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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

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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).

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.

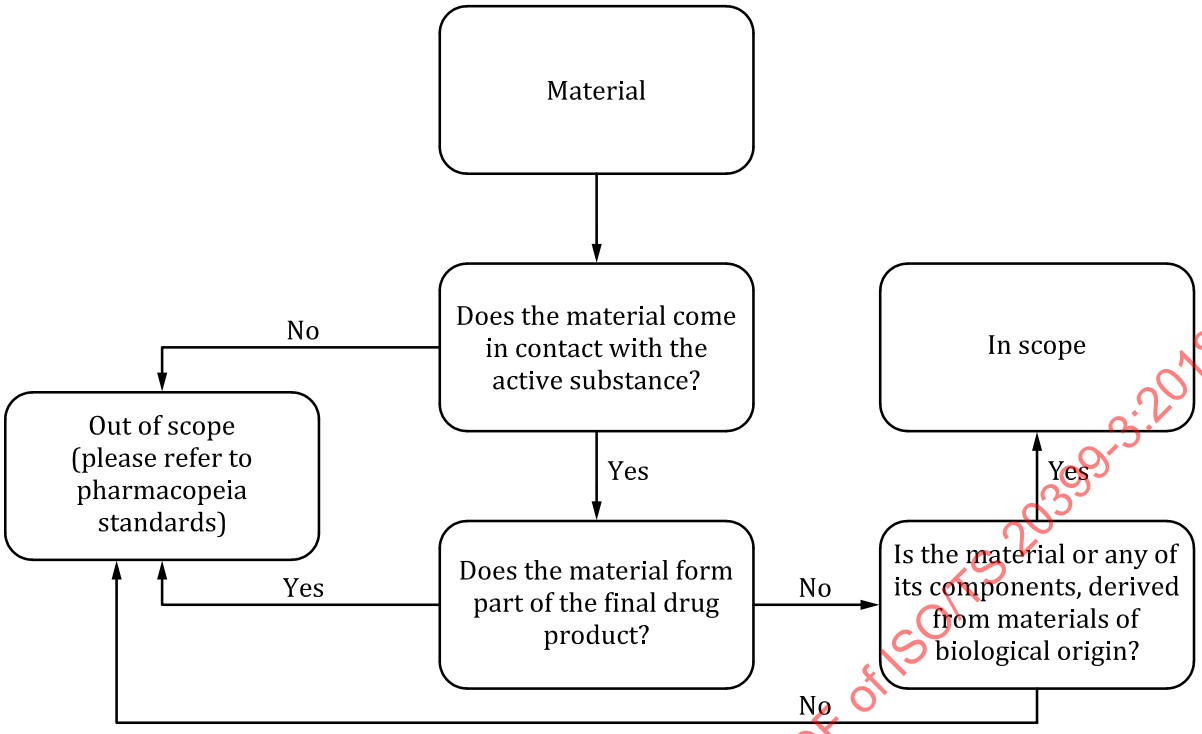

Figure 1 — Decision chart

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.

Table 2 contains examples of quality declarations that are used by suppliers of AMs in the manufacture of cellular therapeutic product. The descriptions provided are commonly used but there is no consensus on the meaning of the terms used and Table 2 is not intended to endorse these descriptions.

AMs bearing these quality declarations should still be assessed thoroughly for their quality, safety and suitability. In particular, the presence or use of animal- or human-derived components as part of the AM or as production material should be assessed, taking into account the considerations regarding animal derived component free (ADCF) or animal origin free (AOF) or xeno-free (see ISO/TS 20399-1).

Table 2 — Frequently used quality declarations made by suppliers of materials in the manufacture of cellular therapeutic product

Quality declaration	Description
GMP or cGMP grade	Manufacturing an AM in compliance with GMP requirements demonstrates that the AM has been manufactured under a robust QMS. However, GMP compliance is not a quality grade, as GMP does not apply to the quality of the product itself, but the systems, processes and procedures used to manufacture it. Some form of regulatory oversight, e.g. inspection, is required to demonstrate that a manufacturing process is GMP compliant, as is the case for the manufacture of medicinal products and active pharmaceutical ingredients. If there is no regulatory oversight, the supplier should only claim to comply with the principles of GMP.
Clinical grade	The term "clinical grade" is used to describe an AM that is suitable for clinical application, i.e. use in humans. However, the term "clinical grade" in isolation is not a recognized quality grade and the use of this term by suppliers is discretionary and a thorough quality and risk assessment should still be carried out.
RUO grade (sometimes referred to as IVUO)	Commonly available from suppliers, the grade makes no claims about suitability for human or clinical application. Therefore, the suitability of a RUO AM for use in clinical applications needs to be assessed on a case by case basis, by undergoing a risk assessment by the product user before being considered for use.
Specific regulatory "ready" or "approved"	Suppliers sometimes use specific regulatory "ready" definitions as measures of quality. However, the use of these terms by suppliers of AMs is either discretionary (and a thorough quality and risk assessment should still be carried out) or it is not a guarantee of quality when used in isolation. If a material in question has been approved for a similar use/application, e.g. by another user, this does not automatically qualify it for use in a different process.
ADCF, AOF, xeno-free	In the context of a cellular therapeutic product, the terms imply the absence of animal or human components e.g. in cell culture media formulations.

6 Evaluation criteria and mitigation of risk

6.1 Evaluation criteria

A number of different grades of AMs, certificates, terminologies and compliance with quality management systems, can be applied or used by suppliers for their product (see Table 1 and Table 2). However, a number of factors should be considered by users when evaluating a biological material for its suitability in the manufacture of cellular therapeutic product, irrespective of the grade or quality standard that is claimed by the supplier of that AM (see Table 3).

Table 3 — Key factors and considerations when evaluating biological materials for use in the manufacture of a cellular therapeutic product

Factor	Key considerations and guidance	Key questions
Source	The need to ensure the identity, activity, purity and quality of biological AMs begins with their sourcing or provenance. Biological AMs present additional risks including transmission of adventitious agents or the introduction of biological impurities. Process development should have the objective of keeping the use of all AMs to a minimum. The use of a risk-based approach to the selection of essential AMs is encouraged. Attention should be drawn to the latest information, including e.g. guidance and regulatory documentation that may provide a good guide to the selection of appropriate sources of biological AMs.	Is the material from a source that reduces the risk of adventitious agents? For example, Reference [4] provides updated information on bovine material from non-TSE countries. Can the biological AM be replaced with another that has a lower risk profile? For example, porcine-derived trypsin replaced by recombinant trypsin.
Manufacture	Users should always seek the maximum level of information related to the manufacturing process applied to a biological AM. For example, an AM may not be of biological origin but its manufacturing process may still have involved the use of a material of biological origin.	Is the product manufactured in a dedicated facility? e.g. to minimize possible contamination. If the AM is not used in a dedicated facility, what safeguards are in place to avoid the contamination of that material? For example, line clearance procedures, cleaning. Have any biological materials been used in the manufacturing process for the AM? If a recombinant protein, was it manufactured using a mammalian or bacterial expression system? If animal-derived components are used in the manufacturing process or if the AM is derived from animal origin, are there pathogen reduction steps implemented and are these steps validated?
Testing	The principles outlined in Reference [3] should be applied, including testing of AMs for viruses, of the viral clearance capability of the manufacturing process and of the product for contaminating viruses. Irradiation or heat inactivation of AMs, e.g. cell culture media or serum, is often applied but may suffer from batch variation.	What characterization is carried out on the biological AM to show identity, purity and activity levels? Has the supplier of the AM performed adequate viral inactivation steps/safety testing before its release? Can batch consistency be demonstrated?
Traceability	Information on the traceability of the AM (from source to supplier) should be as complete as possible to ensure that any subsequent steps along the supply chain have not introduced further risk to the safety or its quality, e.g. through contamination.	Does the supplier have record of the material and of all of its components that ensures the risk control of the material and all of its components? In particular, are those AMs of biological origin traceable to their source? Is the AM manufactured under a quality system? If so, is the quality system appropriate?

Table 3 *(continued)*

Factor	Key considerations and guidance	Key questions
Continuity of supply	Once an AM has been identified, it is important to ensure that the supplier can meet the requirements for the consistent and reliable supply of that material. Any failure on their part to supply the requisite material at the requisite level of quality may have a negative impact on the manufacture of a product based on therapeutic cells. The extent to which alternative supplies of an AM can be considered equivalent needs to be evaluated by the user. Qualification of biological functionality may be necessary as well as material quality. Where the AM is not commercially available with a suitable quality it may be necessary to manufacture it in-house or under contract. However, the consistency of supply needs to be weighed against the ability (in terms of cost and time) of full material QC that would be provided by purchase through a supplier.	What alternatives are available should an AM no longer be available? What characterization is necessary to ensure an alternative AM can be considered equivalent? If a suitable alternative is not available, can the AM be manufactured in-house? Is the supplier willing to sign a supply contract?

6.2 Mitigation of risk

6.2.1 Scientific approach

Once an AM of biological origin has been purchased from the supplier, the responsibility for ensuring the fitness for purpose of the material lies solely with the user. For this reason, a number of considerations should be taken into account when using that material in the processing and/or manufacture of cellular therapeutic product.

Table 4 contains a list of factors and considerations that should be taken into account by users to mitigate risks associated with AMs of biological origin, irrespective of the grade or quality standard that is claimed by the supplier of that material.

Table 4 — Key factors and considerations for the mitigation of risks associated with biological materials used in the manufacture of a product based on therapeutic cells

Factor	Key considerations	Key questions
Validation for the specific application/ process in question	A single AM can be used in multiple different and often complex manufacturing processes to generate many different cellular therapeutic products. For example, certain cytokines and/or growth factors are present in a wide variety of cell culture processes and products. It should not be assumed that because an AM can be used for one process, it is suitable for another. For this reason, validation studies that measure the effects of the biological AM on final product quality, when applied to a particular process, should be considered.	Has the AM been validated for use in a similar process? What are the specific risks/impacts on the final product quality if the AM is not fit for purpose?
Testing/ characterization	A biological AM that does not present a direct safety risk may still not be suitable for use if it does not consistently provide levels of biological activity sufficient for its intended purpose. The specification in the CoA provided by the supplier of the biological AM can be used as a starting point, but it should not be the sole basis for ensuring quality as a CoA often only contains basic information such as sterility and purity. It is the responsibility of the user to characterize each batch of the incoming material. For analytical test methods with direct implications to safety, these methods should be validated from the outset. All methods should be demonstrated to be fit for purpose.	Which are the attributes of the AM that are most critical to final product quality? How is the AM to be tested and are the methods/reagents fit for purpose? Has the potential for batch to batch variability been taken into account where a single lot of AM best suited for manufacturing a cellular therapeutic product cannot be identified and sequestered? What performance metrics need to be ensured between batches?

6.2.2 Supplier audit and questionnaires

One method of increasing the user's confidence in the quality of an AM is through supplier audit. Supplier audit provides the user with an opportunity to ensure the presence of sufficient recorded and documented information demonstrating traceability of the AM from its origin to final distribution. If the supplier is operating to a certified QMS, this can provide further assurances to the user that a system of record keeping is being maintained and procedures are in place to ensure a state of control, i.e. CAPA. These audits are used to assess the entire manufacturing process, the shipment and distribution procedures, along with any testing procedures. For example, for each test carried out by the supplier (e.g. in process testing, final QC testing) a standard operating procedure should be in place along with an associated training record for each member of staff that carries out the test in question.

Users should audit suppliers before the procurement of an AM and at periodic intervals afterwards, to ensure that the same levels of quality are being maintained.

Users can share the audit by undertaking it with another user that also uses that AM, if no conflicting confidentiality agreement exists. However, an AM can be better qualified for use in the processing/ manufacture of one cellular therapeutic product over another, and the user should take this into account when considering combining forces with another user, in addition to any concerns over intellectual property.

Before undertaking an audit of a supplier, the user should submit a questionnaire to the supplier that contains a number of key questions that allows the user to evaluate the suitability and quality of the AM in question and then also assess the need for an audit.

The supplier questionnaire can be used to extract information related to the AM in question, and should be comprehensive enough to ensure that any obvious safety risks are assessed.

Biological AMs should come under additional scrutiny, in addition to any claims that are made by the supplier regarding quality. Table 5 contains sample questions that the user may include in a supplier questionnaire.

The user should request any CoA and CoO that demonstrate the specifications, composition and provenance of the AM.

Table 5 — Example questions that can be included in a supplier questionnaire for the evaluation of a biological material for use in the manufacture of a cellular therapeutic product

Example questions applicable to all materials
a) Where is the AM manufactured and is it segregated from other materials during manufacture?
b) What characterization of the product is carried out, e.g. release tests/specifications?
c) If applicable, what sterilization or other decontamination measures have been applied?
d) Is the AM manufactured under a specific quality system to meet a particular quality standard?
Example questions specific to animal-derived materials
a) Are there any animal components in the AM, and if so please specify the type?
b) If bovine, please specify the source (country) of the animal from which the material is derived?
c) What viral testing was carried out on the AM and have any viral clearance steps been carried out?
d) If bovine material is present, have any steps been taken to minimize the risk of TSE transmission?
NOTE If using bovine serum, check for specific guidelines on the use of bovine serum in the manufacture of cellular therapeutic product.
Example questions specific to human-derived materials
a) What is the type and tissue source of the human material?
b) What level of donor testing was carried out?
c) In what country does the donor reside?
d) Was the donation and procurement of the material carried out under the applicable regulatory requirements?

6.2.3 Risk assessments

The user can use the information provided by the supplier of a biological AM as the basis for a risk assessment. The aim of a risk assessment in such instances is to use a systematic and consistent procedure to assess both the likelihood of occurrence and severity of the outcome associated with a specific risk for a specific AM.

The user should determine the acceptable level of risk and of risk mitigation. The threshold of what is a low, medium or high risk AM should be justified and the methodology applied should be weighted as such to ensure that a low risk status is more difficult to achieve than a medium or high risk. Equally, the degree of risk mitigation applied to the AM in question should be justified using a robust scientific rationale.

Risk assessments can be used to support the use of an AM in clinical and commercial manufacture of cellular therapeutic product. Therefore it can be useful to include these in regulatory submissions. However, it should be noted that the risk assessment is carried out to assess the safety and quality risks associated with an AM and does not provide any assessment of the biological functionality and any resultant impact on product quality and efficacy.

