Foreword

ISO (the International Organization for Standardization) is a worldwide federation of national standards bodies (ISO member bodies). The work of preparing International Standards is normally carried out through ISO technical committees. Each member body interested in a subject for which a technical committee has been established has the right to be represented on that committee. International organizations, governmental and non-governmental, in liaison with ISO, also take part in the work. ISO collaborates closely with the International Electrotechnical Commission (IEC) on all matters of electrotechnical standardization.

International Standards are drafted in accordance with the rules given in the ISO/IEC Directives, Part 2.

The main task of technical committees is to prepare International Standards. Draft International Standards adopted by the technical committees are circulated to the member bodies for voting. Publication as an International Standard requires approval by at least 75 % of the member bodies casting a vote.

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

ISO 13408-1 was prepared by Technical Committee ISO/TC 198, *Sterilization of health care products*.

This second edition cancels and replaces the first edition and has been technically revised.

ISO 13408 consists of the following parts, under the general title *Aseptic processing of health care products*:

— *Part 1: General requirements*

— *Part 2. Filtration*

— *Part 3: Lyophilization (in preparation)*

— *Part 4: Clean-in-place technologies*

— *Part 5: Sterilization in place (in preparation)*

— *Part 6: Isolator systems*

This revision of Part 1 of ISO 13408 is intended to adapt this International Standard to the actual state of technology in the field. In addition, any normative and informative clauses on subjects which have meanwhile been addressed in the Part 2 to Part 6 of ISO 13408 have been removed from this Part.

ISO/TC 198/WG 9 intends to propose development of a further part(s) on aseptic processing of solid medical devices.

Introduction

Health care products that are labelled "sterile" are prepared using appropriate and validated methods under stringent control as part of a quality management system. For pharmaceuticals and medical devices there may be various requirements including compliance with ISO standards, GMP regulations and pharmacopoeial requirements.

Wherever possible healthcare products intended to be sterile should be sterilized in their final sealed container (terminal sterilization). ISO TC 198 has prepared standards for terminal sterilization of health care products by irradiation (series ISO 11137), by moist heat (ISO 17665-1), by liquid chemical sterilants (ISO 14160) and by ethylene oxide (ISO 11135-1).

When a health care product is intended to be sterile, and cannot be terminally sterilized, aseptic processing provides an alternative. Pre-sterilization of product, product parts and/or components and all equipment coming into direct contact with the aseptically processed product is required. Aseptic processing intends to maintain the sterility of the pre-sterilized components and products during assembling. The resulting product is required to be sterile in its final container.

While terminal sterilization involves the control of a well defined process of known lethality delivered to the product and a sterility assurance level (SAL) can be calculated from sterilization data, the calculation of a SAL is not applicable to aseptic processing.

Examples of applications in which aseptic processing are used include:

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

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

— aseptic handling, transfer, and packaging of combination products.

Sterilization procedures which render components and/or parts sterile as a prerequisite for further aseptic processing can be treated as separate procedures which are evaluated and validated separately and it is important that their risk of failure is minimal. The aseptic processing master plan encompasses all production steps following the sterilization of product and components until the final container or package is sealed. To keep the aseptic processing master plan clear and workable, this International Standard is focused on the risks to the maintenance of sterility. Steps to verify sterility of the product in the sealed container or to maintain the integrity of the sealed container are also seen as separate from aseptic processing.

It is important that aseptic processing controls all possible sources of contamination in order to maintain the sterility of all components. To achieve this, a risk-based aseptic processing master plan is established encompassing each product and applied in a comprehensive way considering product, package design, environment and process options. The product is processed in a controlled environment where microbial and particulate levels are maintained at defined minimal levels and where human intervention is minimized. Validated systems, adequately trained personnel, controlled environments and well documented systematic processes are applied to assure a sterile finished product.

The aseptic process is divided into unit operations (e. g. sterilization of product or components including sterile filtration, handling and storage of sterilized product) and it is necessary that each possible source of contamination be considered and minimized. Only if all risks of contamination have been recognized, wherever possible minimized, eliminated or controlled and finally have been evaluated as acceptable the aseptic process can be considered to be under control. Appropriate validation is needed of the elements described in the aseptic processing master plan, of which process simulation studies are an essential part.

Aseptic processing of health care products — Part 1: General requirements

1 Scope

1.1 This International Standard specifies the general requirements for, and offers guidance on, processes, programmes and procedures for development, validation and routine control of the manufacturing process for aseptically processed health care products.

1.2 This part of ISO 13408 includes requirements and guidance relative to the overall topic of aseptic processing. Specific requirements and guidance on various specialized processes and methods related to filtration, lyophilization, clean-in place (CIP) technologies, sterilization in place (SIP) and isolator systems are given in other parts of this series of standards.

NOTE 1 This International Standard does not supersede or replace national regulatory requirements, such as Good Manufacturing Practices (GMPs) and/or pharmacopoeial requirements that pertain in particular national or regional jurisdictions.

NOTE 2 The principles described in this International standard may be applied to products for clinical investigation. However, flexibility in the application of concepts such as the aseptic processing master plan may be needed for clinical trial materials manufacture.

2 Normative references

The following referenced documents are indispensable for the application of this document. For dated references, only the edition cited applies. For undated references, the latest edition of the referenced document (including any amendments) applies.

ISO 9001, *Quality management systems — Requirements*

ISO 11135-1, *Sterilization of health care products — Ethylene oxide — Part 1: Requirements for development, validation and routine control of a sterilization process for medical devices (in preparation)*

ISO 11137-1, *Sterilization of health care products — Radiation — Part 1: Requirements for development, validation and routine control of a sterilization process for medical devices*

ISO 11137-2, *Sterilization of health care products — Radiation — Part 2: Establishing the sterilization dose*

ISO 11137-3, *Sterilization of health care products — Radiation — Part 3: Guidance on dosimetric aspects*

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

ISO 13408-3, *Aseptic processing of health care products — Part 3: Lyophilization (in preparation)*

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

ISO 13408-5, *Aseptic processing of health care products — Part 5: Sterilization in place (in preparation)*

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

ISO 13485, *Medical devices - Quality management systems — Requirements for regulatory purposes*

ISO 14644-1:1999, *Cleanrooms and associated controlled environments — Part 1: Classification of air cleanliness*

ISO 14644-2, *Cleanrooms and associated controlled environments — Part 2: Specifications for testing and monitoring to prove continued compliance with ISO 14644-1*

ISO 14644-3, *Cleanrooms and associated controlled environments — Part 3: Metrology and test methods*

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

ISO 14644-5, *Cleanrooms and associated controlled environments — Part 5: Operations*

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

ISO 14698-1, *Cleanrooms and associated controlled environments — Biocontamination control — Part 1: General principles and methods*

ISO 14698-2, *Cleanrooms and associated controlled environments — Biocontamination control — Part 2: Evaluation and interpretation of biocontamination data*

ISO 17665-1, *Sterilization of health care products — Moist heat — Part 1: Requirements for the development, validation and routine control of a sterilization process for medical devices*

3 Terms and definitions

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

3.1
action level
established microbial or particulate levels requiring immediate follow-up and corrective action

3.2
air lock
a room with interlocked doors designed to maintain pressure control between adjacent rooms of different cleanliness class

3.3
alert level
established microbial or particulate levels giving early warning of potential drift from normal operating conditions which are not necessarily grounds for definitive corrective action but which could require follow-up investigation

3.4
aseptic filling
part of aseptic processing where a sterile product is filled and/or packaged into sterile containers and the containers closed

3.5
aseptic filling line
manufacturing structure or arrangement where product containers and/or devices are aseptically filled

NOTE Generally, the aseptic filling line is arranged to permit the filling of product containers and/or devices in a linear manner; hence the term "line".

3.6
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

3.7
aseptic processing area
APA
controlled environment for aseptic processing, consisting of several zones, in which the air supply, materials, equipment and personnel are regulated to control microbial and particulate contamination to acceptable levels

3.8
bioburden
Population of viable microorganisms on a product and/or a package.

[ISO/TS 11139:2006; definition 2.2]

3.9
bio-decontamination
removal of microbiological contamination or its reduction to an acceptable level

[ISO 13408-6:2005, definition 3.1]

3.10
colony forming unit
cfu
number of microbiological units giving rise to single colonies when incubated on a solid growth substrate

3.11
combination product
a product comprised of a chemical and/or biological pharmaceutical product with or without a medical device physically, chemically, or otherwise combined or mixed and produced as a single entity

3.12
correction
action to eliminate a detected nonconformity

NOTE A correction can be made in conjunction with a corrective action.

[ISO 9000:2005; definition 3.6.6]

3.13
corrective action
action to eliminate the cause of a detected nonconformity or other undesirable situation

NOTE 1 There can be more than one cause for a nonconformity.

NOTE 2 Corrective action is taken to prevent recurrence whereas preventive action is taken to prevent occurrence.

NOTE 3 There is a distinction between correction and corrective action.

[ISO 9000:2005, definition 3.6.5]

3.14
critical processing zone
location within the aseptic processing area in which product and critical surfaces are exposed to the environment

NOTE Aseptic manipulations performed can include aseptic connections, filling, stoppering and closing operations.

3.15
critical surface
surface that may come into contact with or directly affect a product or its containers or closures

3.16
design qualification
verification that the proposed specification for the facility, equipment or system is suitable for the intended use

[ISO/TS 11139:2006, definition 2.12]

3.17
differential air pressure
difference in pressure between designated rooms or areas

3.18
disinfectant
chemical agent which is able to reduce the number of viable microorganisms

3.19
disinfection
removal, destruction or de-activation of micro-organisms on objects or surfaces

[ISO 14644-5:2004;definition 3.1.4]

3.20
endotoxin
a 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

3.21
environmental flora
environmental isolates
microorganisms present in and/or isolated from processing or manufacturing environments

3.22
gowning procedure
defined steps to avoid contamination while putting on the protective garments needed to enter the APA

3.23
health care product
medical device(s), including *in vitro* diagnostic medical device(s), or medicinal product(s), including biopharmaceutical(s)

[ISO/TS 11139:2006, definition 2.20]

3.24
high efficiency particulate air filter
HEPA filter
retentive matrix having a minimum particle-collection efficiency of 99,97% (that is, a maximum particle penetration of 0,03%) for 0,3 μm particles of thermally generated DOP or specified alternative aerosol

3.25
installation qualification
process of obtaining and documenting evidence that equipment has been provided and installed in accordance with its specification

[ISO/TS 11139:2006, definition 2.22]

3.26
isolator
enclosure capable of preventing ingress of contaminants by means of physical interior/exterior separation, and capable of being subject to reproducible interior bio-decontamination

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

3.27
operational qualification
process of obtaining and documenting evidence that installed equipment operates within predetermined limits when used in accordance with its operational procedures

[ISO/TS 11139:2006, definition 2.27]

3.28
performance qualification
process of obtaining and documenting evidence that the equipment, as installed and operated in accordance with operational procedures, consistently performs in accordance with predetermined criteria and thereby yields product meeting its specification

[ISO/TS 11139:2006, definition 2.30]

3.29
preventive action
action to eliminate the cause of a potential nonconformity or other undesirable potential situation

NOTE 1 There can be more than one cause for a potential nonconformity.

NOTE 2 Preventive action is taken to prevent occurrence whereas corrective action is taken to prevent recurrence.

[ISO 9000:2005, definition 3.5.4]

3.30
qualification
documented scientific process used by the health care product manufacturer to assure the reliability and capability of equipment and/or processes before approval for use in manufacturing

NOTE Qualification of equipment and/or processes generally includes installation qualification, operational qualification, and performance qualification (see 3.25, 3.27 and 3.28).

3.31
risk control
process through which decisions are reached and protective measures are implemented for reducing risks to, or maintaining risks within, specified levels

[ISO 14971:2000, definition 2.16]

3.32
separative device
equipment utilizing constructional and dynamic means to create assured levels of separation between the inside and outside of a defined volume

NOTE Some industry-specific examples of separative devices are clean air hoods, containment enclosures, gloveboxes, isolators and mini-environments.

[ISO 14644-7:2004, definition 3.17]

3.33
shift
scheduled period of work or production, usually less than 12 h in length, staffed by a single defined group of workers

3.34
sterile
free from viable microorganisms

[ISO/TS 11139:2006, definition 2.43]]

NOTE In practice, no such absolute statement regarding the absence of microorganisms can be proven (see 3.31, *sterilization*).

3.35
sterilization
validated process used to render a product free from viable microorganisms

NOTE 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.

[ISO/TS 11139:2006, definition 2.47]

3.36
terminal sterilization
process whereby product is sterilized within its sterile barrier system

[ISO/TS 11139:2006, definition 2.52]

3.37
ultra low penetration air filter
ULPA filter
filters with minimum 0,3 μm particle retaining efficiency of 99,999 %

3.38
unidirectional air flow
air flow which has a singular direction of flow and may or may not contain uniform velocities of air flow along parallel flow lines

3.39
unit operations
a defined chemical or physical step in a manufacturing process

NOTE See example of a flowchart in Annex A.

3.40
worst case conditions
set of conditions which represent the greatest challenge to product integrity and safety which will be accepted during routine production

3.41
validation
documented procedure for obtaining, recording and interpreting the results required to establish that a process will consistently yield product complying with predetermined specifications

[ISO/TS 11139:2006, definition 2.55]

4 Quality system elements

4.1 General

4.1.1 A quality management system, appropriate to the nature of the operations, shall be implemented to assure control over all activities affecting aseptic processing. Unless a superseding national, regional, or International Good Manufacturing Practice (e.g. the World Health Organization GMPs) is employed, the quality management system shall be in conformance with the requirements of ISO 9001 and/or ISO 13485.

NOTE Guidance on selecting a suitable model is given in ISO 9004 and ISO/TR 14969 respectively.

4.1.2 Documented procedures for each phase of the development, validation, routine monitoring and control of the aseptic process shall be prepared and implemented.

4.1.3 Documents required by this International Standard shall be reviewed and approved by designated personnel.

4.1.4 Records of development, validation, routine control and monitoring shall be maintained to provide evidence of conformity to the requirements of this International Standard.

4.2 Assignment of responsibilities

4.2.1 The responsibilities and authority for implementing, performing and monitoring the procedures described in this International Standard shall be assigned to qualified personnel as specified in ISO 13485.

4.2.2 Management shall be responsible for ensuring that there are an adequate number of qualified employees to perform required work and that supervision is provided. Management shall periodically review the performance of the quality management system to assess any areas needing improvement.

4.2.3 If the requirements of this International Standard are undertaken by separate organizations with independent quality management systems, the responsibilities and authority of each party shall be specified.

5 Aseptic processing master plan

5.1 General

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

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

5.1.2 An aseptic processing master plan shall be prepared, documented, reviewed and agreed.

In preparing an aseptic processing master plan products may be grouped together based on their characteristics and presentation. The grouping chosen shall be justified.

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

5.1.3 The aseptic processing master plan shall include an assessment of aseptic processing risks and describe provisions, methods and procedures as well as equipment intended to monitor the process and to control these risks, see 5.2. Residual risks shall be justified.

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

5.1.5 The aseptic processing master plan shall consider the complete process and give a rationale describing how each aspect contributes to the attainment and maintenance of a sterile product. The aseptic processing master plan shall address:

a) manufacturing environment, see Clause 6;

b) equipment, see Clause 7;

c) personnel, see Clause 8;

d) manufacture of the product, see Clause 9.

NOTE For requirements for aseptically manufactured medical devices to be designated "Sterile", see also ISO 15223 and EN 556-2.

5.1.6 The aseptic processing master plan shall address technical challenges and risks presented by the nature of the ingredients and its primary packaging components, its characteristics, design, formulation, and intended use.

5.2 Risk assessment and control

NOTE While this International Standard is primarily concerned with microbial contamination issues, there are other contamination risks that are of relevance (e. g. endotoxin, particulate and chemical contamination).

5.2.1 General

5.2.1.1 Risk assessment and control shall be documented.

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

a) identification of microbiological contamination risks;

b) assessment of contamination risks;

c) monitoring and detection of contamination;

d) prevention of microbial contamination.

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

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

Table 1 — Examples of specific risks

Aspect	Examples	Examples of specific microbial risks	Examples of control measures[a]
Ingredients	Biological origin Natural product Synthetic origin Ingredient with biocidal activity	High numbers of yeast, mould and bacteria Mycoplasma Viruses Endotoxin level Prions	Choice of approved suppliers(prions, virus) Supplier audits Supplier certificates Own control of incoming materials Control of pre-filtration bioburden, yeast mould and bacteria) Ultrafiltration (endotoxins)
Nature of the product	Solution Preserved or unpreserved Suspension Crystallized powder Lyophilized powder Cream or ointment Solid device Combination product formulations with biocidal activity	Ability to support microbial growth Bioburden increase Endotoxin contamination Contamination during manufacture	Perform growth studies on product (if water based, non preserved) Formulation: Multidose or single dose formulation (preserved vs not preserved) Water activity determination Hold time limitations of non sterile bulk Refrigeration of non sterile bulk In process bioburden monitoring
Product presentation/ design	Ampoules Vials Pre-filled syringe Form-fill-seal Multi-dose containers	Contamination during manufacture	100 % Leak test (ampoules, vials) Use of RABS or isolators Dual filters, final filter close to pint of fill EM program incl. contin.particle monitoring
Technical complexity of the manufacturing process	Multi-stage manufacturing Manual assembly steps Complicated delivery device	Contamination during manufacture	Use of RABS or isolators Pressurize sterile bulk tanks during hold CIP/SIP of all sterile product contact parts Robotic assembly vs manual Automatic transport and loading/unloading of freeze dried products
Intended clinical use of the product	Topical use Parenteral use Eye care Single dose / Multiple use Implantable	Potential impact of contaminated product	Patient convenience devices Nurse convenience devices (e.g. for reconstitution of vials) In-use time studies New preservative systems Multidose preservative free presentations

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

5.2.2 Identification of microbial contamination risks

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

a) origins of contamination:

   1) contamination sources;

b) routes of contamination:

   1) inappropriate aseptic technique;

   2) ability of microorganisms to cross a segregation barrier;

   3) microorganisms being transported across a processing zone;

c) contamination detection and removal:

   1) detection of microbial contamination;

   2) adequate microbial removal;

d) proliferation of contamination:

   1) conditions conducive to microbial proliferation.

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

5.2.3 Assessment of contamination risks

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

NOTE Established procedures like Failure Mode and Effect Analysis (FMEA) or Hazard Analysis of Critical Control Points (HACCP) may be applied to minimize identified risks.

5.2.4 Monitoring and detection of contamination

5.2.4.1 There shall be procedures for monitoring the process.

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

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

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

a) microbiological quality of the product at defined stages during the manufacturing process (see 6.3, 6.4, 6.5, 6.6);

b) microbiological quality of the manufacturing environment including e. g. air and surfaces of rooms, (see 6.8.1.3), equipment surfaces (see 6.8.1.3), tools (see 6.8.1.9);

c) microbiological status of the gloves and gowns of personnel at defined intervals (see 6.8).

NOTE 1 Observations of activities may also be required for the purposes of identification of potential sources for the introduction of contaminants.

NOTE 2 For liquids monitoring of bioburden to defined levels is a requirement in certain jurisdictions.

5.2.4.5 The monitoring methods employed shall be validated.

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

NOTE 1 Microbiological risks are frequently influenced by minor faults in handling or equipment design that are not easily recognized.

NOTE 2 Microbiological monitoring methods available are not sufficiently sensitive and precise to detect every microbial contaminant.

5.2.4.7 The significance of any monitoring result shall be correlated to the priority a risk is given in the risk management.

5.2.4.8 A documented procedure shall be specified for the calibration of all measuring instruments or measuring systems.

5.2.4.9 The accuracy and tolerance of all measuring instruments shall be adequate for the process to be measured.

5.2.5 Prevention of contamination

5.2.5.1 Data gathered from monitoring shall be evaluated so that appropriate action, including corrective and preventive action, is taken.

5.2.5.2 Once risks have been identified preventive measures shall be applied to minimize or eliminate these risks.

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

5.2.5.3 Appropriate measurements shall be established to demonstrate effectiveness of the preventive measures.

6 Manufacturing environment

6.1 General

6.1.1 The manufacturing environment shall be designed and built in accordance with ISO 14644-4. The objective(s) of the control programme for the manufacturing environment shall be defined.

NOTE Aseptic processing is aimed at product protection. Where highly potent or cytotoxic health care products are to be processed protection of personnel can be a second and equally important objective. A third objective can be protection of the environment.

6.1.2 The control programme for the manufacturing environment shall address:

a) layout and design including:

1) physical attributes of the rooms;

2) segregation for all cleanliness zones;

b) heating, venting and air conditioning (HVAC) system including:

1) air flow velocities, number of air changes per hour and differential pressures;

2) air flow pattern for critical processing (and direct support zones where required);

3) temperature and relative humidity;

c) appropriate monitoring parameters and set control levels for particulates and microorganisms;

d) introduction and exhaust of utilities;

e) introduction and removal of materials, components, product and waste;

f) cleaning and disinfection procedures;

g) provisions and procedures including gowning practices for entering and leaving of personnel;

h) access for service and maintenance;

i) behaviour and activities of personnel in the APA;

j) provisions for corrective measures within the APA.

6.2 Manufacturing environment design

6.2.1 General

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

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

6.2.1.3 A design review procedure shall be conducted for new facilities and documented to demonstrate that the design is in compliance with the aseptic processing master plan.

6.2.1.4 Before significant modifications to the facility are implemented a design review shall be applied.

6.2.2 Construction features

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

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

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

6.2.2.4 Where communications systems are provided to minimize movement of personnel into and out of the cleanrooms they shall be designed to facilitate cleaning and shall be monitored regularly.

6.2.2.5 Where curtains are used to guide air flow, the material used shall be durable and resistant to the cleaning agents and disinfectants used.

6.2.2.6 There shall be no uncleanable recesses and a minimum of projecting ledges, shelves, cupboards and equipment. Doors shall be designed to avoid uncleanable recesses. Sliding doors are undesirable for this reason.

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

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

6.2.2.8 Critical processing zones and direct support zones shall not contain sinks or drains. In other areas sinks 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.

6.3 Layout

6.3.1 General

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

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

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

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

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

6.3.1.3 Where ISO 14644-1:1999 classes are referred to this shall be taken as in the operational state.

6.3.2 Critical processing zone

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

NOTE 1 This International Standards refers to the classification according to ISO 14644-1:1999; for other regional classification systems, see Annex B.

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

a) aseptic assembly of filling equipment;

b) aseptic connections;

c) aseptic compounding and mixing;

d) refilling of product, containers and stoppers;

e) staging and conveying of sterilized primary packaging materials;

f) aseptic filling, stoppering, transfer of open or partially stoppered vials, including interventions;

g) environmental monitoring.

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

6.3.3 Direct support zones

Areas directly supporting the critical processing zone shall prevent contamination of the critical processing zone. For a critical processing zone protected by the sweeping action of the air (airflows) at least a direct support zone with an ISO 14644-1:1999, Class 7 environment shall be provided.

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

a) transport and preparation of packaged materials for introduction into the critical processing zone;

b) removal of closed product from the critical processing zone;

c) preparation of operators for interventions in the critical processing zone (e. g. disinfection of gloves, staging of tools).

6.3.4 Indirect support zones

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

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

NOTE 2 Examples of activities which are usually performed in a indirect support zone include:

a) preparation of product solutions to be filtered;

b) assembly of cleaned equipment to be sterilized;

c) cleaning of equipment.

6.3.5 Material air locks, transfer hatches, and product exit openings

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

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

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

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

6.3.6 Personnel air locks

6.3.6.1 Personnel and materials shall enter through separate air locks.

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

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

Separation of the personnel entering from those leaving the clean room should be achieved either by separation in time or by providing separate entry and exit routes. The latter should be chosen if hazardous or particle generating products are processed.

Personnel air locks shall be fitted with interlocking doors to prevent doors to the clean and less clean areas opening at the same time. Consideration should be given to equip interlocking doors with audio-visual indicators and recorder systems. Emergency exits shall be provided with a means to show that they have been opened.

6.3.6.3 Adequate space shall be provided to put on and remove the appropriate clean room garment without contamination.

6.3.6.4 Space and facilities shall be available for sterile garment storage, soiled garment disposal, hand washing and hand disinfection. In general hand washing facilities should not be provided in ISO 14644-1:1999, Class 7 areas or better.

The proper gowning practice shall be visually displayed.

Gowning airlocks shall be equipped with a mirror to allow the operator to confirm that the gowning has been completed properly.

6.3.7 Ancillary areas

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

6.4 Material and personnel flow

6.4.1 General

6.4.1.1 Material and personnel flow procedures shall be established and documented to determine the flow of personnel and handling and processing of materials, components and equipment delivered to the APA in order to:

a) maintain the integrity of critical processing zones;

b) minimize the entry of contamination from outside the APA, and retain any such contamination so that it does not reach the critical processing zone;

c) prevent cross contamination within the APA and/or within the APA, ensure segregation of clean and dirty items, and ensure segregation of sterilized and non-sterilized components .

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

6.4.2 Introduction of materials and components to the APA

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

6.4.2.2 Contiguous conveyors shall not go between classification zones.

6.4.2.3 Materials entered into the critical processing zone shall be sterilized except in justified cases. When this is not possible (e. g. particle counter) the materials and/or equipment shall be biodecontaminated to render them free from microorganisms. Such material should be part of the monitoring programme.

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

6.4.2.4 Each of the sterilization processes used to sterilize components or materials used in the APA shall be validated separately.

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

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

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

NOTE Solutions are compounded in indirect support areas in adequately protected tanks, particularly if the solution is to be stored prior to filtration.

6.5 HVAC system

6.5.1 General

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

6.5.2 Air handling

6.5.2.1 Within the APA a HEPA-filtered air supply shall maintain a positive pressure relative to surrounding areas of a lower grade under all operational conditions and should flush the area effectively.

For the critical processing zone a unidirectional air flow of sufficient velocity to provide adequate protection shall be demonstrated other than in isolators, see ISO 13408-6:2005, 5.4.

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

6.5.3 Airflow patterns

6.5.3.1 Within the critical processing zone and direct support zone the required air flow pattern shall be specified. This pattern shall be demonstrated, verified and documented for specified operational conditions to ensure that air flows do not present a contamination risk (e.g. distribute particles from a particle-generating person, operation or machine to a zone of higher product risk).

6.5.3.2 Where unidirectional airflow is specified velocities shall be tested at predetermined intervals for each HEPA filter and airflow patterns shall be re-established whenever a configuration change has been introduced.

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

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

6.5.4 Temperature and relative humidity

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

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

6.5.5 HEPA (including ULPA) filters

6.5.5.1 General

Filters shall be tested according to ISO 14644-3.

6.5.5.2 HEPA filter certification

6.5.5.2.1 HEPA filters used to maintain the environmental conditions within the APA shall be evaluated by a defined test (e.g. hot or cold DOP test, paraffin oil, etc) within the filter manufacturer's facility.

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

6.5.5.3 Installed filter leakage test

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

6.5.5.3.2 The integrity of HEPA filters for the critical processing zone and direct support zone shall be confirmed (nominally every 6 months).

6.5.5.4 HEPA filter failure

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

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

6.5.5.4.3 Manufacturers shall have defined procedures concerning the percentage of the filter surface face area that can be repaired.