INTERNATIONAL STANDARD

ISO 21709

First edition
2020-11

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

Reference number
ISO 21709:2020(E)

ISO copyright office
CP 401 • Ch. de Blandonnet 8
CH-1214 Vernier, Geneva
Phone: +41 22 749 01 11
Email: copyright@iso.org
Website: www.iso.org

Published in Switzerland

Contents

Page

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.

Inspection records shall be retained. Details of any deviations shall be documented.

4.5 Reagents

Reagents 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.

The biobank should establish, document and implement a procedure for evaluating the reagent stability; this procedure should define criteria for internal or external quality control (i.e. antibodies, diluents, calibrators).

4.6 Informed consent

4.6.1 General

A procedure for obtaining the informed consent shall be established, documented and implemented. This informed consent procedure applies to human donors/patients and the responsible party for donor animals. In case of donations from animals, the donor's legally designated or nominated representative can be understood as the animal's responsible party.

The informed consent procedure shall comply with the requirements set by relevant ethics review committees. Appropriate approval of the procedure shall be obtained from the relevant ethical committee. Evidence of ethical approval shall be available.

The informed consent procedure shall take into account language barriers, condition and the educational level of the donor through the use of native non-technical language that is understandable to the donor/patient or the donor's/patient's legally designated or nominated representative.

NOTE In case the donor cannot understand the explanation, the responsible proxy can act on behalf.

During the informed consent procedure, it shall be ensured that the donor/patient or the donor's/patient's legally designated or nominated representative is informed about the aspects of his/her voluntary donation, and that these are understood.

Informed consent shall be obtained in writing from the donor/patient or the donor's/patient's legally designated or nominated representative with a personally dated signature, and the informed consent process shall be finalized and documented before a donation of biological material is obtained.

NOTE Dated signatures can be written on paper, electronical or digital.

The informed consent form consists of an information form (see 4.6.4) and an informed consent signature form (see 4.6.5). These two forms can either be combined in one document or separated into two documents.

4.6.2 Procedure of obtaining informed consent

The biobank shall comply with the following elements while obtaining informed consent:

a) all aspects of the potential use are relevant to the donor's/patient's or the donor's/patient's legally designated or nominated representative's decision for the voluntary donation;

b) the agreement on the informed consent shall not be affected by coercion, inducements, improper influences and/or misconduct;

c) do not waive or appear to waive the donor's/patient's legal rights;

d) use native non-technical language that is understandable to the donor/patient or the donor's/patient's legally designated or nominated representative;

e) provide ample time for the donor/patient or the donor's/patient's legally designated or nominated representative to read and understand the informed consent form and to consider the voluntary donation;

f) ensure personally dated signatures of the donor/patient or the donor's/patient's legally designated or nominated representative and the responsible physician or an authorized designee responsible for conducting the informed consent process;

g) provide the donor/patient or the donor's/patient's legally designated or nominated representative with a copy (in paper or digital) of the signed and dated informed consent form, which was approved by the biobank, and any other written information;

h) ensure documentation of the process in the donor's/patient's source documents and maintaining the biobank's signed informed consents with the essential documents;

i) show how informed consent will be obtained and recorded in special circumstances (4.6.3) where the donor/patient is unable to provide it him- or herself.

4.6.3 Special circumstances for informed consent

4.6.3.1 General

The provisions given in 4.6.3.1 and 4.6.3.2 are subject to national regulations.

4.6.3.2 Donor/patient needing legally designated or nominated representatives

Informed consent may be given by legally designated or nominated representatives only if a donor/patient is unable to make the decision to donate (eg. infant, child, juvenile, seriously ill patient, donor/patient with a mental, intellectual disability, animal). In such cases, except for donor animals, the donor/patient shall also be informed about the potential research within his/her ability to understand.

4.6.3.3 Human donor/patient unable to read or write

Informed consent shall be obtained through a supervised oral process, if a donor/patient or legally designated or nominated representative is unable to read or write. An independent and impartial witness shall be present throughout the process. The written informed consent form and any other information shall be read aloud and explained to the donor/patient or his/her legally designated or nominated representative. Wherever possible, either the donor/patient or his/her legally designated or nominated representative shall sign and personally date the informed consent form. The witness shall sign and personally date the informed consent form attesting that the information was accurately explained, and that informed consent was freely given.

4.6.4 Information provided to the donor/patient or the donor's/patient's legally designated or nominated representative

4.6.4.1 All information pertinent to potential use, including at least the following topics, shall be provided in writing and in native non-technical language that is understandable to the donor/patient or the donor's/patient's legally designated or nominated representative:

a) potential research under appropriate conditions;

b) potential use in many laboratories in many countries;

c) research applications;

d) unexpected feedback (for example, the cells' future use);

e) potential commercial exploitation;

f) other issues applicable to the research;

g) statements regarding manipulation, retention and personal data protection.

4.6.4.2 The informed consent form shall make the donor/patient or the donor's/patient's legally designated or nominated representative aware of and give the ability to accept or reject the donation based on the information of:

a) the donation being a set of biological material and its associated data;

b) that these cells will be stored, and may be sequenced, used in animal studies, or sent to other laboratories for analyses;

c) the potential extent of testing to be performed on the tissue and/or the cells derived;

d) that donations will be deidentified, thus either anonymized or pseudonymized/codified to maintain the donor's/patient's confidentiality according to ISO 20387:2018, 4.3.

4.6.4.3 The informed consent form and discussion should cover information that addresses:

— key aspects of human cell research; including but not limited to the fact that an immortal cell line can be established, which is a partial or full genetic match to the biomaterials donor;

— that the cell line can be shared with other researchers outside the institution for other research purposes that are not fully anticipated at this time.

The informed consent form shall include a statement of possible consequences of the consent withdrawal. This shall include that withdrawal of consent means that derivative materials cannot be withdrawn.

4.6.5 Informed consent signature

The informed consent signature form shall contain the following:

a) the agreement on the voluntary donation and to follow the responsible physician's instructions;

b) a statement declaring that refusal of donation incurs no penalty for the donor/patient;

c) a statement declaring that the withdrawal of consent and thereby revoking the informed consent at any time incurs no penalty for the donor/patient;

d) a statement with regard to the possible consequences of withdrawal;

e) an acknowledgement of the information provided and confirmation that all the questions of the donor/patient or those of his/her legally designated or nominated representative were answered, that the donor/patient or his/her legally designated or nominated representative acknowledges the information provided during the informed consent procedure and that (s)he had ample time to consider donating.

f) a statement confirming that the donor/patient or his/her legally designated or nominated representative agrees to the use of the donor's/patient's relevant personal data for the purpose of research.

4.7 Personnel

4.7.1 General

The requirements of ISO 20387:2018, 6.2.1 apply.

Vaccination of personnel is compulsory according to risk assessment.

4.7.2 Personnel competence

The requirements of ISO 20387:2018, 6.2.2 apply.

The biobank shall ensure that all personnel are knowledgeable about the health and safety risks of handling cell lines. The biobank shall provide safety training with regular updates based on the biosafety level of the facilities.

The biobank shall ensure that personnel involved in cell culturing are competent to perform the relevant tasks and knowledgeable in detection and prevention of microbial and cross contamination and misidentification.

4.7.3 Personnel training

The requirements of ISO 20387:2018, 6.2.3 apply.

The biobank shall provide biobank personnel (internal and/or external) with appropriate and relevant training with regular updates. The training subjects include, but are not limited to the following:

a) cell culture techniques, including aseptic laboratory skills;

b) characterization and authentication of cell lines;

c) establishment of cell lines;

d) ethics and data confidentiality and security;

e) health and safety;

f) preservation and storage methods;

g) environment control of cell culture areas;

h) quality control of cell lines, including detection and prevention of microbial and cross contamination and misidentification;

i) transport of cell lines, including e.g. relevant regulations in cell line shipment.

The biobank should periodically verify the knowledge of employees who manually perform the technological process to make sure that the process is carried out in accordance with internal procedure.

4.7.4 Biorisk and biosafety of personnel

The biobank shall assess biorisks of cell lines at the facilities and implement appropriate biosafety measures for the protection of personnel.

5 Process requirements

5.1 Establishment of cell lines within the biobank

5.1.1 General

5.1.1.1 The requirements of ISO 20387:2018, 7.1 apply.

5.1.1.2 The biobank can produce cell lines from cells or tissues derived from mammals, including humans.

5.1.1.3 The biological material which is the source of the cell line shall be collected, transported, and handled according to existing ISO documents or internationally accepted procedures.

EXAMPLE Such ISO documents include ISO/TS 20658.

5.1.1.4 The biobank shall obtain clinical and biological characteristics regarding the source of the cell line, including donor species, origin, ethnic origin, sex, age, collected part (e.g. tissue, blood, etc.), and disease state, as feasible and appropriate. The biobank shall store all the information of ~~to~~ the established cell lines and record their preservation and storage information.

5.1.1.5 The biobank shall ensure that materials are collected and handled in accordance with relevant ethical requirements. The biobank shall handle the clinical information and other data regarding the donor/sources of the cells in such a way as to maintain security and confidentiality of the donor identity.

5.1.1.6 The biobank shall provide a unique identifier to the cell line in an internationally recognized and distinct naming format in accordance with ISO 20387:2018, 7.5 a). Traceability shall be ensured according to ISO 20387:2018, 7.5.

NOTE The biobank can access the International Cell Line Authentication Committee website (ICLAC: https://iclac.org) or Cellosaurus (https://web.expasy.org/cellosaurus/) as references.

5.1.1.7 The biobank shall establish and implement measures to prevent cross contamination.

5.1.1.8 The biobank shall implement correct aseptic technique while handling cell lines. The biobank should refrain from using antibiotics or antimycotic. If the biobank uses antibiotics or antimycotic while handling cell lines, the level of antibiotics or antimycotic should be tested at the end of the culturing process.

5.1.2 Isolation and purification of primary cells

The biobank shall establish, implement, and maintain procedures for receiving and processing sources of primary cells.

NOTE The sources of primary cells include tissue, bone marrow, blood (e.g. mobilized peripheral blood, umbilical cord blood), and embryos.

The biobank shall retain additional source materials for confirmation of origin and, when applicable, for histopathological confirmation.

5.1.3 Primary cultures

5.1.3.1 Culturing

For cell culturing, the biobank shall use appropriate nutrients and additives that can optimize the output of cell culture in terms of its fitness for the intended purpose (e.g. reproducibility, stability, or yield).

5.1.3.2 Characterization

The biobank shall characterize primary cultures in accordance with their cell types and intended uses. The biobank should perform identification and verification for cell cultures when information of characteristic markers is available.

5.1.4 Cell lines

5.1.4.1 Establishment of cell lines

The biobank shall record the method and process used for the establishment of cell lines (e.g. by viral infection or spontaneous induction by radiation exposure or chemical treatment).

5.1.4.2 Authentication and characterization

The biobank shall authenticate and characterize newly established cell lines to confirm their identities and to test for the presence of contaminants, as suggested as follows:

a) tests for defining unique attributes;

b) microbial contamination: visual examination, PCR detection, fluorescence-based DNA detection, culture test, enzyme immunoassay, microscopic observation, or an equivalent method;

c) species verification and authenticity: short tandem repeat (STR) analysis, karyotype analysis, DNA barcoding, or an equivalent method.

5.2 Reception of established cell lines

5.2.1 General

For the reception of cell lines, the requirements of ISO 20387:2018, 7.3.2 and A.2 apply. The biobank shall establish, implement, and document procedures for the reception of cell lines according to ISO 20387:2018, 7.3.2.1.

Access principles shall be defined in accordance with ISO 20387:2018, 7.3.1. The biobank should have reception requirements, procedures, and forms available, preferably online, to clarify the rights and responsibilities of the biobank and the provider.

Traceability of the cells and its associated data shall be ensured in accordance with ISO 20387:2018, 7.5.

The biobank may receive requests for deposit from an external provider or request deposit from a provider. The biobank shall record all deposit requests for future references.

5.2.2 Review of the deposit request

The biobank shall review deposit requests to determine the adequacy of the cell line to be deposited, based on the following criteria:

a) legal considerations or requirements, such as intellectual property issues, the right to distribute and dispose, or any contractual obligations;

b) pre-analytical information (e.g. culture method and condition, preservation method, and storage condition);

c) biosafety level of the cell lines;

d) pre-defined quality criteria (e.g. free from contamination from foreign organisms, free from hazardous material to human health, scientific description including morphology, taxonomic designation, etc.), if necessary.

The biobank shall obtain available characterization information on the cell lines from the provider.

The biobank should ensure that a documented agreement or legally binding document is used when the cell line is accepted for deposit from the provider. Such agreements describe the rights and responsibilities, and immunities of the provider and the biobank with regard to distribution and intellectual property of the cell line.

The biobank should provide interested parties with access criteria for cell lines at the biobank.

5.2.3 Decision on the deposit request

The biobank shall decide whether to accept or to decline the deposit request based on the prescribed policy of the biobank and the result of the review process. The biobank shall document the results of the reception reviews.

When the cell line does not conform to the biobank's criteria, the biobank should notify the deposit requestor.

5.2.4 Transfer of material and associated data

5.2.4.1 Once the biobank has decided to accept a cell line for deposit, the biobank may discuss logistical issues with the provider to establish a transfer date of the cell line and the associated data, and the amount of material to be deposited. The amount of the material to be deposited shall be determined according to the nature of the material, the efficacy of preservation, the storage and thawing techniques, and the conditions applied on the transfer. Recommended deposit units for the reception of cell lines are included in A.1.

5.2.4.2 The biobank should record the amount of units received from the provider and reserve some units for the characterization test. The rest should be stored separately from the existing collection until the characterization test is completed.

5.2.4.3 If the cell line is suspected to be either misidentified, cross-contaminated or contaminated by microbes, the biobank shall ask the provider or a qualified laboratory to examine the identity of the cell line or to test for the presence of contamination and determine its type during the review process. The biobank should confirm if the deposited cell line is previously known to be cross-contaminated or misidentified. Biobanks shall be aware of the limit of a detection method at an authentication process.

NOTE The biobank can check the International Cell Line Authentication Committee (ICLAC) database to identify cell lines known to be cross-contaminated.

5.2.4.4 The biobank shall capture and generate a structured and standardized report of mammalian cell line data.

5.2.4.5 The biobank shall retain related data on the cell line, including the following, as relevant and appropriate:

a) donor information: donor species, origin, ethnicity, sex, age, collected part (e.g. tissue, blood, etc.), and disease state, therapy received;

b) cell line establishment: date of establishment, name and contact information of the originating institution, and reference for the establishment;

c) cell line validation: quality control testing data (see 5.2.5);

d) cell line characterization (see 5.2.5);

e) culture conditions: culture medium, supplement, cryopreservation medium, recommended container for storage, and growth condition (e.g. temperature and gas condition);

f) subculture information: passage number or population doubling time, population doubling level, and subculture requirements (e.g. split ratio).

5.2.5 Characterization and authentication of the cell line

The biobank shall perform pertinent characterization tests to verify the viability of the cell line, the absence of contaminants, or other characteristics reported by the provider. Such tests can include but are not limited to the following:

a) identity verification: short tandem repeat (STR) analysis for human cell lines or an equivalent method;

b) cell morphology: microscopic observation at sparse and confluent conditions;

c) growth: growth curve and population doubling test or an equivalent method;

d) microbial contamination: visual examination, PCR detection in accordance with ISO 20395, fluorescence-based DNA detection, culture test, enzyme immunoassay, or an equivalent method;

NOTE For detection of mycoplasma, mycoplasma colony assay by culturing, PCR, ELISA, and Hoechst stain can be used. For other bacteria and fungi, visual examination can be performed at minimum. For virus, PCR can be performed.

e) species verification: isoenzyme analysis, karyotype analysis, DNA barcoding, or an equivalent method;

f) viability: trypan blue exclusion test, flow cytometry, or an equivalent method.

g) mutation and copy number variation genotyping (e.g. for tumour cell lines).

For stem cells, the following additional tests should be performed:

1) test for differentiation capability;

2) gene expression signature: qPCR or an equivalent method;

3) immunophenotyping: fluorescent microscopy or an equivalent method;

4) test for unique cell surface markers and/or unique cell biofunctions, when applicable.

If a growth test [see 5.2.5 c)] is performed, the biobank shall conduct the cell counting in accordance with ISO 20391-1 and ISO 20391-2.

The biobank shall select and record which characterization tests to perform, based on the types of the cell lines.

The biobank shall perform sufficient characterization tests to confirm that the cell line is authentic and free of contaminants (e.g. mycoplasma) and can be used as a valid research tool.

The biobank shall record the date, the passage number, the test method used, and the results of characterization tests. If the test results do not match the characteristic information submitted by the provider, the biobank may ask the provider to resubmit the cell line.

The biobank may decline to accept the cell line if the characteristics do not match the description submitted by the provider or the provider fails to resubmit the cell line. In such cases, the biobank shall notify the provider of the decline of acceptance and define how the submitted cell line will be handled, either transferring it back to the provider or disposing it in accordance with applicable requirements and policies.

5.2.6 Assignment of accession number

When the biobank decides to accept the deposited cell line, the biobank shall assign a unique identification number and record the information (see 5.1.1.6 and 5.3.2). When possible, relevant information regarding the cell line should be added to an international catalogue.

5.3 Cell line management

5.3.1 Planning for cell banking

The biobank shall establish criteria and methods for propagation, preservation, and storage of cell lines in accordance with their characteristics, stability, ease of distribution, usage frequency, and difficulty of culturing. The biobank should establish short- and long-term plans for storage of cell lines, in accordance with the current amount of cell lines in the inventory, storage scheme, expected amount of distribution, and criteria for characterization and quality control test.

5.3.2 Accession

The biobank shall determine which data are required for accessioning of cell lines (see 5.2.4.5) and which data can be considered as supplementary, and collect data accordingly.

The biobank shall assign a unique identifier in accordance with ISO 20387:2018, 7.5.1, a) to each cell line and record the information at its accession to a database. The following data shall be included in the record:

a) accession date;

b) accession number;

c) batch number;

d) location data;

e) original number assigned by previous handler(s), if relevant;

f) previous accession number assigned by the biobank, if relevant;

g) name and contact information of the responsible personnel.

The biobank shall properly tag vials containing cell lines in accordance with ISO 20387:2018, 7.5.1, a). The label should contain the name of the cell line, accession number, batch number, and other necessary data.

The biobank shall determine whether the cell line and/or related data should be made available for distribution. If the cell line is intended for distribution, the biobank should list the cell line in a catalogue.

5.3.3 Propagation of cell lines

The biobank shall establish, implement, maintain, and document the relevant procedures for culturing cell lines, including necessary preparations of media and consumables. The biobank should validate or verify the relevant procedures.

Prior to culturing cell lines, the biobank shall prepare the cell line intended for culturing (e.g. thawing frozen cell lines) according to the relevant procedures in order to facilitate high cell survival. The biobank should reproduce the original culture conditions of cell lines, as implemented at their establishment, since the change in culture conditions can alter the cell behaviour and selection condition. The biobank shall document all changes to the procedures.

The biobank shall record the culture date, identity information of the personnel performing the culturing, and the culturing conditions, such as medium composition and percentage, serum type (batch number), temperature, gaseous phase, and any additional supplement. Personnel responsible for culturing shall be aware of and implement measures to prevent various types of contamination.

While culturing cell lines, the biobank should frequently inspect their morphology and growth and perform testing for contamination by mycoplasma, bacteria, mould, or yeast. The biobank shall perform frequent tests for identifying common contaminants of cell lines.

When contamination is detected in a cell line (i.e. microbial contamination or contamination with another cell line), the biobank should check if other batches are also contaminated. The biobank may dispose of contaminated cell lines, if at least one other batch is uncontaminated. If, however, there is no uncontaminated batch, the biobank can request another deposit from the provider or perform removal of contaminants and re-culture the cell line. The biobank shall record and track contamination events.

The biobank should manage the amount of cell lines in production and the interval between productions to ensure that the biobank can consistently provide the requested cell line. In case there is evidence in favour of limited passage numbers, the biobank should make a sufficient number of batches in each production.

Subculturing should occur in accordance with the cell line growth profile.

5.3.4 Preservation and storage

The requirements of ISO 20387:2018, 7.6, 7.7, A.4 and A.6 apply.

The biobank shall establish, implement, maintain, and document cryopreservation method and storage condition for cell lines, taking into account of characteristics and viability of each cell line. The biobank should validate or verify cryopreservation and storage methods. The biobank should perform quality control (QC) tests on each batch of the preserved cell stocks.

The biobank should implement seed stock approaches that allow the separate storage of cell lines into a seed stock for long-term storage and a distribution stock for short-term storage and frequent uses. The biobank should set the number of vials produced for each stock and minimum number of vials required to be in stocks prior to the replenishment of vials (see Table 1). The biobank should store an aliquot of each batch or each stock.

Table 1 — Example of cell line storage condition

Purpose	Storage condition	Minimum cell number per vial	Minimum number of vials
Seed stock	Vapour-phase of liquid nitrogen (recommended) (<-130 °C)	1×10^6 cells/ml (each vial)	12
Distribution stock			20

5.3.5 Inventory management

Requirements of ISO 20387:2018, 7.5.1 c) apply.

The biobank should implement a computer-based system for managing its inventory. The biobank should immediately update the database when the biobank receives cell lines, transports them within the biobank, or distributes them to others outside the biobank. A back-up should be available.

The biobank should verify the cell line inventory at planned intervals by a defined procedure. The biobank shall periodically inspect the storage and label conditions by eye or by using a rack scanner. In case of any discrepancy between the record and actual status, the biobank shall examine the cause of such an inconsistency, document it, and modify the record to reflect the actual status.

5.3.6 Disposal management

The requirements of ISO 20387:2018, 4.1.8, 7.1.1, 7.5.3 and A.7 apply.

The biobank shall establish, implement, and document criteria for disposing cell lines, such as for the following conditions:

a) use of cell lines is no longer permitted due to legally binding agreements;

b) withdrawal of consent, where required;

c) cell lines are altered from their original states during processing;

d) cell lines are contaminated and no longer considered useful;

e) storage of cell lines is no longer feasible or necessary.

The biobank shall store cell lines identified for disposal at a separate space or, at least, in a separate container until their collection by a specialized waste service.

5.4 Distribution

5.4.1 General

The requirements of ISO 20387:2018, 7.3.3 apply.

Recommended units for the distribution of cell lines are included in A.2.

5.4.2 Acceptance of order request

The biobank should have distribution requirements, procedures, and forms available, preferably online, to clarify the rights and responsibilities of the biobank and the recipient/user.

The biobank should accept distribution requests of qualified recipient/users and shall record the following information:

a) request number and date;

b) contact information of the requested user and, if applicable, the institutional official;

NOTE Contact information includes but is not limited to name, affiliation, address, phone number, and email address.

c) the requested cell line, including name, amount, and volume.

5.4.3 Distribution review

The biobank shall establish and publish criteria for requestors/users to access the cell lines. The biobank shall check the eligibility of the requestor/user based on these criteria. The biobank shall record all order requests and notify the decision to the requested user.

5.4.4 Transport

5.4.4.1 General

The requirements of ISO 20387:2018, 7.4 apply. The biobank shall document the transport temperature.

5.4.4.2 Preparation for shipment

The biobank should prepare for shipment of the requested cell line after confirming the inventory record and results of quality control tests. In case the cell line is shipped as cultures for local distribution, the biobank shall ensure viability of a substantial proportion of the cell line prior to the shipment.

5.4.4.3 Packaging

The biobank shall package the cell line in a container that is resistant to damage and leakage and with relevant safety labels included both within and outside of the package.

The biobank shall implement procedures to maintain the frozen status of the cell line until the recipient/user receives it. The biobank shall use a type and amount of coolant appropriate to the type of cell line

