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

Part 3: Best practice guidance for ancillary material users

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

Partie 3: Lignes directrices de bonne pratique pour les utilisateurs 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 (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 variation in their lot-to-lot composition can hamper the ability to produce a consistent cellular therapeutic product 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 material is determined by a risk-based approach.

This document specifies guidelines to AM users on best practice considerations for use of AMs, particularly those of biological origin, in the manufacture of cellular therapeutic product 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 material (AM) products and documentation provided by the AM suppliers can help AM users.

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

Part 3: Best practice guidance for ancillary material users

1 Scope

This document provides guidance for ancillary material (AM) users. It 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 focuses primarily on ancillary materials (AMs) of biological (human and animal) origin and their potential impurities and contaminants.

NOTE 1 The decision chart in Figure 1 illustrates the rationale underlying the scope of this document.

However, diverse biological sources, including plants, insects and marine organisms, can also be used in the development of a cellular therapeutic product. Therefore the fundamental principles of risk management also apply for these sources of AMs.

This document does not cover the selection, assessment or control of starting materials and excipients. However, it is anticipated that these are still covered by general risk management procedures.

This document is applicable for users at all stages of clinical development and supply; however maximum benefits can be gained by the implementation of the recommendations in the early stages of development.

NOTE 2 International, regional or national regulations or requirements can also apply to specific topics covered in this document.

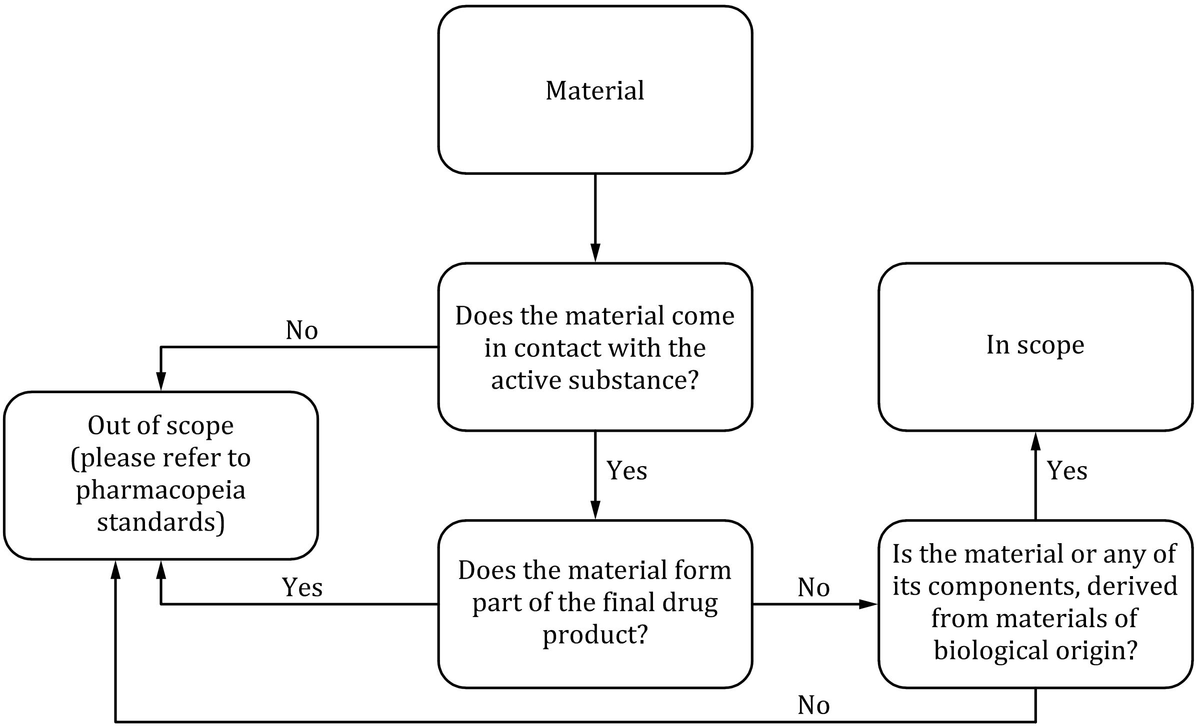

Figure 1 — Decision chart

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

AM	ancillary material
ADCF	animal-derived component free
AOF	animal origin free
CAPA	corrective and preventative action
CEP	certificate of suitability

CoA	certificate of analysis
CoO	certificate of origin
EDQM	European Directorate for the Quality of Medicines and Healthcare
(c)GMP	(current) good manufacturing practice
ICH	International Council for Harmonization of Technical Requirements for Pharmaceuticals for Human Use
IVUO	*in vitro* use only
QC	quality control
QMS	quality assurance/management system
RUO	research use only
TSE	transmissible spongiform encephalopathy

5 Quality declarations for manufactured biological materials used in the manufacture of a cellular therapeutic product

A number of different quality declarations can be applied by suppliers to the biological AMs they market.

Table 1 provides a list of suppliers' quality declarations that confirm that the AM has been approved by a regulatory body and/or complies with a recognized quality grade. However, compliance with any grade/standard does not necessarily mean that the AM is suitable for a specific process, even if it is of demonstrable quality. The user should ensure that the product has the requisite properties, e.g. functionality and safety profile.

Table 1 — Examples of recognized quality declarations used by suppliers of materials in the manufacture of cellular therapeutic product

Quality declaration	Technical and regulatory description
Licensed medicinal product/ drug	By definition, a licensed medicinal product/drug has demonstrated quality, safety and efficacy for its intended use and can therefore be viewed as the highest standard in terms of quality.
Pharmacopoeia grade	If an AM used in the manufacture of a cellular therapeutic product has a monograph in an appropriate pharmacopoeia, the user can reference it as a way of demonstrating conformance with a level of quality deemed sufficient for use in the manufacture of cellular therapeutic product. Chapters may contain more general measures for groups of AMs but they are not measures that relate to any specific AM.
510(k) (pre-market notification)	Cell culture media can fulfil the criteria for being Class II medical devices (medium risk) and therefore can be approved under the 510(k) pre-market notification pathway. Under the provision, users can gain approval for a device by showing substantial equivalence with a Class II device that has already been approved. The 510(k) notification demonstrates that the product has been manufactured under a QMS.
EDQM Certification of Suitability	In order for a supplier of a biological AM (in this context) to be granted a CEP, the EDQM appoint a panel of assessors to review a detailed dossier that contains a description of the manufacturing process and the tests performed on the AMs used along with the final product. The applicant also needs to agree to comply with the relevant GMP and to accept a site inspection at any time at the request of the EDQM. The CEP is recognized in all EU member states and some additional non-EU countries, such as Canada, New Zealand and Australia.