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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

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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).

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.