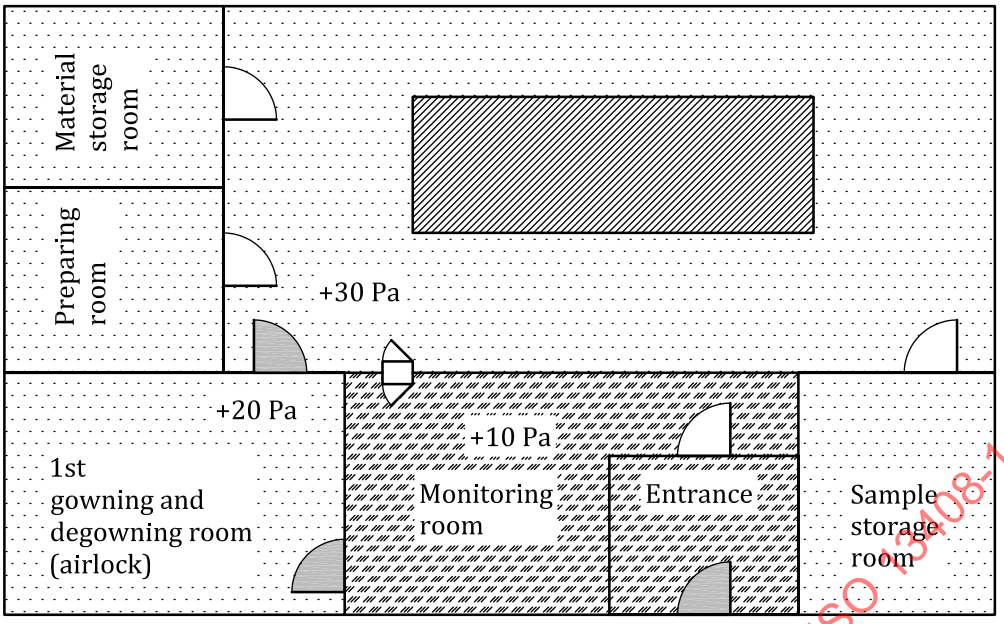
non-classified areas

door for airlock (tight door)

door for non-airlock

material airlock (pass box)

Figure C.2 — Example of an aseptic processing area (APA) configuration using a RABS or biological safety cabinet



Key

critical processing zone (ISO Class 5, isolator)
critical processing zone closed system (sterile)

support zone (ISO Class 8 at rest)

non-classified areas

door for airlock (tight door)

door for non-airlock

material airlock (pass box)

Figure C.3 — Example of an aseptic processing area (APA) configuration using a closed system

Figure C.3 illustrates an example of an APA configuration using a closed system.

NOTE In house limits for the support zone in operation, according to ISO 14644-1, are specified by the manufacturer.

Annex D
(informative)

Comparison of classification of cleanrooms and filters

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

Classification of cleanrooms is based on requirements in Table D.1. Cleanroom air filters are a critical part of demonstrating these requirements. HEPA and ULPA filters are specified globally, however types of filters to be used are not specified. Table D.2 provides information on various filter types that can be used.

Table D.1 — Classification systems

ISO 14644-1	FDA guidance for aseptic processing, September 2004[40]		EU GMP Guide:2008, Annex 1[38]			
ISO class number: N (particles ≧ 0,5 µm/m³) defined in "as-built," " at-rest" or "in operation“ [a]	Clean area classification (particles ≧ 0,5 µm/ft³) (particles ≧ 0,5 µm/m³) "in operation"	Microbiological active air action levels (cfu/m³)	Classifica-tion (particles ≧ 0,5 µm/m³) “at-rest"	Microbio-logical air sample (cfu/m³) “at-rest"	Classifica-tion (particles ≧ 0,5 µm/m³ “in operation"	Microbio-logical air sample (cfu/m³) “in operation"
5 (3 520)	100 (100) (3 520)	1	Grade A/B (3 520)	< 1/10	Grade A (3 520)	< 1
6 (35 200)	1 000 (1 000) (35 200)	7	Not defined	Not defined	Not defined	Not defined
7 (352 000)	10 000 (10 000) (352 000)	10	Grade C (352 000)	100	Grade B (352 000)	10
8 (3 520 000)	100 000 (100 000) (3 520 000)	100	Grade D (3 520 000)	200	Grade C (3 520 000)	100

[a] According to ISO 14644-1, the air cleanliness class by particle concentration of air in a cleanroom or clean zone shall be defined in one or more of three occupancy states, i.e. "as-built," "at-rest" or “in operation". It is appropriate to apply the “operational (in operation)” state in associating class numbers with grades.

[b] The requirements and limits depend on the nature of the operations carried out.

NOTE Former JP specifications have been aligned with EU GMP Guide (Eudralex Volume 4) – Annex 1:2022 specifications through the PIC/S.