INTERNATIONAL STANDARD

ISO 20399

First edition
2022-12

Biotechnology — Ancillary materials present during the production of cellular therapeutic products and gene therapy products

Biotechnologie — Matériaux auxiliaires présents lors de la production de produits thérapeutiques cellulaires et de produits de thérapie génique

Reference number
ISO 20399:2022(E)

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Published in Switzerland

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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).

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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*.

This first edition cancels and replaces ISO/TS 20399-1:2018, ISO/TS 20399-2:2018 and ISO/TS 20399-3:2018, which have been technically revised.

The main changes are as follows:

— merging of the three parts of the ISO 20399 series;

— change in definitions of key terms including “ancillary material” and “cellular therapeutic product”;

— addition of Clause 5 “Strategy”, including key concepts, animal-derived components, mutual responsibilities and qualification;

— revision and rearrangement of requirements and recommendations with emphasis on clarifying responsibility of involved parties and emphasis of a risk-based approach.

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.

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Introduction

Ancillary materials (AMs) refer to materials that come into contact with the cellular therapeutic product during cell processing but are not intended to be part of the final product formulation. See Annex A for a list of AM examples.

AM can be a complex mixture of many components. AMs include, for example, salts, buffers, culture media, supplements such as growth factors, enzymes and antibodies for immuno-purification. Where a material is composed of multiple materials such as culture media, all components are AMs. Variation in their lot-to-lot composition can hamper the ability to produce consistent cell and gene therapy products with specified quality attributes.

As such, AMs can have implications with regard to the safety and effectiveness of cell and gene therapy products. Appropriate control of AMs is determined by a risk-based approach.

This document specifies definitions for AMs.

This document provides recommendations and requirements to the AM suppliers and the AM users to ensure consistent manufacture and performance of AMs. This document also describes the information that can be obtained and provided to the AM users to demonstrate lot-to-lot consistency of the AM with respect to identity, purity, storage and stability, traceability, biosafety, and performance. Furthermore, this document provides recommendations and requirements to ensure that the quality of AMs enables the production of safe and effective final products.

Presently, a number of standards and guidance documents define the proper processing of cell and gene therapy products to ensure safety and efficacy. However, these standards only indirectly relate to AMs. This document is separate from the standards governing cell processing requirements. This document addresses issues with AMs and makes the expectations of the AM suppliers and the AM users clear.

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Biotechnology — Ancillary materials present during the production of cellular therapeutic products and gene therapy products

1 Scope

This document specifies requirements and gives guidance to suppliers and users of ancillary materials (AMs) to improve the consistency and quality of AMs of biological (human and animal) and chemical origin used in the production of cellular therapeutic products and gene therapy products for human use.

This document is applicable to materials that are used for cell processing and that come into contact with the active substance and that do not intentionally form part of the final cell and gene therapy product.

EXAMPLE 1 Reagents, anticoagulants, cytokines, growth factors, enzymes, antibodies, serum (human or bovine), buffered solutions, culture media, dishes (coated with biological material), beads (coated with biological material), cryoprotectants (agents for cryopreservation), activation agents/reagents, non-mammalian cell (e.g. insect cell, bacterial cell), plasmid, viral vector.

This document does not apply to materials that are not used for cell processing, materials that do not come into contact with the active substance, or materials that intentionally form part of the final cell and gene therapy product.

EXAMPLE 2 Cells that are either starting materials, intermediates or final form of a cellular therapeutic product, feeder cells, additives used post bioprocessing, scaffolds, non-biological consumables (e.g. beads, dishes, tissue culture flasks, bags, tubing, pipettes, needles), other plasticware that come into contact with the cell or tissue, apparatus, instruments.

A decision flowchart is given in Annex A.

NOTE International, regional or national 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 8601-1, *Date and time — Representations for information interchange — Part 1: Basic rules*

3 Terms and definitions

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

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

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

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

3.1
active substance
substance that has biological activity in a *cellular therapeutic product* (3.9) for its intended use

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3.2
AM
ancillary material
raw material
material that comes into contact with the *cellular therapeutic product* (3.9) during cell processing, but is not intended to be part of the final product formulation, excluding scaffold, non-biological consumable and plasticware

Note 1 to entry: An AM can be critical to the quality and safety of a cellular therapeutic product due to its contact during cell processing.

Note 2 to entry: A decision chart that indicates whether or not a material is in scope of this document is given in Annex A.

3.3
AM impurity
ancillary material impurity
any component present in an *AM* (3.2) that is not the desired entity

3.4
AM supplier
ancillary material supplier
entity who manufactures or supplies, or both, *AMs* (3.2) for the *AM user* (3.5)

3.5
AM user
ancillary material user
entity who makes use of *AMs* (3.2) and conducts cell-processing for a *cellular therapeutic product* (3.9)

3.6
animal-derived component free
ADCF
absence of animal or human origin material(s)

Note 1 to entry: The main purpose of defining the types of ADCF is to provide necessary information for a user's *risk assessment* (3.13) of *ancillary material* (3.2).

Note 2 to entry: In some cases, ADCF is described as "animal origin free (AOF)".

Note 3 to entry: In cases where there is absence of non-human animal components, the term "xeno-free" is commonly used.

3.7
biological material
any substance derived or part obtained from an organic entity such as a human, animal, plant, microorganism(s) or multicellular organism(s) that is(are) neither animal nor plant (e.g. brown seaweed, fungi)

[SOURCE: ISO 20387:2018, 3.7]

3.8
biosafety
practices and controls that reduce the risk of unintentional exposure or release of *biological materials* (3.7)

Note 1 to entry: This definition includes unintentional exposure, for example, to pathogens and toxins, or their accidental release as a biosafety risk.

[SOURCE: ISO 35001:2019, 3.22, modified — Note 1 to entry added.]

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3.9
cellular therapeutic product
product containing cells as the *active substance* (3.1) used for cell therapy or gene therapy

EXAMPLE Cell and gene therapy products, tissue engineered products, drug products.

Note 1 to entry: Products produced from cells for gene therapies are included in the definition of cellular therapeutic product, as cells are not necessarily the active substance for all gene therapies.

Note 2 to entry: Recombinant proteins are not included in this definition of cellular therapeutic product.

3.10
chain of custody
responsibility for, or control of, materials as they move through each step of a process

Note 1 to entry: Chain of custody is the unbroken path of an *ancillary material (AM)* (3.2) from the production of the AM to the end *AM user* (3.5). It covers controls, distribution and logistics to the AM user.

3.11
chemically defined component
substance whose chemical structure is identified/known at the molecular level

3.12
CoA
certificate of analysis
document attesting that an *ancillary material (AM)* (3.2) has undergone specified testing with specified results

Note 1 to entry: A CoA commonly contains the actual results obtained from the testing performed as a part of quality control of an individual batch of an AM.

Note 2 to entry: Often the CoA represents an agreement between the *AM supplier* (3.4) and the *AM user* (3.5).

3.13
risk assessment
overall process of risk identification, risk analysis and risk evaluation

[SOURCE: ISO Guide 73:2009, 3.4.1]

3.14
risk management
coordinated activities to direct and control an organization with regard to risk

[SOURCE: ISO Guide 73:2009, 2.1]

3.15
shelf life
period during which an *ancillary material* (3.2) is expected to comply with the *specifications* (3.16), if stored under defined conditions

3.16
specification
list of tests, references to analytical procedures and appropriate acceptance criteria that are expected to be met to demonstrate suitability for its intended use

3.17
stability
characteristic of a material, when stored under specified conditions, to maintain a value(s) for a stated property(ies) within specified limits, for a specified period of time

[SOURCE: ISO Guide 30:2015, 2.1.15, modified — “reference material” replaced by “material”. “a specified property value” replaced by “a value(s) for a stated property(ies)”. Note 1 to entry deleted.]

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3.18
traceability
ability to trace the history, application or location of an object

Note 1 to entry: When considering a product or a service, traceability can relate to:

— the origin of materials and parts;

— the processing history;

— the distribution and location of the product or service after delivery.

Note 2 to entry: In the field of metrology, the definition in ISO/IEC Guide 99 is the accepted definition.

[SOURCE: ISO 9000:2015, 3.6.13]

3.19
user requirement specification
URS
document that states *specifications* (3.16) for an *ancillary material (AM)* (3.2) based on the *AM user's* (3.5) requirements for the manufacture of a desired *cellular therapeutic product* (3.9) and gene therapy product

4 Abbreviated terms

ADCF	animal-derived component free
AM	ancillary material
AOF	animal origin free
BSE	bovine spongiform encephalopathy
CoA	certificate of analysis
CoC	certificate of compliance
CoI	certificate of irradiation
CoO	certificate of origin
EDQM CEP	European Directorate for the Quality of Medicines and Healthcare certificate of suitability
GMP	good manufacturing practice
ICH	International Council for Harmonization of Technical Requirements for Pharmaceuticals for Human Use
QC	quality control
QMS	quality management system
RP-HPLC	reverse phase high performance liquid chromatography
SDS	safety data sheet
SDS-PAGE	sodium dodecyl sulfate poly acrylamide gel electrophoresis
TSE	transmissible spongiform encephalopathy
USP	United States Pharmacopeia

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