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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

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.

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*.

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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.

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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.

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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*

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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.

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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.

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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”.]

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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).

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