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Manufacture of cell-based health care products — Control of microbial risks during processing

Manufacture de produits de soins de santé fondés sur les cellules — Contrôle des risques microbiaux durant le processus

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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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For an explanation on the meaning of ISO specific terms and expressions related to conformity assessment, as well as information about ISO's adherence to the WTO principles in the Technical Barriers to Trade (TBT) see the following URL: Foreword - Supplementary information

The committee responsible for this document is ISO/TC 198, *Sterilization of health care products*.

Introduction

0.1 General

A cell-based health care product (CBHP) comprises prokaryotic or eukaryotic cells or cell derived biological entities as an essential ingredient. Cell-based or cell derived starting material used in the manufacture of a CBHP can be viable or non-viable and of human, animal, microbial or plant origin. A common feature of CBHPs is that their efficacy is based on their biological properties. They are classified as medicines, medical devices, biologics or combination products depending on the international, national and/or regional regulations that govern supply of these products.

CBHPs might be limited in their ability to withstand sterilization and purification methods. This International Standard focuses on process rather than product. It describes the minimum elements necessary for a risk-based approach to the processing of a CBHP in order to reduce the potential for an increase in intrinsic contamination of product and to avoid extrinsic contamination of product. The design of the processes, equipment, facilities, utilities, the conditions of preparation and addition of buffers and reagents, and training of the operators are key considerations to minimize contamination.

0.2 CBHPs labelled as 'sterile'

A CBHP that is labelled as 'sterile' is sterilized by a terminal sterilization process or is aseptically processed.

Examples of CBHPs that are terminally sterilized include, but are not restricted to, cancellous bone, demineralized bone matrix, catgut sutures, biological heart valves and tissue patches. Sterility assurance for these CBHPs is achieved through suitable design and control of the environment, controls on starting materials and packaging, suitable design and qualification of manufacturing processes including the terminal sterilization process, and the application of appropriate in-process controls and testing. Requirements and guidance for terminal sterilization of CBHPs are contained in ISO 17665-1, ISO/TS 17665-2, ISO 11137-1, ISO 11137-2, ISO 11137-3, ISO 11135, ISO 14160, ISO 20857, ISO 14937 and ISO 25424, as applicable.

Controls for some infectious agents, e.g. viruses and protozoa, might require a multifaceted approach to ensure product quality and safety. Such agents are not specifically considered in the existing standards for terminal sterilization or aseptic processing.

A CBHP that is labelled 'sterile' and which cannot be terminally sterilized is aseptically processed. Sterility assurance for these CBHPs is achieved through suitable design and control of the environment, controls on starting materials and packaging, suitable design and qualification of manufacturing processes, process simulation (in accordance with the requirements of the ISO 13408-series), the application of appropriate in-process controls during manufacture, and testing to demonstrate achievement of aseptic processing conditions. As a prerequisite, starting materials and packaging materials are sterilized by validated processes. In this regard this International Standard does not reiterate requirements for specific processes that are used during processing of a CBHP that is labelled 'sterile'. In cases where a CBHP is aseptically processed and labelled as 'sterile' refer to the ISO 13408-series.

0.3 CBHPs supplied without a label claim for sterility

For a CBHP that is supplied without a label claim for sterility, e.g. corneal tissue or viable skin grafts, processing involves the use of appropriate aseptic techniques at all stages during the process. Components might be subject to bioburden reduction during preparation prior to their assembly or combining to form finished product. This is necessary to minimize the potential for intrinsic contamination of product to increase during processing and to avoid extrinsic contamination of product. The controls and techniques to maintain product quality during processing of these CBHPs might be different from those used for processing of a CBHP that is labelled 'sterile'.

Controls for some infectious agents, e.g. viruses and protozoa, can require a multifaceted approach to ensure product quality and safety.

Microbiological quality assurance for a CBHP that is supplied without a label claim for sterility is achieved through control of the environment, controls on starting materials and packaging, suitable design and qualification of manufacturing processes, process confirmation and process simulation studies and the application of appropriate in-process controls and testing. Risk assessment underpins selection of suitable microbiological quality criteria for a CBHP that is supplied without a label claim for sterility. These criteria define the acceptability of product based on the absence or presence, or number of microorganisms, per defined quantity of product, to ensure finished product does not pose a microbiological risk to the patient.

Manufacture of cell-based health care products — Control of microbial risks during processing

1 Scope

This International Standard 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 both to CBHPs labelled 'sterile' and to CBHPs not labelled 'sterile'.

This International Standard is not applicable to:

— procurement and transport of cell-based starting material used in processing of a CBHP,

— cell banking,

— control of genetic material,

— control of non-microbial product contamination,

— *in vitro* diagnostics (IVDs), or

— natural medicines.

EXAMPLE Vitamins and minerals, herbal remedies, homoeopathic medicines, traditional medicines such as traditional Chinese medicines, probiotics, other products such as amino acids and essential fatty acids.

This International Standard does not define biosafety containment requirements.

This International Standard does not replace national or regional regulations that apply to the manufacture and quality control of a CBHP.

2 Normative references

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

ISO 11135, *Sterilization of health-care products — Ethylene oxide — Requirements for the development, validation and routine control of a sterilization process for medical devices*

ISO 11137 (all parts), *Sterilization of health-care products — Radiation*

ISO 13022:2012, *Medical products containing viable human cells — Application of risk management and requirements for processing practices*

ISO 13408-1:2008, *Aseptic processing of health care products — Part 1: General requirements*

ISO 13408-1:2008/Amd.1:2013, *Aseptic processing of health care products — Part 1: General requirements / Amendment 1*

ISO 13408-7:2012, *Aseptic processing of health care products — Part 7: Alternative processes for medical devices and combination products*

ISO 14160, *Sterilization of health care products — Liquid chemical sterilizing agents for single-use medical devices utilizing animal tissues and their derivatives — Requirements for characterization, development, validation and routine control of a sterilization process for medical devices*

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

ISO 14937, *Sterilization of health care products — General requirements for characterization of a sterilizing agent and the development, validation and routine control of a sterilization process for medical devices*

ISO 14971, *Medical devices — Application of risk management to medical devices*

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

ISO 20857, *Sterilization of health care products — Dry heat — Requirements for the development, validation and routine control of a sterilization process for medical devices*

ISO 22442 (all parts), *Medical devices utilizing animal tissues and their derivatives*

ISO 25424, *Sterilization of medical devices — Low temperature steam and formaldehyde — Requirements for development, validation and routine control of a sterilization process for medical devices*

ICH Q7, *Good manufacturing practice guide for active pharmaceutical ingredients*, International Conference for Harmonization; identical to Annex 18 of the EU-GMP-Guideline

ICH Q9, *Quality Risk Management*

European GMP Part II — Good Manufacturing Practice — Medicinal Products for Human and Veterinary Use — Part II: Basic Requirements for Active Substances used as Starting Materials

3 Terms and definitions

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

3.1
active ingredient
any chemical or biological component that is included in the formulation of a cell-based health care product in sufficient concentration to achieve the intended therapeutic purpose of the specific product

3.2
animal
any vertebrate or invertebrate [including amphibian, arthropod (e.g. crustacean), bird, coral, fish, reptile, mollusc and mammal] excluding humans (*Homo sapiens*)

[SOURCE: ISO 22442-1:2007, 3.1]

3.3
aseptic technique
conditions and procedures used to exclude the introduction of microbial contamination

[SOURCE: ISO 14161:2009, 3.2]

3.4
biological contamination
presence of cells or biological entities other than the intended components

Note 1 to entry: This can include extrinsic and/or intrinsic contamination.

EXAMPLE Viruses, bacteria, fungi, protozoa, multicellular parasites, contaminating eukaryotic cells, aberrant proteins known as prions, endotoxins or active DNA/RNA.

3.5
biological entity
functional assembly of biological molecules or structures

Note 1 to entry: A biological entity can be an enzyme complex, a membranous structure, ribosomes, etc., or a combination thereof that is kept assembled to maintain its biological functionality.

3.6
CBHP
cell-based health care product
health care product that contains or consists of pro- or eukaryotic cells or cell derived biological entities as an essential ingredient

3.7
cell-based starting material
any cell-based or cell derived material, ingredient, component or reagent that is used in the production of cell-based health care products

Note 1 to entry: Cell derived materials are procured cells, tissues, biological entity intermediates.

Note 2 to entry: This can include tissue samples and/or biological fluids without a well-defined structure. This exceeds the scope of the definition of active pharmaceutical ingredients (API) starting material as given in ICH Q7.

3.8
CPA
cell-processing area
area for processing cell-based materials consisting of different zones for processing and, where applicable, for containment

Note 1 to entry: The zones can include zones for aseptic processing areas (APA) (for a definition for APA see ISO 13408-1:2008, 3.5) and/or other zones where the processing environment is controlled to minimize extrinsic contamination of the product.

3.9
closed system
system preventing egress of hazardous agents and ingress of extrinsic contamination

3.10
containment
combination of buildings, engineering functions, equipment and work practices to allow safe handling of hazardous biological or chemical agents to prevent accidental release of these agents to the environment outside of the facility

3.11
containment area
designated area that comprises cell processing area and associated degowning room

Note 1 to entry: Isolators are considered to be a containment area.

3.12
containment facility
combination of manufacturing rooms including the containment area and associated rooms within a physical containment barrier

Note 1 to entry: This can include airlocks, access and support rooms, laboratories and interconnecting corridors.

Note 2 to entry: A containment facility uses a series of barriers (primary, secondary and tertiary) to minimize the escape of hazardous agents to facility workers, the general population and the environment, e.g. isolators (if necessary, negative pressure type); biological safety cabinets (Class I, II or III); negative air pressure cleanroom; personnel protective clothing; appropriate work practices; appropriate disposal of hazardous waste; restriction of access to the facility.

3.13
extrinsic contamination
ingress of extraneous material (viable and non-viable) during the manufacturing process

3.14
health care product(s)
medical device(s), including *in vitro* diagnostic medical device(s), or medicinal product(s), including biopharmaceutical(s)

[SOURCE: ISO/TS 11139:2006, 2.20]

3.15
inactive ingredient
any chemical or biological component other than an active ingredient that is included in the formulation

Note 1 to entry: An inactive ingredient is also known as an excipient.

EXAMPLE Buffer agents, scaffolds, water.

3.16
intrinsic contamination
foreign matter (viable and non-viable) present in cell-based starting material

3.17
microbial contamination
presence of unintended bacteria, fungi, protozoa, viruses

Note 1 to entry: This can include extrinsic and/or intrinsic contamination.

3.18
microorganism
entity of microscopic size, encompassing bacteria, fungi, protozoa and viruses

[SOURCE: ISO/TS 11139:2006, 2.26]

3.19
negative air pressure room
room where the ventilation system has been designed in such a way that the pressure in the room is below that of the surrounding areas

Note 1 to entry: The design of the room and the ventilation system for the room ensures that airborne contamination generated in the room does not disperse to other parts of the facility.

3.20
process confirmation studies
exercise designed to verify the specified state of intrinsic microbial control of manufacturing processes for cell-based health care products

3.21
process simulation
exercise that simulates the manufacturing process or portions of the process in order to demonstrate the capability of the aseptic process to prevent microbial contamination

Note 1 to entry: Process simulation using sterile surrogate can be used to demonstrate the absence of ingress of extrinsic microbial contamination in processes using non-sterile starting materials that are processed using aseptic techniques.

Note 2 to entry: Viruses are excluded from process simulation.

[SOURCE: ISO 13408-7:2012, 3.2, modified – The phrase “microbial contamination” has replaced “biological contamination”.]

3.22
processing of cell-based health care products
handling of cell-based health care products in a controlled environment, in which the air supply, materials, equipment and personnel are regulated to avoid extrinsic biological contamination of the product and to minimise the potential for intrinsic biological contamination of the product to increase

3.23
reagent
material used for cellular growth, differentiation, selection, purification or other critical manufacturing steps but that is not intended to be part of the final product

EXAMPLE Fetal bovine sera, culture media.

4 Quality system elements

A quality management system, appropriate to the nature of the operations, shall be implemented to ensure control over all activities affecting CBHP processing. Unless a superseding national, regional, or international Good Manufacturing Practice (GMP) is employed (e.g. the World Health Organization GMPs), a quality management system shall be applied, e.g. ISO 13485, Good Tissue Practice (GTP), Good Clinical Practice (GCP).

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

5 Process definition

5.1 General

5.1.1 Depending on the end product specifications processing of CBHPs can involve many individual operations that need to be effectively combined and controlled to:

a) minimize potential for intrinsic biological contamination in the starting material,

b) limit proliferation of intrinsic biological contamination in the process,

c) avoid extrinsic biological contamination of the product, and

d) ensure finished product with defined biological characteristics.

The purpose of the process definition is to obtain a comprehensive understanding of the integration of all the different elements required to successfully and safely manufacture the CBHP. Typical elements are given in Annex F.

5.1.2 The process definition for a CBHP shall be conducted after the starting material specification and CBHP finished product specification have been established. Acceptance criteria defined in these documents shall be used as input requirements.

5.1.3 When a CBHP is sterilized by a terminal sterilization process, ISO 14937, the ISO 11137-series, ISO 17665-1, ISO 20857, ISO 14160, ISO 11135 and ISO 25424 (as applicable), shall be followed.

Specific consideration shall be given to the

a) systematic analysis of cell-based starting materials to identify the risk of microbial contamination in the course of processing (see examples listed in Table A.1),

b) systematic analysis of the potential for introduction of extrinsic microbial contamination in the process, and

c) development of process confirmation studies (e.g. pre-sterilization bioburden treatment).

5.1.4 When a CBHP is intended to be sterile, and cannot be terminally sterilized, it shall be aseptically processed. ISO 13408-1 and ISO 13408-7 (as applicable) shall be followed.

Specific consideration shall be given to systematic analysis of cell-based starting materials to identify the risk of microbial contamination in the course of processing (see examples listed in Table A.1).

5.1.5 When a CBHP cannot be terminally sterilized or aseptically processed, the following shall apply:

a) systematic analysis of cell-based starting materials to identify the risk of intrinsic microbial contamination in the course of processing (see examples listed in Table A.1);

b) systematic analysis of the potential for introduction of extrinsic microbial contamination in the process;

c) development of process confirmation studies.

5.1.6 Based on the CBHP process definition an assessment of processing risks shall be conducted. Methods and/or procedures to minimize and control these risks shall be described and implemented (see 5.2). Residual risks shall be justified.

NOTE 1 Examples of specific process risks associated with CBHP include: use of starting material with intrinsic biological contamination, insufficient inactivation (or selective enhancement) of intrinsic biological contamination, ingress of extrinsic contamination, inactivation of biological activity and accidental release of hazardous material from a containment facility.

NOTE 2 Examples of specific contamination risks for CBHP are given in Annex A.

5.1.7 The process definition shall consider the complete process and give a rationale describing how each element involved in processing contributes to the attainment of product specification. The process definition shall be documented and approved by designated personnel.

5.1.8 The process definition shall be reviewed whenever a change occurs.

NOTE Guidance on identifying critical quality attributes, process parameters and material attributes, which are necessary in the development of a process definition, is given in ICH Q8.

5.2 Risk management

5.2.1 General considerations

For materials used during processing of CBHPs, consideration shall be given to the prevention, removal or inactivation of contaminants during the risk assessment process.

a) A risk management process shall be established and implemented according to ISO 14971 and ICH Q9.

b) Risk assessment shall be conducted to identify and evaluate risks associated with the processing and risks associated with the specific CBHP, and to understand interaction of these risks. The results of risk assessment shall be used as input for risk mitigation measures and to design process simulation and process confirmation studies.

   NOTE 1 Intrinsic biological contamination risks caused by cell-based starting materials and their contribution to inter-batch cross contamination risks are of major importance in the processing of CBHP.

   NOTE 2 Risk management tools can be selected and employed throughout the life cycle of the product, for example, in the product and process design, development and validation stages.

c) Measures to control process risks for the manufacture of CBHP shall be defined and implemented. Residual risks deemed to be acceptable shall be documented and justified.

d) The output/results of the risk management process shall be reviewed to take into account new knowledge and experience. Once a quality risk management process has been initiated, that process shall continue to be utilized for events that might affect the original quality risk management decision.

5.2.2 Cell-based starting material risk assessment

a) A cell-based starting material risk assessment process shall be established and implemented (see also Figure B.1).

b) For risk assessment of viable materials of human origin, ISO 13022 shall apply. For risk assessment of materials of animal origin, ISO 22442 (all parts) shall apply. For materials of plant origin, infectious agents (e.g. mycoplasma, bacteria, fungi, yeasts, protozoa and viruses) shall be considered according to local regulatory requirements.

c) It is recognized that intrinsic biological contamination can exist in starting materials. Acceptance criteria associated with such contamination in starting materials shall be established and confirmed in the risk assessment, documented in the starting material specification and addressed in process validation and release criteria.

5.2.3 CBHP process risk assessment

a) During the design and development of a CBHP process, risk assessment shall be used to identify and quantify biological contamination hazards for each step in the process in order to avoid cross-contamination. This includes ingress of extrinsic biological contamination and dissemination of intrinsic biological contamination. Mitigating procedures shall be implemented where identified as being necessary.

b) Both the quantification of contamination risk and the verification of the effectiveness of mitigating procedures shall be determined and controlled. This shall include but is not limited to:

1) intrinsic biological contamination control of product including specified microorganisms,

2) extrinsic biological contamination of the product or the manufacturing environment, and

3) particulate monitoring of the environment (viable and non-viable) depending on the level of cleanliness.

c) Risk assessment shall be used to design the process simulation for aseptically processed products as in ISO 13408-1 and ISO 13408-7.

NOTE 1 Process simulation is employed to verify that the overall residual risk of extrinsic microbial contamination of the entire process is acceptable.

NOTE 2 The CBHP process can be simulated in one continuous process or can be divided into two or more stages for the purposes of process simulation, e.g. employing two or more different approaches for process simulation based on the process steps, provided that the entire process is simulated.

d) For non-sterile product or product where biological contamination control steps are required (see Clause 10), starting material risk assessment shall be used to design process simulation and/or process confirmation studies.

NOTE 3 The results of the risk assessment can be used in the design of process simulation and/or process confirmation studies (where applicable) to demonstrate that the process prevents extrinsic contamination and that intrinsic contamination is controlled.

e) The application of risk assessment and biological testing is usually an iterative process. As the process develops and is further enhanced, the CBHP process simulation shall be modified, where necessary, to ensure that it reflects the entire process.

f) The original risk assessment shall be reviewed, and where necessary modified, to ensure that all risks associated with the entire process are identified, assessed and controlled.

g) The container closure integrity of primary packaging shall be assessed.

5.2.4 Use of risk assessment methods and tools for supply of CBHPs for use in clinical trials

Development and qualification of the process for production of CBHPs for clinical trials shall follow national or regional regulatory requirements.

6 Manufacturing environment

6.1 General

ISO 13408-1:2008, Clause 6 applies to aseptically processed CBHP. The principles contained therein apply to all CBHPs. If there are cogent reasons for not applying ISO 13408-1:2008 the rationale for this decision shall be documented.

Additional requirements, see 6.2 to 6.8, shall apply if they are applicable based on process definition and risk assessment.

6.2 Alternative processes

The nature of the product and the source of starting materials might require additional or alternative precautions with respect to facilities and equipment. Alternative processes might be acceptable for starting materials, intermediates and final products that are unsuitable for processing under the conditions required by ISO 13408-1. These alternative processes shall be justified, validated and documented.

The following requirements shall be considered:

a) quarantine of potentially contaminated material;

b) use of air locks for equipment, material and personnel;

c) suitability of containers and packaging;

d) need for protective equipment for employees;

e) need for specialized disposal and management of potentially hazardous and hazardous waste;

f) need for specialized hygiene measures;

g) need for containment, including where applicable, negative air pressure rooms;

h) level of environmental control based on the processing step and level of contamination risk (e.g. cell processing areas);

i) need for use of single use/ disposable components;

j) need for the control of potentially contaminated documents covering their entry, exit and archiving.

6.3 Manufacturing environment design

6.3.1 Containment area

Consideration shall be given to the requirement for containment.

The containment area shall be designed in agreement with process definition and risk assessment. The design review shall be documented.

6.3.2 Construction containment features

a) Facilities shall be constructed to prevent escape of contaminated air and discharges from the containment facility to other parts of the facility and to the external environment. See Annex C for further information about containment facilities.

b) The facility shall be designed so that all areas of the facility can be readily sanitized or bio-decontaminated, if necessary.

NOTE Attention is drawn to national and/or regional regulations for the design of containment facilities.

6.4 Layout

a) Facilities shall be designed in agreement with the process definition and based on risk management (examples are given in Figures C.1 to C.8). A design review shall be carried out and recorded for each facility as part of the process definition.

b) Where CBHP production and testing (e.g. quality control, diagnostic service) is carried out in the same building, separate containment systems shall be established and maintained. The containment level required shall be based on risk management.

c) Where negative air pressure areas or biological safety cabinets are used for CBHP processing, they shall be surrounded by cleanrooms as specified in ISO 14644-4 and/or regional GMP regulations.

d) Biological safety cabinets shall be subject to at least annual certification according to national or regional requirements. The heating, ventilation, and air conditioning system (HVAC system) shall not interfere with the air flow of the biological safety cabinet.

e) Correct management and control of air flow and pressure differentials in the containment facility is a critical aspect in ensuring effective containment. Air locks for containment facilities shall separate the contained area inside a facility from other facilities, or other spaces outside the facility. Airlocks shall be designed to allow movement of personnel, equipment and materials without affecting the inward flow of air into the contained area.

f) Where applicable, viral clearance processes shall be single pass flow with physical separation of pre and post viral manufacturing areas.

g) The need for installation of a de-gowning room including sinks and/or personnel showers shall be considered.

6.5 Material and personnel flow

6.5.1 General

Material and personnel flow procedures shall be specified in agreement with the process definition to ensure

a) prevention of cross contamination, and

b) no breach of containment.

6.5.2 Equipment

Processes for the transfer of equipment to or from the containment facility shall be designed to prevent contamination.

If a double-door moist heat sterilizer is installed across a barrier between two cleanroom classes, it shall have interlocked doors.

NOTE Bio-decontamination can be achieved by thermal or chemical means.

6.5.3 Handling of waste material

a) The flow of waste material shall be designed to prevent any kind of cross contamination.

b) Contaminated consumables (e.g. filters) shall be removed using a safe method.

c) Contaminated waste material (e.g. solid or liquid waste cell material, non-cell based materials, contaminated condensate of sterilizers, fermenter, etc.) shall be disposed of according to national or regional regulations.

6.6 HVAC system

a) An appropriate air handling system shall be provided based on the process definition.

b) Once-through ventilation shall be considered and installed where deemed necessary to prevent spread of contamination or the likelihood of cross contamination.

NOTE 1 For cleanroom HVAC design, area segregation is normally accomplished by using a separate air handling system dedicated to each area of the process operation.

c) Visual and audible indication of ventilation failure shall be provided.

d) All exhaust air from the containment area that is to be released to the environment shall pass through filters appropriate to the nature of contamination identified during the process risk assessment (e.g. HEPA filters ISO Class H45 for bacterial contamination).

e) The exhaust air from the containment area shall not be recirculated to other areas of the containment facility.

NOTE 2 See Annex C for further information about containment facilities.

6.7 Utility services and ancillary equipment

Utilities entering the containment facility shall be of suitable quality to prevent biological contamination of product, equipment and personnel.

NOTE Utility lines (e.g. steam, air, water, vacuum) that are connected directly to process equipment are at risk of becoming contaminated or can be a significant source of biological contamination.

6.8 Environmental and personnel monitoring programmes

The facility and personnel shall be monitored for biological contamination arising from the process in accordance with a documented programme.

7 Equipment

7.1 General

ISO 13408-1:2008, Clause 7 applies to aseptically processed CBHP. The principles contained therein apply to all CBHPs. If there are cogent reasons for not applying ISO 13408-1:2008 the rationale for this decision shall be documented.

Additional requirements, see 7.2, shall apply if they are applicable based on process definition and risk assessment.

7.2 Additional requirements

a) Specific risks or requirements for equipment shall be considered as part of the process definition.

NOTE The requirements for equipment can be different from or exceed those detailed in ISO 13408-1 (e.g. the equipment can have an impact on biocompatibility).

b) Process dedicated or product dedicated equipment shall be used.

c) Containment capabilities shall be assessed for all equipment used in the containment area. This includes but is not restricted to centrifuges, filters, solvent extraction units, cell disruption devices, freeze dryers, sterilizers, pumps, valves, pipes, heat exchangers, downstream purification units and waste treatment systems.

8 Personnel

8.1 General

ISO 13408-1:2008, Clause 8 applies to aseptically processed CBHP. The principles contained therein apply to all CBHPs. If there are cogent reasons for not applying ISO 13408-1:2008 the rationale for this decision shall be documented.

Additional requirements, see 8.2 to 8.4 shall apply if they are applicable based on process definition and risk assessment.

8.2 Personnel procedures

a) The personnel flow for viral clearance processes shall be single pass.

b) Process definition shall consider whether work carried out by an individual operator with a CBHP precludes work by that operator in other processing areas during the same shift.

c) Where personnel are required to perform work with different CBHP and non-CBHP during the same shift, then suitable measures and controls shall be established and implemented to ensure that cross contamination from personnel, equipment and material does not occur.

8.3 Gowning procedures

Once the operator has entered the containment facility their outer garment is considered contaminated and shall be removed prior to leaving the containment facility. The following shall be required:

a) the requirements and procedures for de-gowning for leaving the containment facility shall be based on process definition and risk assessment;

b) outer garment surface treatment requirements shall be defined based on process definition to avoid exposure of personnel to biological contaminants.

NOTE Surface treatment of outer garments can require that the operators need to enter a separate room prior to the de-gowning suite.

8.4 General employee health

The immunological and health status of personnel shall be considered with respect to product and personnel safety.

NOTE Vaccination can be required before working in the APA/CPA.

Any changes in the health status of personnel that could adversely affect the quality of the product shall preclude work in the production area.

For operator safety, regional or national guidelines or regulations for occupational medicine shall apply.

9 Manufacture of product

9.1 General

ISO 13408-1:2008, Clause 9 applies to aseptically processed CBHP. The principles contained therein apply to all CBHPs. If there are cogent reasons for not applying ISO 13408-1:2008 the rationale for this decision shall be documented.

Additional requirements, see 9.2 to 9.5, shall apply if they are applicable based on process definition and risk assessment.

9.2 Control of starting material

9.2.1 Cell-based starting material

a) A documented procedure shall be established and implemented for procurement and storage of cell-based starting material. The procedure shall comply with applicable clauses of ISO 13485, GMP Part II and/or ICH Q7 (for active pharmaceutical ingredients), ISO 13022, ISO 22442 (all parts) and applicable national or regional regulatory requirements.

b) Special containment requirements for procured starting material shall be defined (see also Annexes D and E).

c) Specifications for cell-based starting materials shall be defined to ensure quality of the starting material. Specifications shall be documented. Analytical procedures to assess the suitability of cell-based starting materials shall be appropriate for their intended purpose and shall be documented.

d) The overall responsibility for final release of starting materials shall be with the manufacturer of the CBHP. Any deviations from the starting material specification shall be justified and the rationale for decisions reached documented (see also Annex D).

NOTE 1 Evaluation can be performed by the supplier, a third party or the manufacturer of the CBHP.

e) The extent and acceptability of supplier or third party documentation shall be defined.

NOTE 2 Documentation can include for example, CoA (Certificate of Analysis), CEP (Certificate European Pharmacopoeia of EDQM), patient protocol and procurement protocol.

9.2.2 Other starting materials

a) Specific requirements for non-cell-based starting materials to be used in manufacture of CBHP shall be defined. Non-cell-based starting materials shall not introduce contamination that interferes with the biological activity of the CBHP.

NOTE 1 Non-cell-based starting materials include inactive ingredients, reagents, and all other materials that come into contact with the product and which can influence the activity of cells or biological entities in the product.

b) Specifications for non-cell-based starting materials shall be defined to ensure quality of the starting material. Specifications shall be documented. Analytical procedures to assess the suitability of non-cell-based starting materials shall be appropriate for their intended purpose and shall be documented. Components and reagents shall be evaluated.

c) Biological contamination shall be removed from all solutions, including reagents, rinse, examination, storage and transport solutions, used during the processing of a CBHP (where applicable).

d) The overall responsibility for final release shall be with the manufacturer of the CBHP. Any deviations from the starting material specification shall be justified and the rationale for decisions reached documented.

NOTE 2 Evaluation can be performed by the supplier, a third party or the manufacturer of the CBHP.

9.3 Manufacturing procedures

a) The flow of materials, product and personnel shall be designed to avoid cross contamination.

NOTE 1 This can be accomplished by unidirectional process flow.

NOTE 2 Not all starting materials will be free from contamination. Intrinsically contaminated starting materials can pass into the clean area if they cannot be decontaminated first and can emerge from the clean area still in an intrinsically contaminated state.

b) Where retention of samples of starting material or finished product for re-testing purposes is not possible (e.g. autologous cells or limited quantity of material), the use of surrogate or rejected samples shall be considered, justified and documented.

9.4 In-process controls and process monitoring

a) The steps in a manufacturing process for a CBHP that are critical to ensure the microbial quality and safety of a product shall be identified and controlled. Specifications for in-process control and monitoring tests shall be developed. Tests and their acceptance criteria shall be documented. In-process control and process monitoring results shall provide information on

1) on-going assurance that the production process remains in a state of appropriate microbial control, and

2) documentation of relevant process trends.

b) Written procedures shall describe the sampling methods and plans for starting materials and intermediates.

9.5 Virus elimination and inactivation

a) The steps in a manufacturing process for a CBHP that are critical to ensure virus safety of a product shall be identified and controlled.

b) Virus elimination and inactivation methods shall be qualified and validated.

c) Precautions shall be implemented to prevent viral contamination from pre-viral to post-viral elimination and inactivation steps.

NOTE For further information see ISO 22442-3 and ICH Q5A(R1).

10 Process simulation and process confirmation

10.1 General

Process simulation and/or process confirmation studies might be required components of overall validation. The requirements are determined by the status of starting materials and whether or not the final CBHP is sterilized and/or needs biological contamination control, see Table 1.

Table 1 — Application of process simulation and process confirmation studies to the manufacture of CBHPs

Starting materials	CBHP	Process simulation (see 10.2) mandatory?	Process confirmation (see 10.3) mandatory?
Sterilized	Terminally sterilized	No	No
	Aseptically processed[a]	Yes	No
Sterilizable[b]	Terminally sterilized	No	No
	Aseptically processed[a]	Yes	No
Non-sterilizable	Manufactured using aseptic techniques	Yes	Yes

[a] Aseptically processed includes starting materials sterilized by, for example, filtration.

[b] Sterilizable means the starting material is still non-sterile but can be sterilized during processing.

10.2 Process simulation

Process simulation as defined in ISO 13408-1:2008, Clause 10 and/or ISO 13408-7:2012, Clause 10 applies to CBHPs that are not terminally sterilized.

Process simulations for non-sterile components shall be conducted with sterile surrogate material.

If the cell-based material negatively affects a test method to be employed, then the use of a surrogate material that does not adversely affect the test shall be considered. The appropriateness of the surrogate material and any potential effect or change to the process as a result of its use shall be justified and documented. If the test of sterility for a CBHP during process simulation is different from a pharmacopoeial test for sterility, the inspection approach post-incubation shall be established and documented.

10.3 Process confirmation studies

During the development of the CBHP manufacturing process, critical steps shall be identified. In a series of studies in-process and finished product shall be sampled and tested for microbial contamination to ensure that the finished product meets all design characteristics, quality attributes and specifications. The results of these studies shall be used to establish the in-process controls and process monitoring parameters described in 9.4.

The process confirmation approach, both for initial confirmation and periodic re-confirmation, is based on product specifications and product type.

10.4 Media selection and growth support

Depending on the biological release criteria of the final CBHP the process simulation and/or process confirmation approach shall be capable of detecting microbial contaminants. The microbial contaminants to be detected shall be determined and can include prokaryotic or eukaryotic cells (e.g. protozoa, parasites, cell embedded microorganisms). The rationale for the qualification or validation approach including detection method(s) and sampling plan(s) shall be documented.

It shall be demonstrated that the selected culture media is capable of neutralizing any inhibitory agents in/on the CBHP if present.

It shall be demonstrated that the selected culture media minimize the risk of adventitious contamination, e.g. Transmissible Spongiform Encephalopathy.

11 Finished product release: test for sterility

11.1 General

ISO 13408-1:2008, Clause 11 applies to aseptically processed CBHP. The principles contained therein apply to all CBHPs. If there are cogent reasons for not applying ISO 13408-1:2008 the rationale for this decision shall be documented.

Additional requirements, see 11.2, shall apply if they are applicable based on process definition and risk assessment.

11.2 Additional requirements

a) For products where a test for sterility according to European Pharmacopoeia, United States Pharmacopoeia, Japanese Pharmacopoeia and/or additional national requirements cannot be applied an alternative test design shall be established and justified (see also ISO 13408-7:2012, Annex B).

b) Alternative approaches shall include at least the following:

   1) risk assessment;

   2) sampling requirements;

   3) test methodology;

   4) incubation period;

   5) inspection process post-incubation;

   6) validation against the reference method or comparability study;

   7) demonstration of the suitability of the alternative test method in the presence of the actual product to be tested.

   The alternative approach for release of product shall be justified and documented.

   NOTE The alternative approach to the test for sterility can also be applicable for process simulation.

c) For a product where due to limited quantities a compendial test for sterility cannot be applied, an alternative programme for sterility testing shall be developed as a quality control release test.

d) For sterile products with a shelf life shorter than the duration of the test for sterility, it will be necessary to release the batch before the results of the test for sterility are available. The test for sterility then serves as a retrospective control of the quality of the aseptic manufacturing process and batch disposition. Where a product is released before the final results of the test for sterility or comparable test are known, a procedure shall address the actions to be taken in the event of release of a non-sterile product. This shall include notification to the attending physician.

e) The release procedure shall include the responsibilities of the personnel involved in assessment for release and shall define requirements for the review of production and analytical data.

f) There shall be a regular assessment of the effectiveness of the quality assurance system including records kept in a manner which permit trend evaluation.

12 Finished product release: testing for biological contamination that cannot be detected by the test for sterility

12.1 General

The following requirements apply to testing for biological contamination that cannot be detected by the test for sterility.

Documentation shall define what is considered to be acceptable and unacceptable biological contamination (e.g. mycoplasma, endotoxin, viruses) in the final CBHP and what other contaminants could be present based on risk and knowledge of the process and product.

There shall be a regular assessment of the effectiveness of the quality assurance system including records kept in a manner which permit trend evaluation.

Consideration shall be given to a test programme covering at least the following items:

a) sampling requirements;

b) description of the test methods;

c) method validation;

d) finished product specification.

12.2 Extrinsic biological contamination

12.2.1 Where risk assessment determines that testing for extrinsic biological contaminants is required for a product, then this testing shall be conducted for each batch.

12.2.2 The types of contamination to be tested for shall be determined based on risk and knowledge of the process and product.

12.2.3 Test methods shall be defined and documented. Pharmacopeial tests shall be used where these methods are suitable. Where there is no pharmacopeial method, or where the pharmacopeial method is not suitable, then the manufacturer shall specify and justify the method to be used. Test methods shall be validated.

NOTE ISO 11737-1 provides guidance on determination of a population of microorganisms on products.

12.2.4 Release criteria shall be established and documented for the product.

12.3 Intrinsic biological contamination

If the product specification permits release of a product with intrinsic biological contamination, a test programme shall be established to ensure conformance to microbial quality aspects of the finished product specification.

Annex A
(informative)

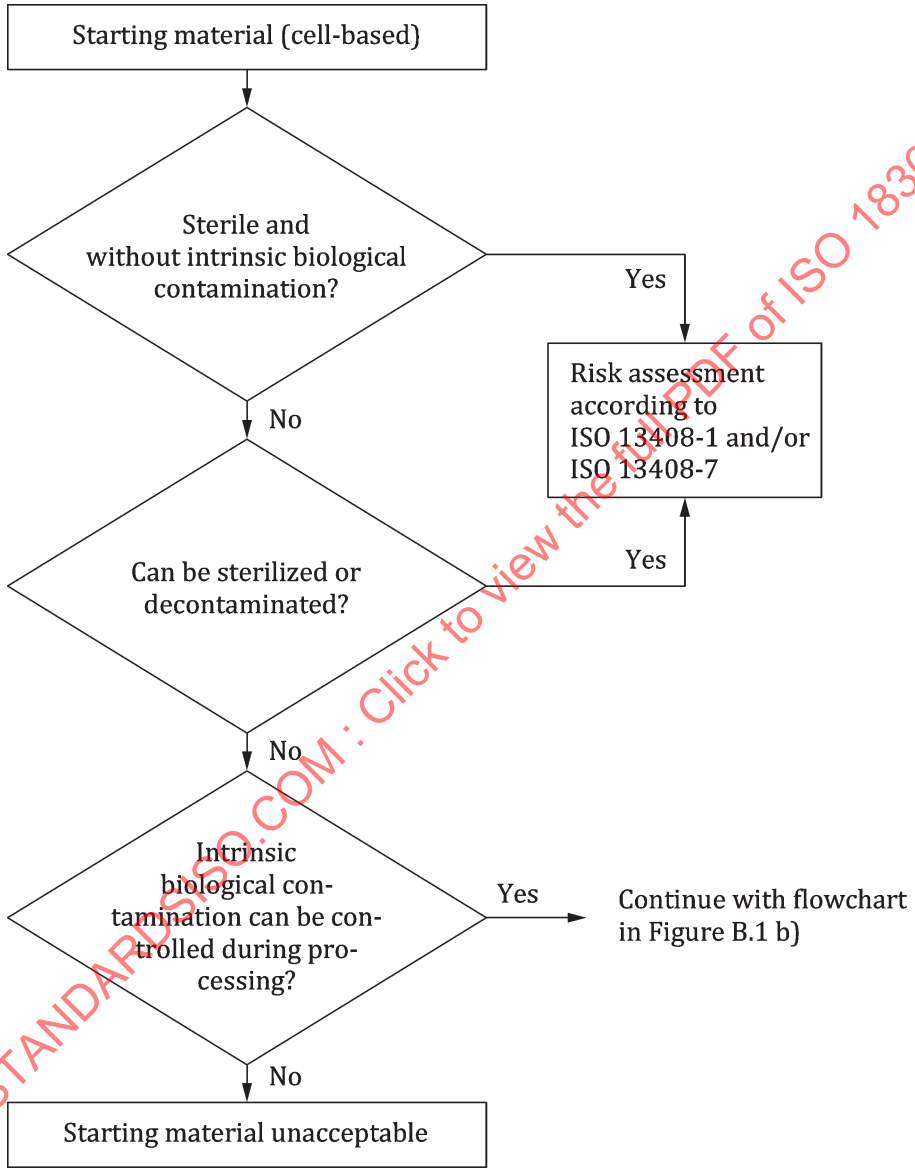
Examples of microbial risks for CBHP

Table A.1 — Examples of specific risks for CBHP

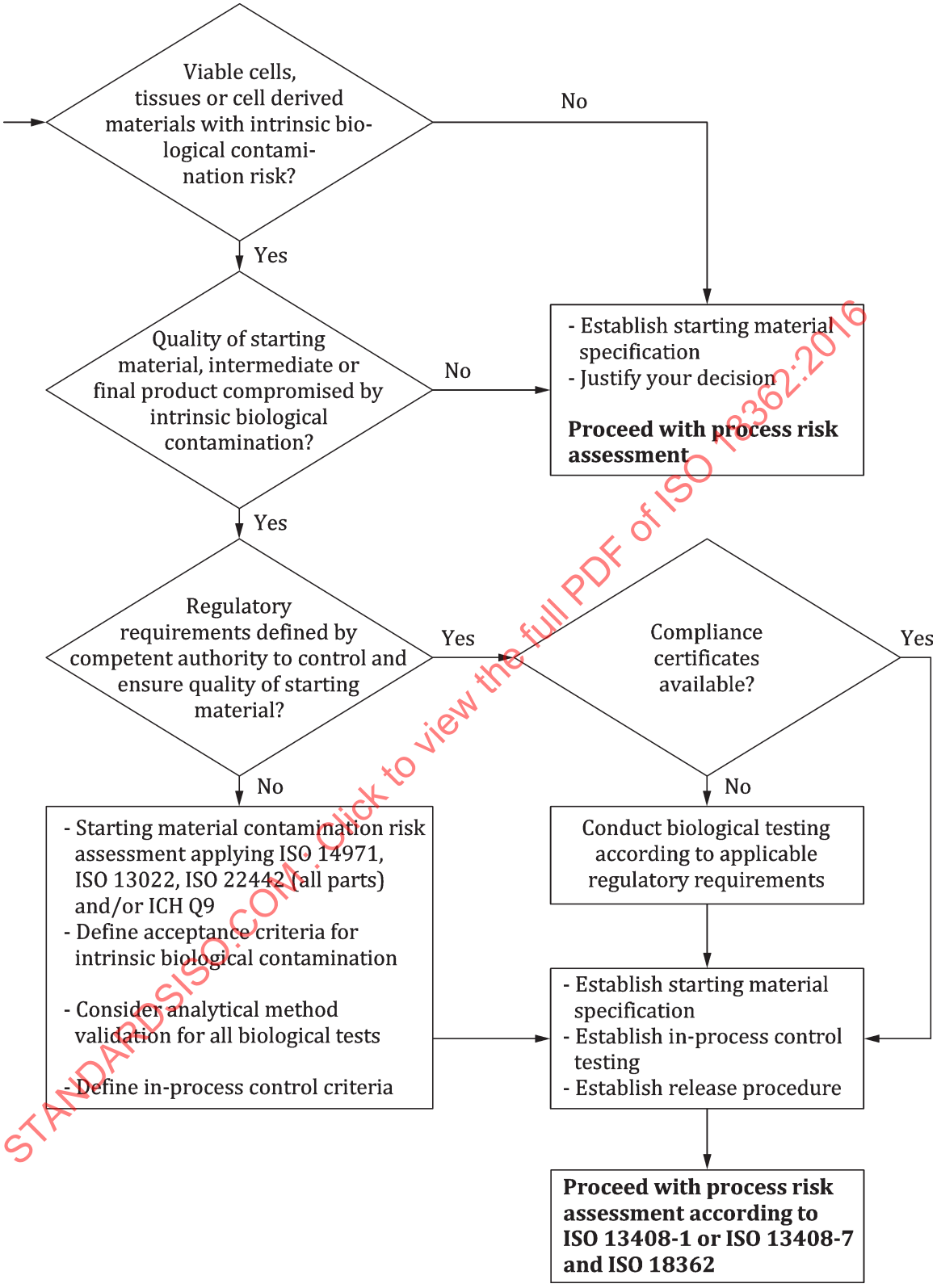
Products	Examples	Examples of specific contamination risks
Different cell types/ Somatic cell therapy	Chrondrocytes, keratinocytes	Chemical contaminations, endotoxins, pyrogens, prions, viruses (e.g. parvovirus B19, HIV, Epstein Barr)
	Periost-cells, osteocytes, fibroblasts, endothelial cells	
	Melanocytes, muscle-cells, liver-cells	Intracellular microorganisms (e.g. mycoplasmas, chlamydiae), yeasts, moulds and bacteria, pathogenic microorganisms
	Stem cells, allogenic cells, insulin cells, etc.	Contaminating eukaryotic cells, contaminating genetic materials
Live vaccines (viral or prokaryotic)	Childhood vaccines, rubella, measles	Viruses, retroviruses, parts of decayed viruses or cells, viral oncogenes, mycoplasmas, nanobacteria, amoebae
Monoclonal/ polyclonal antibody and gamma-globulin products	Breast cancer, psoriasis, Crohn's disease, multiple sclerosis	Prions, viruses, pathogenic microorganisms, nanobacteria
Tissue/ organ based products	Heart valves, cornea, bone grafts, scaffolds, cartilage, skin etc.	Intracellular microorganisms, viruses, yeasts, moulds and bacteria, pathogenic microorganisms, endotoxins, exotoxins
Combination products	Wound dressings, tissue sealants	Intracellular microorganisms, viruses, yeasts, moulds and bacteria, pathogenic microorganisms, endotoxins

Annex B
(normative)

Decision trees for application of risk assessment for cell-based starting materials



a) Step 1



b) Step 2

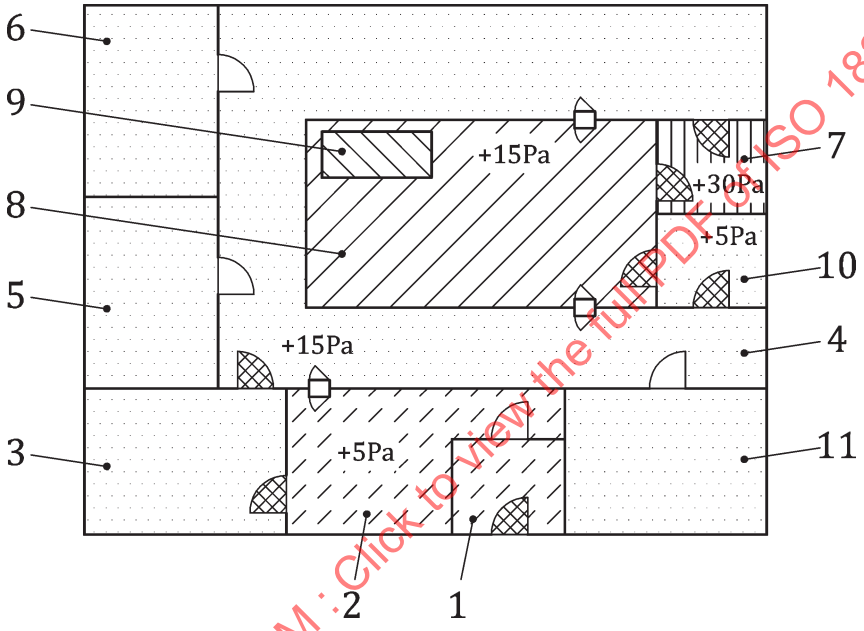
Figure B.1 — Decision tree for risk assessment for cell-based starting materials (aseptically processed or processed without a label claim for sterility)

Annex C
(informative)

Containment facilities

C.1 Manufacturing environment design with biological safety cabinet

Figures C.1 to C.4 show examples of layouts; however, depending on production process other configurations may be considered.



Key

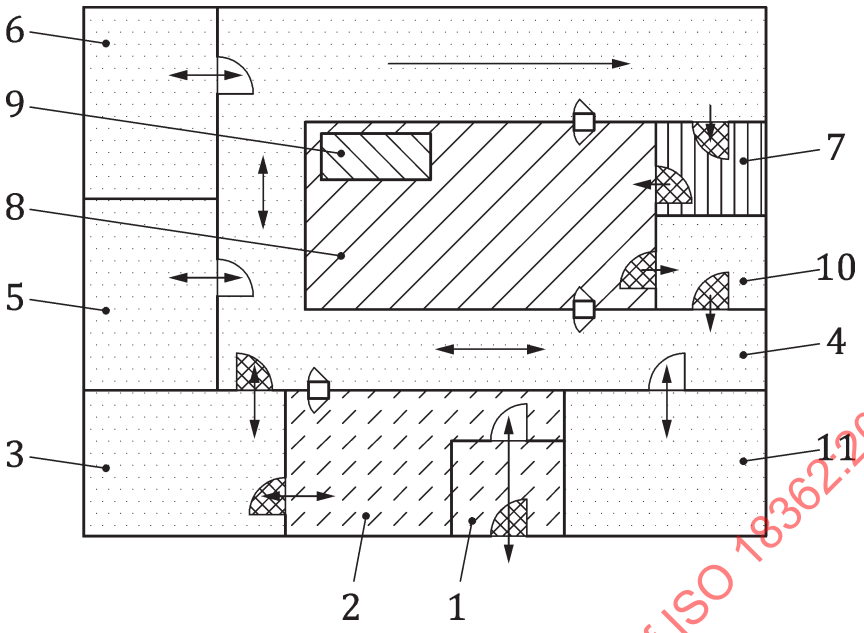
1	entrance	5	preparing room	9	safety cabinet
2	monitoring room	6	material storage room	10	second degowning room
3	first gowning and degowning room	7	second gowning room	11	sample storage room
4	buffer area	8	cell processing room		

critical processing zone | direct support zone | indirect support zone | non-classified areas | direct support zone at rest | door for airlock (tight door) | door for non-airlock | material airlock

NOTE 1 This layout permits entry of and working with non-sterile starting materials under appropriate clean room conditions in a designated area without compromising the integrity of the remainder of the aseptic processing area.

NOTE 2 For pressure differentials see Figure C.4.

Figure C.1 — Example of a containment facility for CBHP with safety cabinet



Key

1	entrance	5	preparing room	9	safety cabinet
2	monitoring room	6	material storage room	10	second degowning room
3	first gowning and degowning room	7	second gowning room	11	sample storage room
4	buffer area	8	cell processing room		

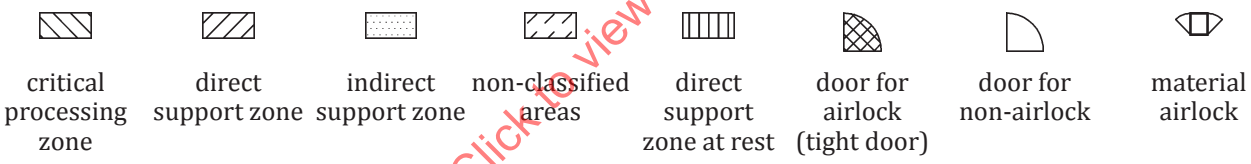
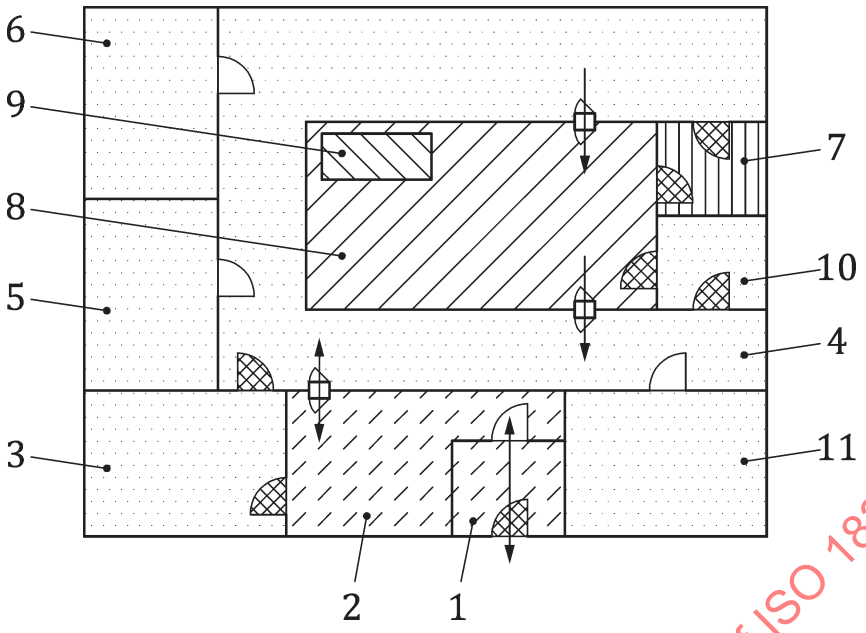


Figure C.2 — Example of personnel flow in a containment facility with safety cabinet



Key

1	entrance	5	preparing room	9	safety cabinet
2	monitoring room	6	material storage room	10	second degowning room
3	first gowning and degowning room	7	second gowning room	11	sample storage room
4	buffer area	8	cell processing room		

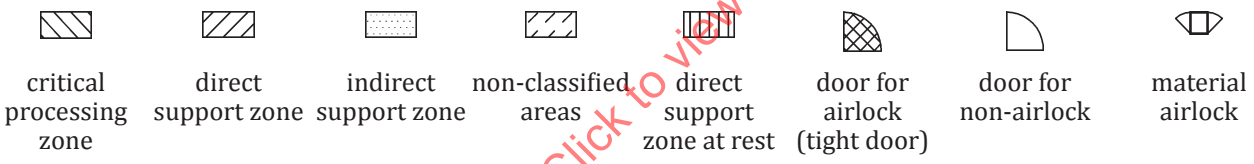


Figure C.3 — Example of material flow in a containment facility with safety cabinet

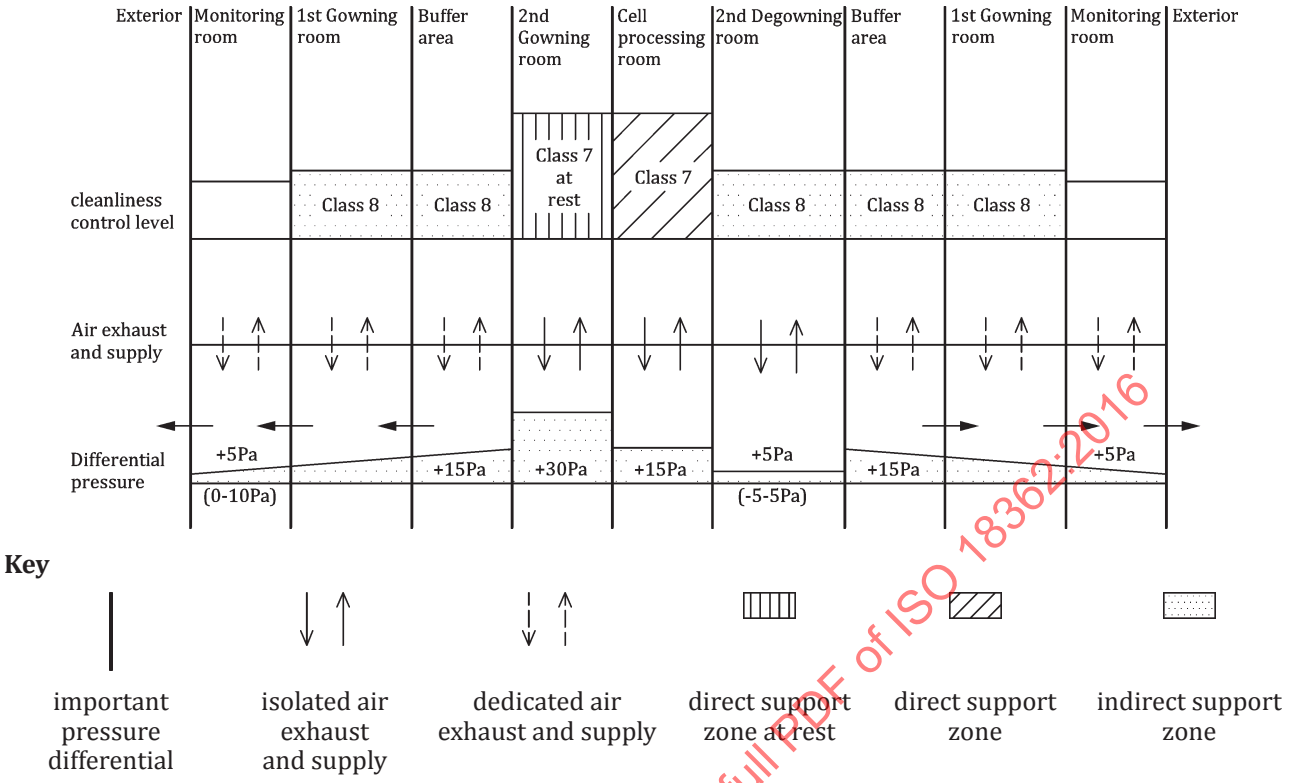
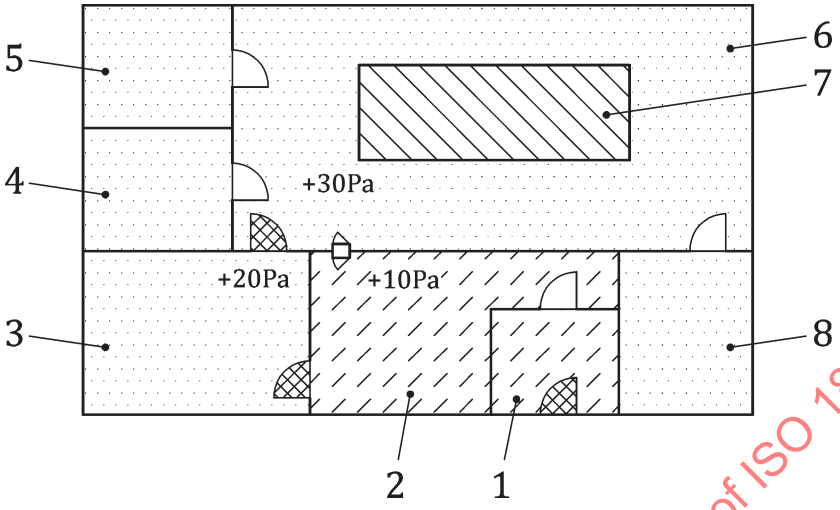


Figure C.4 — Example for segregation within the containment facility with safety cabinet achieved by the sweeping action of the air, pressure differentials and physical barriers

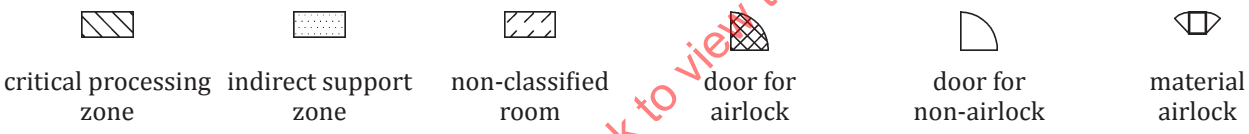
C.2 Manufacturing environment design with isolator or closed system(s)

Figures C.5 to C.8 show examples of layouts; however, depending on production process other configurations could be considered.



Key

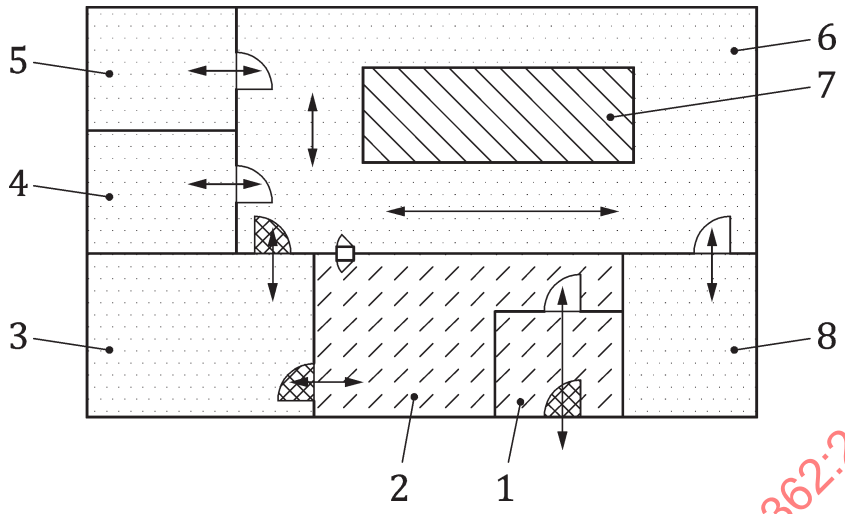
1	entrance	4	preparing room	7	isolator or closed system
2	monitoring room	5	material storage room	8	sample storage room
3	first gowning and degowning room	6	cell processing room		



NOTE 1 This layout permits entry of and working with non-sterile starting materials under appropriate clean room conditions in a designated area without compromising the integrity of the remainder of the aseptic processing area.

NOTE 2 For pressure differentials see Figure C.8.

Figure C.5 — Example of a containment facility for CBHP with isolator



Key

1	entrance	4	preparing room	7	isolator or closed system
2	monitoring room	5	material storage room	8	sample storage room
3	first gowning and degowning room	6	cell processing room		

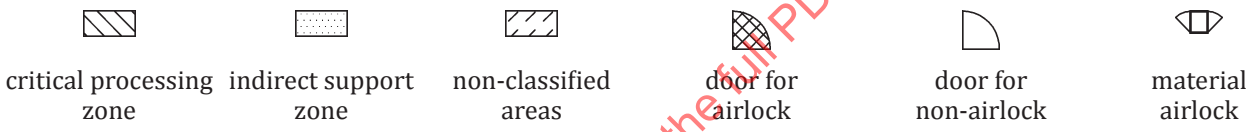
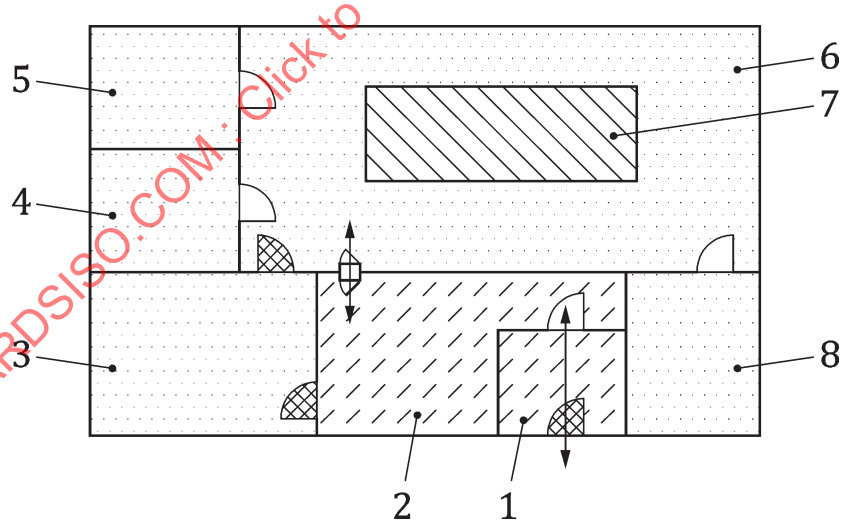


Figure C.6 — Example of personnel flow in containment facility with isolator



Key

1	entrance	4	preparing room	7	isolator or closed system
2	monitoring room	5	material storage room	8	sample storage room
3	first gowning and degowning room	6	cell processing room		

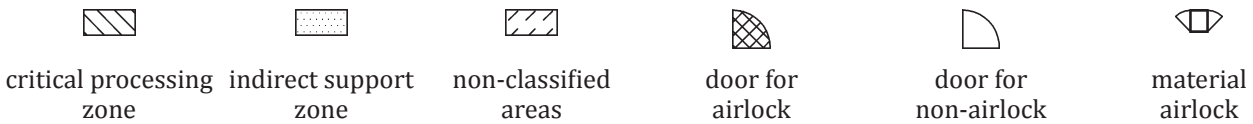


Figure C.7 — Example of material flow in a containment facility with isolator