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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

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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.

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.

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

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.]

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.]

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

5 Strategy

5.1 Key concepts on AM

AMs for each cellular therapeutic product are defined by the manufacturing process and the final form of the cellular therapeutic product (see Annex A).

AM users have the responsibility to establish and maintain a qualified status for AMs within their processes, including any oversight required for any AM. The level of such oversight should be proportionate to the risks posed by a specified AM, with reference to origin, manufacture or supply chain integrity. It is necessary to undertake a risk-based approach to AM selection and qualification.

AM can affect quality attributes of cell-based therapeutic products:

a) quality and consistency are important for AMs known to be critical for cell manufacturing;

b) safety and the chain of custody are critical for AMs of cellular therapeutic products.

Activities to assess and control the impact of AMs on the quality attributes of a cellular therapeutic product by the AM user are based on:

— information provided by the AM supplier;

— information obtained by either the AM user or the AM supplier, or both, through either characterization and testing of AMs or manufacturing of cellular therapeutic product;

— published standards or other peer-reviewed scientific methods (or equivalent).

5.2 AM-related responsibilities

A typical workflow to determine the supply of an AM from the AM supplier to the AM user is described in Annex B.

The AM user and the AM supplier can agree upon the specifications of AMs intended for cellular therapeutic products by using such workflow.

The general workflow is intended to hold the accountabilities of AM user(s) and AM supplier(s) for using an AM in the production of a cellular therapeutic product.

Table 1 describes recommendations for responsibilities and responsible parties leading these activities.

NOTE It is important that the relationship between the AM user and the AM supplier is cooperative and transparent. Many responsibilities are determined together as their combined efforts. These activities benefit from a supplier-user relationship. Without such relationship, an additional risk for the user, e.g. lack of technical support from the supplier, can happen. Although the responsibility for these activities is determined on a case-by-case basis.

Table 1 — Recommendations of responsibilities and responsible parties leading this activity

Activity	Responsible party	Reference for more information
Provide documented evidence that the AM is safe with respect to source-relevant animal diseases (e.g. BSE/TSE)	AM supplier	6.1 (Table 2), 6.2.1 (Table 3), 8.4 P3[a], Annex C, Annex E
Prepare and submit a master file for AM, if applicable	AM supplier	7.1.4 P3, Annex C
Assess the stability of the AM	AM supplier	7.2.2
Inform the AM user of any changes that will very likely or with certainty impact the AM (e.g. under a quality agreement)	AM supplier	8.1 P1, Clause 11

[a] "P" represents paragraph. For example, "8.4 P3" means "8.4 Paragraph 3.

Table 1 *(continued)*

Activity	Responsible party	Reference for more information
Conduct an assessment of the AM container closure system	AM supplier	8.3
Provide a CoA, CoO and SDS for the AM	AM supplier	10.2 P2 and P4, 10.3, 10.4.1
Conduct characterization testing of the AM and prepare a specifications document (e.g. identity, purity, functionality, viral contamination, animal origin)	AM supplier and AM user	6.1 (Table 2), 6.2.1 (Table 3), 6.2.2 P1, Clause 7, 8.4, 8.5, Clause 9, 10.3, Annex C, Annex D
Execute a quality and supply agreement	AM supplier and AM user	9.3 P6, 10.2 P2, 11.2, Annex C
Provide user requirement specifications to the AM supplier	AM user	Annex B
Conduct a risk-based AM supplier qualification process, generally including initial screening, onsite audit, formalized approval, continuous monitoring/oversight	AM user	5.3, Clause 6, 8.4 NOTE, 9.2, 9.3, Annex E
Determine if biocompatibility, biodistribution, cytotoxicity or adventitious agent testing is needed (or if testing results are available from the AM supplier, if applicable)	AM user	5.4, 6.1 (Table 2), 8.2 P2 and P3, 10.3, Annex D
Conduct a risk assessment for the use of an AM, based on information provided by the AM supplier, or in collaboration with the AM supplier, e.g. failure modes and effects analysis	AM user	5.4.2, 6.2.3, 8.4 P1, 9.3 P5, Annex E
Establish similar assurances and plans for alternative suppliers	AM user	5.4.2 P2, 6.1 (Table 2), 11.2
Qualify the performance of the AM in the intended application	AM user	6.1 (Table 2), 6.2.1 (Table 3), Clause 9, 10.2, 10.3, Annex D
Confirm the CoA test result(s) critical to the cell product (e.g. functional assay)	AM user	6.1 (Table 2), 6.2.2 P7, 9.3 P6, 10.3, Annex C, Annex D
Assess the effect of lot-to-lot variation of the AM on the final cell product	AM user	7.1.4, Clause 11
Establish and implement a qualification plan for the use of an AM	AM user	9.3 P6

[a] "P" represents paragraph. For example, "8.4 P3" means "8.4 Paragraph 3.

5.3 Qualification considerations of AM

The qualification of an AM includes:

a) the physiochemical characteristics of AM, including characteristics and material attributes (e.g. identity, purity, stability, functionality and performance);

b) the documentation for all AMs, including, its composition, quality or grade, the source of each component, the concentration and the purity;

NOTE 1 The composition and concentration of each component can be considered proprietary. Reference to a drug master file (DMF) is desirable.

NOTE 2 See Annex E for examples of quality declarations for manufactured biological materials used in the manufacture of a cellular therapeutic product.

c) the demonstration of lot-to-lot consistency of AMs for the intended cell manufacturing step, specifically regarding the identity and performance of the AM;

d) an appropriate level of biosafety, including avoidance of introduction of unwanted agents that can cause harm to the therapeutic, and directly or indirectly to patients;

e) the risk of introduction of pathogenic or toxic contaminations from biological and non-biological agents; relevant index, such as limit of detection (LOD) or limit of tolerance (LOT) to be determined and validated when feasible;

f) the performance of AMs in delivering the intended effects with consistency and robustness:

— an AM shall perform its intended function within a model cell manufacturing process selected by the AM supplier appropriate for the AM's intended use;

g) accompanying documentation:

— AM supplier shall provide sufficient documentation that communicates information of AM for the purpose of AM users ensuring the quality of their cellular therapeutic products;

NOTE 3 There are cases where documentation is limited due to protecting intellectual property.

h) quality declarations and mitigation of risk in use of AMs for manufactured biological materials used in the manufacture of cells for therapeutic use;

i) the characterization of biological materials;

j) managing changes to AMs.

The AM supplier is responsible for the qualification with regard to general performance, but the AM user is responsible for the qualification for the intended use.

The AM user is responsible for the qualification of all AMs used in the manufacturing of their cellular therapeutic products. Identification (ID) or purity tests should be provided by AM suppliers, if available. If sub-suppliers are used, AM suppliers should have a plan, if sub-suppliers fail qualification.

If applicable, the AM user should assess the presence of residual AM in the final cell product.

The AM user should audit the AM supplier to ensure qualification of material.

5.4 Animal-derived components of AM

5.4.1 General

Materials of biological origin, particularly of human or animal origin, can present particular risks, including transmission of adventitious agents or introduction of biological impurities. This does not necessarily limit the use of biologically derived components for manufacturing AMs or materials used further downstream in the manufacturing of cellular therapeutic products. The use of a risk-based approach for the selection and qualification of AMs is therefore recommended.

5.4.2 Key considerations in the use of animal-derived components

A risk assessment approach shall be used in reference to the safety of animal-derived components.

The following are the key questions that shall be addressed, particularly for human or animal origin:

a) Is the component terminally sterilized?

b) What is the origin of the biological material(s)?

c) Is (are) the biological material(s) traceable to its(their) source?

d) Which risk mitigation measures have been applied to the biological material(s), besides audit of AM supplier(s)?

EXAMPLE 1 Sourcing from a TSE-low risk origin, virus removal or inactivation steps, use of pharmaceutical grade material, virus removal from AM, its component or subcomponent, or adventitious agent testing.