TECHNICAL SPECIFICATION

ISO/TS 20399-1

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

Part 1: General requirements

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

Partie 1: Exigences générales

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Contents

Page

Foreword

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The procedures used to develop this document and those intended for its further maintenance are described in the ISO/IEC Directives, Part 1. In particular, the different approval criteria needed for the different types of ISO documents should be noted. This document was drafted in accordance with the editorial rules of the ISO/IEC Directives, Part 2 (see www.iso.org/directives).

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

A list of all parts in the ISO/TS 20399 series can be found on the ISO website.

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) are materials that come into contact with the cellular therapeutic product during the manufacturing process, but are not intended to be in the final product.

AMs include culture media and growth factors, among other biological and non-biological components. They can be a complex mixture of many components, and a variation in their lot-to-lot composition can hamper the ability to produce consistent cellular therapeutic products with specified quality attributes.

As such, AMs can have implications with regard to the safety and effectiveness of a cellular therapeutic product. Appropriate control of ancillary materials is determined by a risk-based approach.

This document specifies definitions and general requirements for AMs and contributes to their control by suppliers and users of such materials.

The ISO/TS 20399 series provides general requirements and guidance regarding ancillary materials to maintain a high level of lot-to-lot consistency, as well as the accompanying documentation, so that consistent ancillary materials products and documentation provided by the suppliers can help AM users.

It is intended to ensure the quality and consistency of AMs used in the manufacturing of cellular therapeutic products. Good manufacturing practice (GMP) is taken into account, when necessary.

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

Part 1: General requirements

1 Scope

This document specifies definitions and general requirements for ancillary materials (AMs) used in cell processing of cellular therapeutic products.

This document is applicable to cellular therapeutic products, including those gene therapy products whereby cells form part of the final product. It does not apply to products without cells.

This document does not cover the selection, assessment or control of starting materials and excipients.

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

2 Normative references

There are no normative references in this document.

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
ancillary material
AM
material that comes into contact with the cell or tissue product during cell-processing, but is not intended to be part of the final product formulation

Note 1 to entry: AMs exclude non-biological consumables (e.g. tissue culture flasks, bags, tubing, pipettes, needles) and other plastic ware that comes into contact with the cell or tissue, but include consumables which can have a biological component (e.g. coated dishes or beads).

Note 2 to entry: AMs exclude cells (e.g. feeder cells).

Note 3 to entry: In some cases AM is described as raw material.

3.2
AM user
entity who makes use of *AM* (3.1) and conducts cell-processing for cellular therapeutic product

3.3
AM supplier
entity who manufactures and/or supplies the *AM* (3.1) for *AM user* (3.2)

3.4
animal-derived component free
ADCF
absence of animal or human origin material(s)

Note 1 to entry: The main purpose of defining ADCF is to provide necessary information for a user's risk assessment of ancillary material.

Note 2 to entry: There are levels of ADCF, which are listed in 5.2.2.

Note 3 to entry: In some cases, animal-derived component free (ADCF) is described as animal origin free.

Note 4 to entry: In cases where there is absence of non-human animal components, the term xeno-free is commonly used.

3.5
cellular therapeutic product
product containing cells as the active substance

EXAMPLE Cell therapy medicinal product, tissue engineered product.

3.6
chain of custody
responsibility for or control of materials as they move through each step of a process

Note 1 to entry: For the purpose of this document, "chain of custody" is the unbroken path of an AM product from the production of AM to the end customer. It covers controls, distribution and logistics to the end-user.

3.7
excipient
material that is present in the *cellular therapeutic product* (3.5) administered to a patient(s), other than the active substance(s)

EXAMPLE Cryopreservation components.

Note 1 to entry: For the purpose of this document, "active substance" corresponds to cellular therapeutic product.

3.8
maximum shelf life
period during which an *AM* (3.1) is expected to comply with the specifications, if stored under defined conditions

3.9
specification
list of tests, references to analytical procedures, and appropriate acceptance criteria that would be expected to be met to demonstrate suitability for its intended use definition

3.10
stability
characteristic of a material, when stored under specified conditions, to maintain a value(s) for stated property(ies) within specified limits for a specified period of time

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

3.11
starting material
any substance of cellular origin that constitutes the *cellular therapeutic product* (3.5)

4 Abbreviated terms

ADCF	animal-derived component free
AM	ancillary material
BSE	bovine spongiform encephalopathy
CoA	certificate of analysis
CoO	certificate of origin
SDS	safety data sheet
GHS	globally harmonized system
TSE	transmissible spongiform encephalopathy

5 Considerations

5.1 General considerations

Ancillary materials described in this document are materials introduced during manufacturing of cellular therapeutic products generally used to control or enhance cell expansion. These materials are referred to as AM.

AM can affect quality attributes of cellular therapeutic products.

— Quality and consistency are critical for AMs known to affect cell processing.

— Safety and the chain of custody are critical for AMs, particularly animal-derived AMs, which potentially remain as components of the cellular therapeutic product.

5.2 Animal-derived components of AM

5.2.1 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 of essential materials is therefore essential.

5.2.2 Levels of ADCF

The main purpose of defining ADCF is to provide necessary information for a user's risk assessment of AM.

An AM is designated ADCF level 1 or 2, when one of the following definitions is fulfilled.

a) Level 1 (product level): the AM does not contain any materials from animal or human source as its ingredients.

NOTE Level 1 is intended to address the level of risk to be considered. It indicates that materials from an animal or human source are not an intended part of the product, but it does not technically ensure that materials from an animal or human source are not carried over into the AM during production.

b) Level 2 (production level): in addition to ADCF level 1, AM is produced without the use of any materials from an animal or human source. This includes excipients, equipment or containers that come into contact with the AM during production.

5.2.3 Key considerations in the use of animal-derived components

Use of animal-derived components in the production of AM should be addressed by the AM user through the analysis and mitigation of risk of the use of such AMs in an AM user's product manufacturing.

The following are the key questions to address the ADCF for AM:

a) Is the AM product free of materials of biological origin, particularly of human or animal origin?

EXAMPLE ADCF level 1, product level

b) Is the AM produced without the use of any materials from animal or human source? And does the AM not come into contact with equipment or containers of human or animal origin during production?

EXAMPLE ADCF level 2, production level

c) What is the origin of the biological materials of human or animal origin?

d) Are the biological materials of human or animal origin traceable to their source?

e) Which risk mitigation measures have been applied to the biological materials of human or animal origin, besides audit of suppliers?

EXAMPLE Sourcing from a TSE-free origin, virus removal or inactivation steps, use of pharmaceutical grade material etc.

f) Are there remaining potential risk factors of using biological materials?

EXAMPLE Insufficiently validated virus removal or inactivation steps, no adequate pest control etc.

It is important to ensure that the AM supplier can consistently and reliably supply such material.

5.2.4 Viral inactivation

When animal- and/or human-derived biological materials are used in the production or formulation of AM, and depending on the risk assessment of the AM's exposure to a cellular therapeutic product, step(s) for removal or inactivation of viruses should be included. These processes require validation studies and documentation so that they are available to the AM user.

5.3 Mutual responsibilities for AMs

Table 1 describes recommendations for responsibilities and responsible parties leading this activity.

Although the responsibility for these activities is determined on a case-by-case basis, Table 1 provides information regarding the major player for each of these activities.

Table 1 — Recommendations for responsibilities and responsible parties leading the activity

Activity	Responsible party	Reference for more information
Qualify performance of AM in the intended application	AM user	ISO/TS 20399-3:2018, Clause 6
Provide CoA, CoO, and SDS for AM	AM supplier	ISO/TS 20399-2:2018, 9.1, 9.2, 9.3
Ensure that the AM is safe with respect to source-relevant animal diseases (e.g. BSE/TSE)	AM supplier	ISO/TS 20399-2:2018, 7.2 ISO/TS 20399-3:2018, 6.1

Table 1 *(continued)*

Activity	Responsible party	Reference for more information
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, for example, failure modes and effects analysis	AM user	ISO/TS 20399-3:2018, 6.2.3
Establish and implement a qualification plan for any AM	AM user	—
Confirm CoA test result(s) critical to the cell product (e.g. functional assay)	AM user	ISO/TS 20399-3:2018, 6.2.1
Conduct characterization testing of the AM and set specifications (e.g. identity, purity, functionality, viral contamination, animal origin, etc.)	AM supplier	ISO/TS 20399-2:2018, Clause 8
Assess the effect of lot-to-lot variation of the AM on the final cell product	AM user	ISO/TS 20399-3:2018, Clause 7
Determine, if biocompatibility, biodistribution, cytotoxicity or adventitious agent testing is needed (or if testing results are available from the supplier, if applicable)	AM user	ISO/TS 20399-3:2018, Clause 7
Assess the presence of residual AM in the final cell product (the AM supplier can provide specific assays, if available)	AM user	ISO/TS 20399-3:2018, Clause 7
Assess the stability of the AM	AM supplier	ISO/TS 20399-2:2018, 6.2
Conduct risk-based supplier qualification process, generally including initial screening, optional onsite audit, formalized approval, continuous monitoring/oversight	AM user	ISO/TS 20399-3:2018, 6.2.2
Execute quality and supply agreement	AM user and AM supplier	ISO/TS 20399-2:2018, 7.4, 9.3 ISO/TS 20399-3:2018, 8.2
Implement higher manufacturing standards, custom formulation or replacement of substandard components	AM user and AM supplier	ISO/TS 20399-2:2018, 7.1 ISO/TS 20399-3:2018, 8.2
Inform the user of any changes that very likely or with certainty impact the AM product as specified (e.g. under a quality agreement)	AM supplier	ISO/TS 20399-2:2018, 7.1
Prepare and submit a master file for AM, if applicable	AM supplier	ISO/TS 20399-2:2018, Clause 5

SDS should be produced for all substances and mixtures, e.g. following the criteria for physical, health or environmental hazards described in Reference [12], and for all mixtures which contain ingredients that meet the criteria for carcinogenic, toxic to reproduction or target organ toxicity in concentrations exceeding relevant documented cut-off limits.

Information should include any prohibitions or restrictions that may apply depending on the country or region into which the AM is being supplied.

5.4 Example workflow

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

The AM user and AM supplier agree upon the specifications of AMs intended for cellular therapeutic product.

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

The general requirements of AMs are described in this document. Additional recommendations for suppliers and users are described in ISO/TS 20399-2 and ISO/TS 20399-3.

6 Ancillary material requirements

6.1 Quality management system

AM shall be produced under a quality management system (QMS).

AM supplier shall establish, document, implement and maintain a QMS and continually improve its effectiveness on its production.

NOTE ISO 9001 is an example of a relevant quality management system.

Typical elements of a QMS are:

— general principles;

— manufacturing facility, environment;

— manufacturing supply ability, delivery date, supply system;

— manufacturing record-keeping systems;

— maintenance system based on the Plan Do Check Act (PDCA) cycle;

— education and training records;

— safety management;

— keeping traceability records of materials used to produce AM.

6.2 Information on ancillary material products and materials used to produce ancillary materials

AM shall be produced under an established and maintained system ensuring that the AM and its ingredients can be traced through their production process(es), including sourcing, manufacturing, packaging, and storage.

AM shall be supplied together with all necessary information specifying the product.

Examples of such information are described in Annex B. Necessary information can differ by the nature of the AM and by the content of the agreement between the AM supplier and the AM user.

Annex A
(informative)

Example of workflow from AM supplier to AM user

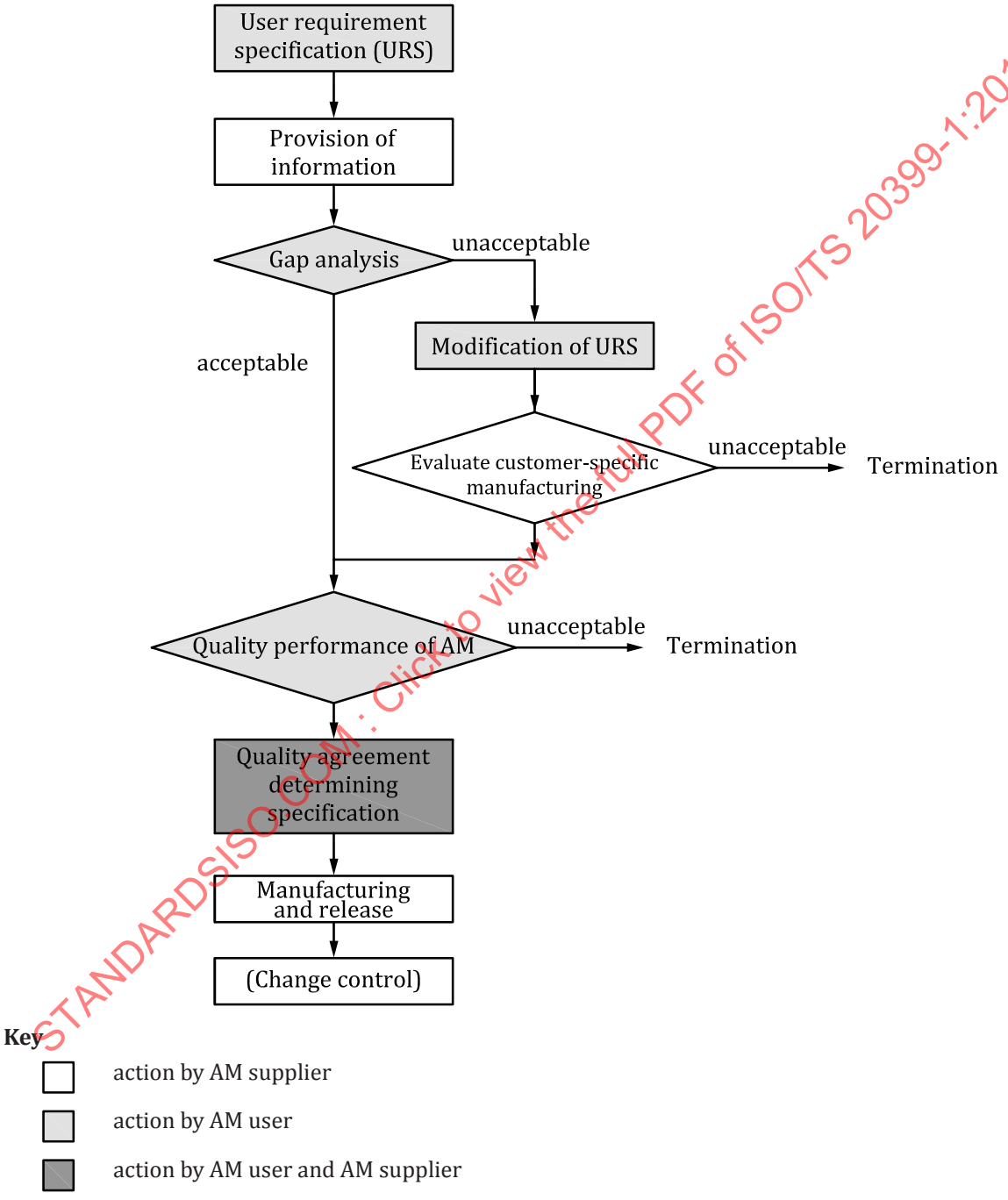

Figure A.1 — Example of workflow from AM supplier to AM user

Annex B
(informative)

Information on AM products and materials used to produce AM

This information can be provided through non-confidential documents or through confidential documents. The provision of confidential information can be subject to a mutual confidential disclosure agreement.

a) Information representing the AM to be supplied, included in specification document and/or supply agreement and/or drug master file:

   1) product profile:

      — product name (name of AM);

      — catalogue number;

      — storage condition and maximum shelf life;

      — manufacturer;

      — import source name and sales agency name;

   2) quality information:

      — specification and test methods;

   3) components:

      — component materials;

      — concentration of components;

   4) information on materials used to produce AM:

      — existence or non-existence of human and animal-derived components (see 5.2);

      — presence of hazardous material, if applicable;

      — heavy metal component (see for example Reference [7] class 1, 2a, 2b, 3);

      — country of origin.

   5) information necessary in case of biological-origin materials used to produce AM:

      — pathogen safety, including viruses and TSE/BSE;

      EXAMPLES Cell bank characterization tests, virus depletion or inactivation tests, viral inactivation validation, if applicable, in serums or plasma human or animal-derived products.

      — microbial contamination test results;

   6) quality agreement;

   7) other information:

      — development history.