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Biotechnology — Biobanking — Process and quality requirements for establishment, maintenance and characterization of mammalian cell lines

Biotechnologie — Biobanking — Exigences de processus et de qualité pour la génération, le maintien et la caractérisation des lignées cellulaires de mammifères

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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).

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. Details of any patent rights identified during the development of the document will be in the Introduction and/or on the ISO list of patent declarations received (see www.iso.org/patents).

Any trade name used in this document is information given for the convenience of users and does not constitute an endorsement.

For an explanation of the voluntary nature of standards, the meaning of ISO specific terms and expressions related to conformity assessment, as well as information about ISO's adherence to the World Trade Organization (WTO) principles in the Technical Barriers to Trade (TBT) see www.iso.org/iso/foreword.html.

This document was prepared by Technical Committee ISO/TC 276, *Biotechnology*.

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

Introduction

Scientific research using cell lines has contributed greatly to the understanding of human health. Cell cultures are increasingly used to complement studies using animal models. Although cell lines are important research tools, potential problems have recently been identified.

Cell lines have unique characteristics and behaviour that can change as they continue to be passaged. The original phenotype (e.g. expression of specific biomarkers) can be lost or new characteristics or behaviour (e.g. development of tumorigenicity) may develop. It is important to minimize passaging to retain the original characteristics that were present when the cell line was first established.

Other problems such as contamination, either with microorganisms or another cell line, and misidentification can also arise. Cultures can become contaminated during cell line establishment or later when cultures are passaged. These problems are often not visible by eye and require specific testing to be detected.

In order to help address these issues, the research community has called for an international effort to create standards for biobanks. ISO 20387 was published to provide an overarching standard for biobanks. This document provides additional technical specifications for biobanks that handle mammalian cell lines. Such biobanks can demonstrate their competence in biobanking by complying with the specifications within this document, in addition to the requirements prescribed in ISO 20387.

In this document, the following verbal forms are used:

— “shall” indicates a requirement;

— “should” indicates a recommendation;

— “may” indicates a permission;

— “can” indicates a possibility or a capability.

Further details can be found in the ISO/IEC Directives, Part 2.

Biotechnology — Biobanking — Process and quality requirements for establishment, maintenance and characterization of mammalian cell lines

1 Scope

This document specifies process and quality requirements for the biobanking of mammalian (including human) cell lines. It describes requirements for the fundamental procedures of the biobank handling cell lines, such as establishment, reception, identification, propagation, preservation, storage, quality control, and distribution of cell lines.

This document can be used by organizations performing biobanking activities with mammalian cell lines used for research and development, biobank users, organizations and schemes using peer-assessment and accreditation bodies.

This document does not apply to biological material intended for therapeutic use.

NOTE International, national or regional regulations or requirements can also apply to specific topics covered in this document.

2 Normative references

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

ISO 20387:2018, *Biotechnology — Biobanking — General requirements for biobanking*

ISO 20391-1, *Biotechnology — Cell counting — Part 1: General guidance on cell counting methods*

ISO 20391-2, *Biotechnology — Cell counting — Part 2: Experimental design and statistical analysis to quantify counting method performance*

3 Terms and definitions

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

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

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

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

3.1
cell culture
growth of cells dissociated from the parent tissue by spontaneous migration or mechanical or enzymatic dispersal for propagation and consecutive passages in vitro

Note 1 to entry: Additional information can be found in Reference [6].

3.2
cell line
progeny of a *primary culture* (3.16) after it has been passaged beyond crises or beyond senescence either spontaneously or after introduction of immortalizing factors

Note 1 to entry: A cell line is continuous for proliferation.

Note 2 to entry: Additional information can be found in Reference [7].

3.3
cell morphology
form and structure of the cell

Note 1 to entry: Morphology can be represented by a single parameter or a combination of two or more parameters.

3.4
cell strain
progeny of a *primary culture* (3.16) before it has been passaged beyond crises or beyond senescence or immortalized by introduction of immortalizing factors

Note 1 to entry: Not all the cell strains will continue proliferation to reach the cell lines.

3.5
cell type
classification used to distinguish among distinct cell forms

3.6
cryopreservation
process by which cells are maintained in a low temperature (e.g. –70 °C to –80 °C) at an inactive state so they can be revived later

3.7
derivative material
biological material that was derived from the original donation

EXAMPLE Derivative materials can be cell lines.

3.8
doubling time
time taken for cultured cell count to double

3.9
establishment of cell line
process of producing a cell line capable of indefinite proliferation

3.10
identity verification
part of the process of verifying authenticity of a cell line in which cell origin is genetically confirmed

3.11
informed consent
process by which an individual or its designated legal representative or nominated representative voluntarily confirms willingness to donate biological material for research purposes, after having been informed of all aspects of the potential research that are relevant for the decision to donate

3.12
microbe
microorganism
unicellular living cells which cannot be observed with naked eye but only under a microscope

3.13
passage number
number of subculturing that occurred

3.14
population doubling level
PDL
total number of population doublings of a *cell line* (3.2) or *cell strain* (3.4) since its initiation in vitro

Note 1 to entry: Additional information can be found in Reference [7].

3.15
primary cells
cells isolated directly from tissue or organs taken directly from an organism, using enzymatic or mechanical methods

3.16
primary culture
culture started from cells, tissues, or organs taken directly from an organism, and before the first subculture, propagation and consecutive passages *in vitro*

Note 1 to entry: Additional information can be found in Reference [6].

3.17
viability
attribute of being alive (e.g. metabolically active, capable of reproducing, have intact cell membrane, or have the capacity to resume these functions) as defined based on the intended use

4 Requirements

4.1 General

During the whole cell culture workflow, precautions shall be taken to avoid cross contamination between different samples/specimens, e.g. by using disposable material whenever feasible or appropriate cleaning procedures between processing of different specimens/samples.

The biobank shall establish, implement, and maintain a quality management system as described in ISO 20387:2018, Clause 8.

4.2 Legal and ethical requirements

ISO 20387:2018, 4.3 shall be followed.

The biobank shall consult an ethics review committee, which is responsible for the investigation and evaluation of any related ethical principles/requirements.

The biobank shall comply with ISO 20387:2018, 4.1.6. The biological material, which is the source of the cell line, shall be collected, transported, and handled according to internationally accepted procedures.

The biobank shall be aware of and able to demonstrate compliance with relevant national, regional and international approved ethics, laws and regulations relating to the biological material held in the biobank.

Further ethical requirements related to the informed consent are included in 4.6.

The biobank shall meet the organizational structure, resource, process, and quality requirements described in ISO 20387:2018, Clauses 5, 6 and 7, in addition to those in this document.

4.3 Facilities

4.3.1 General

ISO 20387:2018, 6.3 shall be followed.

The processing facility shall be constructed and operated to minimize the introduction, generation, and retention of particles and microorganisms.

The biobank shall define a protocol to test the quality of the biobanking environment(s).

Where appropriate, test methods proposed in the ISO 14644 series can be considered.

4.3.2 Cell culture facility

The biobank culturing and preserving cell lines shall establish a cell culture facility.

The biobank shall assess the biological safety level of the cell lines that will be handled. The biobank shall assess the risk of asphyxiation based on the number and condition of liquid nitrogen tanks and storage methods and install an oxygen monitor accordingly.

The biobank shall meet biological safety and security requirements for its facilities to minimize the risk to personnel and surroundings from handling the cell lines.

The biobank shall take necessary measures to control airflow.

The biobank should make efforts to secure a separate space for storage of duplicated cell lines in order to prevent the loss of collections in emergency situations. If the biobank cannot secure a separate alternate space for storage, the biobank should duplicate cell lines and store them in separate liquid nitrogen tanks. If the biobank cannot duplicate all stored cell lines, the biobank should make duplicates of the relevant cell lines or those that can be required by contractual agreements.

The biobank shall designate a separate area for handling deposited cell lines and/or tissues until they are determined to be free of microbial contamination.

4.4 Equipment

4.4.1 General

ISO 20387:2018, 6.5 shall be followed.

Equipment used in biobanking should be selected under quality specific criteria defined by the biobank, and for managing risks that can affect or impact performed assays, tests or their validity.

All incubators used, for working in accordance with this document, shall be monitored.

The biobank shall be furnished with or have controlled access to the following equipment as minimum requirements for cell culturing and ensure quality and safety requirements regarding the equipment.

a) Biological safety cabinet (Class II, Class III): physical structure protecting cell cultures from contaminants and personnel from potentially harmful biological substances. The cabinet can require appropriate biosafety measures, depending upon the biosafety level of the biological materials being handled.

b) Cell counting equipment: an automated cell counting feature is recommended, manual cell counting slide (e.g. hemocytometer slide) may also be used.

c) CO_2 incubator: a self-cleaning feature is recommended;

d) Freezer: data logger, alarming system and backup system are recommended.

e) Refrigerator: data logger, alarming system and backup system are recommended.

f) Liquid nitrogen tank for vapor/liquid phase storage of cell lines with temperature monitor and alarming system are recommended.

g) microscope: a camera for documentation is recommended;

h) Other general laboratory equipment (e.g. autoclave, deep freezer, refrigerator, centrifuge).

i) Inverted microscope (equipped with a camera).

The biobank should be furnished with or have controlled access to the equipment used for controlled rate freezing of cell lines.

The biobank shall equip its facility with appropriate biosafety equipment based on the assessed biological safety level (documented risk analysis); see 4.3.2. A biobank facility that uses liquid nitrogen shall have adequate ventilation.

The biobank shall have personal protective equipment available in accordance with the biosafety level of the facility and the nature of the cell line. Personnel within the facility shall wear appropriate personal protective equipment during cell culturing to prevent contact with culture media or aerosol that can be produced during the process.

Personnel handling frozen materials or liquid nitrogen shall use cryogenic personal protective equipment.

Storage equipment for cell lines should have a monitoring system and an alarming device or remote control system for immediate response to equipment malfunction or breakdown. The biobank shall keep records of equipment malfunction or breakdown and appropriate follow-up measures. The biobank should have an emergency generator or other equipment necessary to protect cell lines when power is lost.

The biobank should have the necessary backup equipment (e.g. vacant gas CO_2 incubators, freezers, and liquid nitrogen tanks) available in the case of equipment malfunction or failure.

4.4.2 Equipment inspection

The biobank shall inspect at planned intervals the following pieces of equipment, and their characteristics, used for cell lines, when applicable:

a) autoclave: according to the safety level, pressure, temperature, safety valve, steam outlet, cleaning and microbiological and chemical control of the process;

b) biological safety cabinet: airflow, HEPA filter condition, sterility and cleaning;

c) CO_2 incubator: temperature, humidity, CO_2 system, sterility and cleaning;

d) liquid nitrogen tank: liquid nitrogen level, temperature and inspection of alarming system;

e) microscope: components and cleaning;

f) refrigerator: temperature and stability of electric supply;

g) ultra-low temperature freezer: status of compressor, temperature system, and stability of electric supply;

h) ventilation system: inspection;

i) oxygen monitor devices: inspection;

j) backup equipment: status and stability of electrical supply and/or supply of nitrogen or CO_2 at emergency of electricity failure.