TECHNICAL SPECIFICATION

ISO/TS 20399-2

First edition
2018-11

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

Part 2: Best practice guidance for ancillary material suppliers

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

Partie 2: Lignes directrices de bonne pratique pour les fournisseurs de matériaux auxiliaires

Reference number
ISO/TS 20399-2:2018(E)

ISO copyright office
CP 401 • Ch. de Blandonnet 8
CH-1214 Vernier, Geneva
Phone: +41 22 749 01 11
Fax: +41 22 749 09 47
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*.

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 (AM) 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, growth factors, and other biological and non-biological components. They can be a complex mixture of multiple components and variation in their lot-to-lot compositions can hamper the ability to produce a consistent product based on therapeutic cells with specified quality attributes.

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

This document provides guidelines to AM suppliers on best practice to ensure consistent manufacture of AM products. It also describes the information that should be obtained and provided to the AM user to demonstrate lot-to-lot consistency of the AM product with respect to AM characteristics and quality attributes, biosafety, and performance.

A number of standards and guidance documents define the proper processing of cell based therapeutic products to ensure safety and efficacy. However, these standards only indirectly relate to the suppliers of AM products. This document clarifies the expectations for AM suppliers which are distinct from the standards governing cell processing requirements.

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 (AM) products and documentation provided by the suppliers can help AM users.

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

Part 2: Best practice guidance for ancillary material suppliers

1 Scope

This document provides guidance for ancillary material (AM) suppliers to maintain a high level of lot-to-lot consistency in the aspects of identity, purity, stability, biosafety, performance, as well as the accompanying documentation.

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

The AMs described in this document include those of biological origin [e.g. sera, media (including media additives), growth factors, and monoclonal antibodies] and chemical origin. This document does not address dimethyl sulfoxide (DMSO) for cryopreservation, beads, scaffolds, feeder cells, apparatus and instruments, or additives used post bioprocessing.

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

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/TS 20399-1, *Biotechnology — Ancillary materials present during the production of cellular therapeutic products — Part 1: General requirements*

3 Terms and definitions

For the purposes of this document, the terms and definitions given in ISO/TS 20399-1 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/

4 Abbreviated terms

ADCF	animal-derived component free
AM	ancillary material
CoA	certificate of analysis

CoC	certificate of compliance
CoI	certificate of irradiation
CoO	certificate of origin
DNA	deoxyribonucleic acid
EP	European Pharmacopoeia (Ph. Eur.)
JP	Japanese Pharmacopoeia
RP-HPLC	reverse phase high performance liquid chromatography
SDS	safety data sheet
SDS-PAGE	sodium dodecyl sulfate poly acrylamide gel electrophoresis
USP	United States Pharmacopeia

5 General considerations

This document provides guidance for AM suppliers to maintain a high level lot-to-lot consistency, as well as for the accompanying documentation for AM users.

Aspects covered include the following.

a) Information of AM products, including characteristics and quality attributes (i.e. identity, purity, stability, functionality and performance).

b) Documentation for all AM products including composition, the source of each component, the concentration, and purity.

c) Demonstration of lot-to-lot consistency of AM products for the intended cell culture process, specifically regarding the identity and performance of the AM product.

d) Appropriate level of biosafety, including avoidance of introduction of unwanted agents that may cause harm to the therapeutic products, and directly or indirectly to patients.

e) 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) Performance of AM products in delivering the intended effects with consistency and robustness; an AM product should perform its intended function within a model cell manufacturing process selected by the AM supplier appropriate for AM's intended use.

g) Accompanying documentation from the AM supplier to provide sufficient information on AM products for the purpose of AM users ensuring the quality of their cellular therapeutic products.

NOTE Though not provided to AM users, AM suppliers can choose to prepare a drug master file (DMF) for an AM product to support AM user's regulatory submission where DMF is accepted. Where DMF is not accepted, a regulatory support file (RSF) can be provided to AM users.

6 AM characteristics and quality attributes

6.1 AM components, identity and purity

6.1.1 General

The AM supplier should make every effort to demonstrate the lot-to-lot consistency with respect to the composition of AM products. If a monograph exists for the AM product (e.g. USP, EP, or JP monograph), it is expected to comply with those tests in the country where the AM product will be used. Otherwise the minimum tests listed below apply, as applicable.

6.1.2 Identity and quantity of component(s)

For AM products that consist of chemically defined substance(s), the identity of that substance should be documented. For products that are mixtures of several components, the identity of all known molecular components and their relative concentrations should be documented. Information regarding the variation of lots and the general acceptable range should be recorded.

If the identity of all substances cannot be defined and/or cannot be disclosed, the quantity of active components can be documented by its activity.

The inclusion of any proprietary component(s) individually or collectively and its relative concentrations should be noted; any information that can be shared regarding the type of molecular composition or purpose should be provided.

For animal-derived materials, a certificate of origin (CoO) should document, for each batch, the country of origin, a health statement of the animal, and evidence documenting absence of pathogens. When feasible, the age of the animals at the time of collection should be documented.

For human derived materials, viral panel testing is required. Requirements in the country of use shall be met.

6.1.3 Purity/impurity

For AM products that consist of one isolated and/or purified molecular substance, the purity of that substance within the product should be defined, measured and provided. For products that consist of multiple components, the purity of active ingredients should be defined, measured and documented.

If the purity varies from lot to lot within an acceptable range, the acceptable range should be provided as well as information on the distribution of lots within the acceptable range if possible.

Impurities need to be identified and documented. Tests to measure impurities and acceptable limits need to be established.

NOTE For recombinant proteins and vector based AMs, the presence of host protein or DNA in the form of a contaminant can pose an immunogenic risk or affect the function of the material.

If available, the AM supplier should report suitable tests that AM users can qualify for the purpose of detecting residuals of the AM product.

6.1.4 Lot-to-lot consistency for AMs containing proprietary components

Efforts should be made to demonstrate the lot-to-lot consistency without naming specific molecular components or concentrations if the molecular component information cannot be disclosed. For example, a statement should be provided for each of the unnamed molecular components with respect to its lot-to-lot variation by a specific percentage of the total mixture or within a specific percentage of error around a pre-determined target percentage.

The inclusion of evidence for performance consistency should be considered for AMs containing unknown/undisclosed components with unknown/undisclosed concentrations.

6.2 AM storage and stability

6.2.1 General

AM suppliers should provide sufficient information on the proper storage conditions for the AMs as well as the corresponding stability information associated with those storage conditions.

For AMs that are reconstituted or diluted prior to use (e.g. growth factors and cytokines), additional information related to the stability for a recommended concentration or concentration range as well as recommendations for storage conditions should be provided when available.

It is recommended to report any addition of stabilizers as well as formulation composition.

6.2.2 Storage conditions

AM suppliers should provide the recommendations for storage conditions. Example conditions are:

— temperature;

— exposure to light;

— humidity.

If the AM product is delivered in a different form/state than the form/state that it is used (e.g. reconstituted, thawed, etc.), the appropriate storage conditions for alternative forms/states may be recommended, together with stability data, if available. The procedure for reconstitution should be provided, and changes associated with reconstitution in terms of stability and other properties should be reported.

If the AM product is intended to be kept frozen at any point during shipping and storage, the AM supplier should provide the following information:

— whether freezing-and-thawing affects the AM product stability and activity;

— a maximum recommended number of freeze–thaw cycles.

6.2.3 Stability and expiration dating

Stability testing should be conducted to determine the maximum shelf life for all AM product forms and recommended storage conditions.

The following information should be provided:

— manufacturing date;

— expiration date, or maximum shelf life;

— stability at a single temperature or several individual temperatures;

— stability for each available product form.

Stability information and expiration dates should be determined by measurement data generated by the AM supplier and should be based on the AM product's ability to maintain a critical level of activity or performance as well as integrity, i.e. its degradation and impurity profile.

An AM product's activity should remain consistent throughout the recommended storage times under appropriate storage conditions.

If there is an acceptable range of performance or integrity for an AM product, maximum storage times should be determined such that the product remains within the acceptable ranges throughout the storage period.

7 AM manufacturing and biosafety

7.1 Quality management system

Manufacturers of AM products should implement a quality management system (QMS) and undergo regular audits (see ISO/TS 20399-1). QMS certification by an independent standard or government agency is also recommended.

AM suppliers should implement quality risk management process under QMS.

AM suppliers should implement a process that can be audited by AM users, and includes plans for implementing effective corrective actions and timely remediation for identified critical issues.

In the event of a change being made to AM products, such as changes in AM manufacturing process, composition, container/closer, the AM supplier should notify AM users with sufficient lead time before changes being effected.

AM suppliers should have a robust supply chain and the ability to meet the demands of the AM users.

7.2 Manufacturing process

Known aspects of the manufacturing process that impact the quality and consistency of AM products should be controlled and documented.

Known aspects of the manufacturing process that may change the risks of adventitious agents or endotoxin contamination should be controlled and documented.

Known aspects of the manufacturing process that involves the use of animal- and human-derived components should be communicated. Steps for reducing the risk of adventitious agents should be provided in addition to documentation of the country of origin.

The use of antibiotics should be generally minimized. If used, the identity and quantity of antibiotics in AM products should be provided.

NOTE The use of beta lactam antibiotics can pose an immunogenic risk.

Manufacturing processes that lead to product degradation should be documented. These include degraded products from processing and enzymatic cleavage of biologic products.

Use of manufacturing process to remove particulates in the components of AM product, excipients or consumables should be noted. When available, measurement and quantity of particulates in the AM product should be provided.

Manufacturing processes that involve the use of chemical or physical treatments to reduce or eliminate contamination should be noted and demonstrated to be effective.

Manufacturing processes that involve the use of irradiation should be noted. The range of irradiation doses should be validated.

Contamination may be controlled through the manufacturing process, environmental controls, segregation, engineering controls, use of dedicated equipment and cleaning process. Contamination by endotoxin should be minimized.

7.3 Container and closure systems

The container closure integrity should be determined to ensure that the materials are not contaminated or tampered with. The use of specific closure systems for extreme temperatures and during accidents due to transportation should be validated.

When possible, single use containers are recommended. Leachable and extractable potentials should be provided for the container of choice to customers.

7.4 Animal- and human-derived materials

For AM products from an animal or human source, a chain of custody should be established and strictly followed. Documentation should be available to demonstrate the traceability and chain of custody. All component materials should be screened for relevant diseases according to the source of the materials. CoO that includes registration of establishment where materials were collected as well as any relevant testing and documented results should be kept in AM suppliers' document control and made available, as necessary.

For AM products consisted of recombinant protein(s), if animal- and/or human-derived materials are used in the manufacturing and/or formulation of the AM product, the animal- and/or human-derived materials should be identified and documented.

Human-derived AM products should be obtained from licensed facilities. Materials need to be tested and documented by the collection sites.

Animal and human-derived materials may have specific requirements of storage conditions. The freeze–thaw cycle may lead to precipitation, which may adversely affect AM product function. Results from temperature studies related to shipping as well as storage in extreme conditions should be provided when appropriate and kept as a part of quality agreements.

The definition of animal-derived component free (ADCF) as given in ISO/TS 20399-1 should be applied to document the use of animal or human origin free materials in the manufacture of AM products.

7.5 Safety to cells and humans

All AM products should conform to the AM supplier's specifications for contamination, including microbial and viral contamination, non-biological contamination and cross-contamination from other products.

Additional testing to demonstrate safety to cells and potentially humans should be performed to evaluate the effect of the AM product on cell characteristics.

Depending on the risks of AM products such tests include but products may not be limited to the following:

— cell proliferation;

— genotoxicity;

— cytotoxicity;

— cell plasticity;

— cell migration;

— cell morphology;

— gene expression;

— chromosomal stability;

— any other appropriate tests.

8 AM performance

8.1 General

The AM supplier should provide results for one or more performance tests if a claim is to be made regarding product consistency, particularly performance consistency.

In addition, in the case where the exact component identity and concentration is not known or cannot be disclosed, performance testing may be used as an alternative method to demonstrate the product consistency.

NOTE It is also important to include performance testing data when small variations across components have the potential to cause measurable changes to the AM product interaction with cells (e.g. in the case of complex cell culture media or serum).

8.2 Performance assay

8.2.1 General

Performance assays should be designed and validated to demonstrate the effect of the AM product on cells and/or demonstrate lot-to-lot consistency. Assays may include those that measure normal cell functions (i.e. cell survival and/or proliferation) or those that measure more specific cell identity and function (i.e. cell specific gene expressions or a performance assay of a cellular function).

Performance assay selection should be based on the intended use of the AM product (see 8.2.3), and adequate details of the assay should be provided to AM users to assess whether the performance data generated from the assay is applicable to their use of the AM product.

8.2.2 AMs that support cell survival and function

Based on the intended use, assessment of basic cell functions may include:

— cell doubling time;

— cell survival;

— expression and level of housekeeping genes;

— other methods as relevant to the product.

8.2.3 AMs that are intended to promote specific cell functions

Performance assay specific to the intended use of the AM product should be selected. Selected assays may include:

— functional assays, such as cell proliferation, cell differentiation, or cell proliferation inhibition assays;

— gene expression assays;

— cell morphology assays;

— cell migration assays;

— other assays/methods as relevant to the AM product and its intended use.

NOTE AMs can have multiple uses; AMs can also elicit different effects depending on the cell types, and/or therapeutic indications, it is reasonable to use one basic cell function assay, with the understanding that it is meant to inform AM product selection. AM products such as cytokines, and small molecule inhibitors can fall into this category depending on their intended use.

8.3 Cells used for performance assays

Appropriate cells should be used for the selected performance assay and for the intended use of the AM product. When available, well characterized cell lines should be used, and the passage number, culture condition, and other pertinent information should be provided.

For assays that test specific cell characteristics, an appropriate cell line should be selected that considers the likely application and assay design.

For AMs that are intended for a specific cell type, such as T lymphocytes, that cell type with samples collected from different donors should be employed for the performance assays. The selected performance assays should be appropriated to support the AM's intended use.

For assays that test specific cell characteristics or functions, the selected cell type should have the capacity to exhibit those specific characteristics and/or perform the relevant functions.

8.4 Performance assay results

Results from performance assays should be documented. The results, when available, should be provided in a manner that enables appropriate selection of AM products, and/or fit-for-purpose.

The result demonstrating AM product's lot-to-lot consistency may be provided upon request.

The performance assay results may include:

— quantified result;

— the distribution of lots within an acceptable range;

— the uncertainty in the assay result, when biological assays are used.

The AM supplier should define the amount of data to be considered sufficient. Balancing the amount of information, as well as deciding on the specificity of the performance assay, should be done with a focus on providing a sufficient level of information to demonstrate the lot-to-lot consistency for its intended use.

9 AM documentation

9.1 General

As AMs are intended for manufacturing cellular therapeutic products under this document, AM suppliers should label their products accordingly, i.e. "for further manufacturing use".

9.2 Certificate of analysis (CoA)

All AM products should be accompanied by a CoA containing quantity, lot number, lot specific test results and expiration date, with testing that covers (sometimes more than one for each category) the following.

a) Identity

— Methods for identification should be as specific as possible (e.g. N-terminal protein sequence identification).

b) Quantity

— Methods for quantification should be as specific as possible (e.g. specific absorption of proteins).

— Specific density of some liquids to allow measurement of quantity by weighing in addition to the volume.

c) Purity and impurities

— Tests that measure the amount of the required material and potential contaminants (e.g. SDS-PAGE, RP-HPLC).

d) Safety

— The testing for safety should use compendial tests and/or validated tests with sufficient quantities to meet the applicable requirements. The tests may include sterility, endotoxin, mycoplasma, and adventitious viruses depending on the materials and the potential safety.

