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

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

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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*.

This first edition cancels and replaces ISO/TS 20399-1:2018, ISO/TS 20399-2:2018 and ISO/TS 20399-3:2018, which have been technically revised.

The main changes are as follows:

— merging of the three parts of the ISO 20399 series;

— change in definitions of key terms including “ancillary material” and “cellular therapeutic product”;

— addition of Clause 5 “Strategy”, including key concepts, animal-derived components, mutual responsibilities and qualification;

— revision and rearrangement of requirements and recommendations with emphasis on clarifying responsibility of involved parties and emphasis of a risk-based approach.

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) refer to materials that come into contact with the cellular therapeutic product during cell processing but are not intended to be part of the final product formulation. See Annex A for a list of AM examples.

AM can be a complex mixture of many components. AMs include, for example, salts, buffers, culture media, supplements such as growth factors, enzymes and antibodies for immuno-purification. Where a material is composed of multiple materials such as culture media, all components are AMs. Variation in their lot-to-lot composition can hamper the ability to produce consistent cell and gene therapy products with specified quality attributes.

As such, AMs can have implications with regard to the safety and effectiveness of cell and gene therapy products. Appropriate control of AMs is determined by a risk-based approach.

This document specifies definitions for AMs.

This document provides recommendations and requirements to the AM suppliers and the AM users to ensure consistent manufacture and performance of AMs. This document also describes the information that can be obtained and provided to the AM users to demonstrate lot-to-lot consistency of the AM with respect to identity, purity, storage and stability, traceability, biosafety, and performance. Furthermore, this document provides recommendations and requirements to ensure that the quality of AMs enables the production of safe and effective final products.

Presently, a number of standards and guidance documents define the proper processing of cell and gene therapy products to ensure safety and efficacy. However, these standards only indirectly relate to AMs. This document is separate from the standards governing cell processing requirements. This document addresses issues with AMs and makes the expectations of the AM suppliers and the AM users clear.

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

1 Scope

This document specifies requirements and gives guidance to suppliers and users of ancillary materials (AMs) to improve the consistency and quality of AMs of biological (human and animal) and chemical origin used in the production of cellular therapeutic products and gene therapy products for human use.

This document is applicable to materials that are used for cell processing and that come into contact with the active substance and that do not intentionally form part of the final cell and gene therapy product.

EXAMPLE 1 Reagents, anticoagulants, cytokines, growth factors, enzymes, antibodies, serum (human or bovine), buffered solutions, culture media, dishes (coated with biological material), beads (coated with biological material), cryoprotectants (agents for cryopreservation), activation agents/reagents, non-mammalian cell (e.g. insect cell, bacterial cell), plasmid, viral vector.

This document does not apply to materials that are not used for cell processing, materials that do not come into contact with the active substance, or materials that intentionally form part of the final cell and gene therapy product.

EXAMPLE 2 Cells that are either starting materials, intermediates or final form of a cellular therapeutic product, feeder cells, additives used post bioprocessing, scaffolds, non-biological consumables (e.g. beads, dishes, tissue culture flasks, bags, tubing, pipettes, needles), other plasticware that come into contact with the cell or tissue, apparatus, instruments.

A decision flowchart is given in Annex A.

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 8601-1, *Date and time — Representations for information interchange — Part 1: Basic rules*

3 Terms and definitions

For the purposes of this document, the following terms and definitions apply.

ISO and IEC maintain terminology databases for use in standardization at the following addresses:

— ISO Online browsing platform: available at https://www.iso.org/obp

— IEC Electropedia: available at https://www.electropedia.org/

3.1
active substance
substance that has biological activity in a *cellular therapeutic product* (3.9) for its intended use

3.2
AM
ancillary material
raw material
material that comes into contact with the *cellular therapeutic product* (3.9) during cell processing, but is not intended to be part of the final product formulation, excluding scaffold, non-biological consumable and plasticware

Note 1 to entry: An AM can be critical to the quality and safety of a cellular therapeutic product due to its contact during cell processing.

Note 2 to entry: A decision chart that indicates whether or not a material is in scope of this document is given in Annex A.

3.3
AM impurity
ancillary material impurity
any component present in an *AM* (3.2) that is not the desired entity

3.4
AM supplier
ancillary material supplier
entity who manufactures or supplies, or both, *AMs* (3.2) for the *AM user* (3.5)

3.5
AM user
ancillary material user
entity who makes use of *AMs* (3.2) and conducts cell-processing for a *cellular therapeutic product* (3.9)

3.6
animal-derived component free
ADCF
absence of animal or human origin material(s)

Note 1 to entry: The main purpose of defining the types of ADCF is to provide necessary information for a user's *risk assessment* (3.13) of *ancillary material* (3.2).

Note 2 to entry: In some cases, ADCF is described as "animal origin free (AOF)".

Note 3 to entry: In cases where there is absence of non-human animal components, the term "xeno-free" is commonly used.

3.7
biological material
any substance derived or part obtained from an organic entity such as a human, animal, plant, microorganism(s) or multicellular organism(s) that is(are) neither animal nor plant (e.g. brown seaweed, fungi)

[SOURCE: ISO 20387:2018, 3.7]

3.8
biosafety
practices and controls that reduce the risk of unintentional exposure or release of *biological materials* (3.7)

Note 1 to entry: This definition includes unintentional exposure, for example, to pathogens and toxins, or their accidental release as a biosafety risk.

[SOURCE: ISO 35001:2019, 3.22, modified — Note 1 to entry added.]

3.9
cellular therapeutic product
product containing cells as the *active substance* (3.1) used for cell therapy or gene therapy

EXAMPLE Cell and gene therapy products, tissue engineered products, drug products.

Note 1 to entry: Products produced from cells for gene therapies are included in the definition of cellular therapeutic product, as cells are not necessarily the active substance for all gene therapies.

Note 2 to entry: Recombinant proteins are not included in this definition of cellular therapeutic product.

3.10
chain of custody
responsibility for, or control of, materials as they move through each step of a process

Note 1 to entry: Chain of custody is the unbroken path of an *ancillary material (AM)* (3.2) from the production of the AM to the end *AM user* (3.5). It covers controls, distribution and logistics to the AM user.

3.11
chemically defined component
substance whose chemical structure is identified/known at the molecular level

3.12
CoA
certificate of analysis
document attesting that an *ancillary material (AM)* (3.2) has undergone specified testing with specified results

Note 1 to entry: A CoA commonly contains the actual results obtained from the testing performed as a part of quality control of an individual batch of an AM.

Note 2 to entry: Often the CoA represents an agreement between the *AM supplier* (3.4) and the *AM user* (3.5).

3.13
risk assessment
overall process of risk identification, risk analysis and risk evaluation

[SOURCE: ISO Guide 73:2009, 3.4.1]

3.14
risk management
coordinated activities to direct and control an organization with regard to risk

[SOURCE: ISO Guide 73:2009, 2.1]

3.15
shelf life
period during which an *ancillary material* (3.2) is expected to comply with the *specifications* (3.16), if stored under defined conditions

3.16
specification
list of tests, references to analytical procedures and appropriate acceptance criteria that are expected to be met to demonstrate suitability for its intended use

3.17
stability
characteristic of a material, when stored under specified conditions, to maintain a value(s) for a stated property(ies) within specified limits, for a specified period of time

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

3.18
traceability
ability to trace the history, application or location of an object

Note 1 to entry: When considering a product or a service, traceability can relate to:

— the origin of materials and parts;

— the processing history;

— the distribution and location of the product or service after delivery.

Note 2 to entry: In the field of metrology, the definition in ISO/IEC Guide 99 is the accepted definition.

[SOURCE: ISO 9000:2015, 3.6.13]

3.19
user requirement specification
URS
document that states *specifications* (3.16) for an *ancillary material (AM)* (3.2) based on the *AM user's* (3.5) requirements for the manufacture of a desired *cellular therapeutic product* (3.9) and gene therapy product

4 Abbreviated terms

ADCF	animal-derived component free
AM	ancillary material
AOF	animal origin free
BSE	bovine spongiform encephalopathy
CoA	certificate of analysis
CoC	certificate of compliance
CoI	certificate of irradiation
CoO	certificate of origin
EDQM CEP	European Directorate for the Quality of Medicines and Healthcare certificate of suitability
GMP	good manufacturing practice
ICH	International Council for Harmonization of Technical Requirements for Pharmaceuticals for Human Use
QC	quality control
QMS	quality management system
RP-HPLC	reverse phase high performance liquid chromatography
SDS	safety data sheet
SDS-PAGE	sodium dodecyl sulfate poly acrylamide gel electrophoresis
TSE	transmissible spongiform encephalopathy
USP	United States Pharmacopeia

5 Strategy

5.1 Key concepts on AM

AMs for each cellular therapeutic product are defined by the manufacturing process and the final form of the cellular therapeutic product (see Annex A).

AM users have the responsibility to establish and maintain a qualified status for AMs within their processes, including any oversight required for any AM. The level of such oversight should be proportionate to the risks posed by a specified AM, with reference to origin, manufacture or supply chain integrity. It is necessary to undertake a risk-based approach to AM selection and qualification.

AM can affect quality attributes of cell-based therapeutic products:

a) quality and consistency are important for AMs known to be critical for cell manufacturing;

b) safety and the chain of custody are critical for AMs of cellular therapeutic products.

Activities to assess and control the impact of AMs on the quality attributes of a cellular therapeutic product by the AM user are based on:

— information provided by the AM supplier;

— information obtained by either the AM user or the AM supplier, or both, through either characterization and testing of AMs or manufacturing of cellular therapeutic product;

— published standards or other peer-reviewed scientific methods (or equivalent).

5.2 AM-related responsibilities

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

The AM user and the AM supplier can agree upon the specifications of AMs intended for cellular therapeutic products by using such workflow.

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

Table 1 describes recommendations for responsibilities and responsible parties leading these activities.

NOTE It is important that the relationship between the AM user and the AM supplier is cooperative and transparent. Many responsibilities are determined together as their combined efforts. These activities benefit from a supplier-user relationship. Without such relationship, an additional risk for the user, e.g. lack of technical support from the supplier, can happen. Although the responsibility for these activities is determined on a case-by-case basis.

Table 1 — Recommendations of responsibilities and responsible parties leading this activity

Activity	Responsible party	Reference for more information
Provide documented evidence that the AM is safe with respect to source-relevant animal diseases (e.g. BSE/TSE)	AM supplier	6.1 (Table 2), 6.2.1 (Table 3), 8.4 P3[a], Annex C, Annex E
Prepare and submit a master file for AM, if applicable	AM supplier	7.1.4 P3, Annex C
Assess the stability of the AM	AM supplier	7.2.2
Inform the AM user of any changes that will very likely or with certainty impact the AM (e.g. under a quality agreement)	AM supplier	8.1 P1, Clause 11

[a] "P" represents paragraph. For example, "8.4 P3" means "8.4 Paragraph 3.

Table 1 *(continued)*

Activity	Responsible party	Reference for more information
Conduct an assessment of the AM container closure system	AM supplier	8.3
Provide a CoA, CoO and SDS for the AM	AM supplier	10.2 P2 and P4, 10.3, 10.4.1
Conduct characterization testing of the AM and prepare a specifications document (e.g. identity, purity, functionality, viral contamination, animal origin)	AM supplier and AM user	6.1 (Table 2), 6.2.1 (Table 3), 6.2.2 P1, Clause 7, 8.4, 8.5, Clause 9, 10.3, Annex C, Annex D
Execute a quality and supply agreement	AM supplier and AM user	9.3 P6, 10.2 P2, 11.2, Annex C
Provide user requirement specifications to the AM supplier	AM user	Annex B
Conduct a risk-based AM supplier qualification process, generally including initial screening, onsite audit, formalized approval, continuous monitoring/oversight	AM user	5.3, Clause 6, 8.4 NOTE, 9.2, 9.3, Annex E
Determine if biocompatibility, biodistribution, cytotoxicity or adventitious agent testing is needed (or if testing results are available from the AM supplier, if applicable)	AM user	5.4, 6.1 (Table 2), 8.2 P2 and P3, 10.3, Annex D
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, e.g. failure modes and effects analysis	AM user	5.4.2, 6.2.3, 8.4 P1, 9.3 P5, Annex E
Establish similar assurances and plans for alternative suppliers	AM user	5.4.2 P2, 6.1 (Table 2), 11.2
Qualify the performance of the AM in the intended application	AM user	6.1 (Table 2), 6.2.1 (Table 3), Clause 9, 10.2, 10.3, Annex D
Confirm the CoA test result(s) critical to the cell product (e.g. functional assay)	AM user	6.1 (Table 2), 6.2.2 P7, 9.3 P6, 10.3, Annex C, Annex D
Assess the effect of lot-to-lot variation of the AM on the final cell product	AM user	7.1.4, Clause 11
Establish and implement a qualification plan for the use of an AM	AM user	9.3 P6

[a] "P" represents paragraph. For example, "8.4 P3" means "8.4 Paragraph 3.

5.3 Qualification considerations of AM

The qualification of an AM includes:

a) the physiochemical characteristics of AM, including characteristics and material attributes (e.g. identity, purity, stability, functionality and performance);

b) the documentation for all AMs, including, its composition, quality or grade, the source of each component, the concentration and the purity;

NOTE 1 The composition and concentration of each component can be considered proprietary. Reference to a drug master file (DMF) is desirable.

NOTE 2 See Annex E for examples of quality declarations for manufactured biological materials used in the manufacture of a cellular therapeutic product.

c) the demonstration of lot-to-lot consistency of AMs for the intended cell manufacturing step, specifically regarding the identity and performance of the AM;

d) an appropriate level of biosafety, including avoidance of introduction of unwanted agents that can cause harm to the therapeutic, and directly or indirectly to patients;

e) the 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) the performance of AMs in delivering the intended effects with consistency and robustness:

— an AM shall perform its intended function within a model cell manufacturing process selected by the AM supplier appropriate for the AM's intended use;

g) accompanying documentation:

— AM supplier shall provide sufficient documentation that communicates information of AM for the purpose of AM users ensuring the quality of their cellular therapeutic products;

NOTE 3 There are cases where documentation is limited due to protecting intellectual property.

h) quality declarations and mitigation of risk in use of AMs for manufactured biological materials used in the manufacture of cells for therapeutic use;

i) the characterization of biological materials;

j) managing changes to AMs.

The AM supplier is responsible for the qualification with regard to general performance, but the AM user is responsible for the qualification for the intended use.

The AM user is responsible for the qualification of all AMs used in the manufacturing of their cellular therapeutic products. Identification (ID) or purity tests should be provided by AM suppliers, if available. If sub-suppliers are used, AM suppliers should have a plan, if sub-suppliers fail qualification.

If applicable, the AM user should assess the presence of residual AM in the final cell product.

The AM user should audit the AM supplier to ensure qualification of material.

5.4 Animal-derived components of AM

5.4.1 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 and qualification of AMs is therefore recommended.

5.4.2 Key considerations in the use of animal-derived components

A risk assessment approach shall be used in reference to the safety of animal-derived components.

The following are the key questions that shall be addressed, particularly for human or animal origin:

a) Is the component terminally sterilized?

b) What is the origin of the biological material(s)?

c) Is (are) the biological material(s) traceable to its(their) source?

d) Which risk mitigation measures have been applied to the biological material(s), besides audit of AM supplier(s)?

EXAMPLE 1 Sourcing from a TSE-low risk origin, virus removal or inactivation steps, use of pharmaceutical grade material, virus removal from AM, its component or subcomponent, or adventitious agent testing.

e) Is there a risk of contamination of the AM through contact with slip agents (additives used to reduce friction between films and between film and equipment) and during production?

EXAMPLE 2 Insufficiently validated virus removal or inactivation steps, no adventitious agent testing, no adequate pest control.

The AM supplier should consistently and reliably supply such AM to the AM user. The AM user should establish a similar relationship with alternative AM suppliers.

5.4.3 Viral inactivation

When either animal-derived biological materials or human-derived biological materials, or both, are used in the production or formulation of an 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. This can be conducted either at the AM level, the component level or at the combination of these levels. These processes require validation studies, and documentation that should be available to the AM user.

Human blood products used in AM manufacturing should undergo viral clearance/inactivation.

Evidence of adventitious agent testing or mitigation without viral inactivation processing shall be documented, e.g. testing or mitigation of porcine trypsin for relevant porcine viruses when the sub-supplier does not conduct viral removal processing steps.

6 Evaluation criteria and risk mitigation for AM containing biological material

6.1 Evaluation criteria for AM selection

A number of factors shall be taken into account by AM users when evaluating a biological material for its suitability in the manufacture of a cellular therapeutic product, irrespective of the grade or quality standard that is claimed by the supplier of that AM (see Table 2).

Table 2 — Factors, key requirements and recommendations, and key questions when evaluating materials for use in the manufacture of a cell-based therapeutic product

Factor	Key requirements and recommendations	Key questions
Source	The need to ensure the identity, activity, purity and quality of AMs begins with their sourcing or provenance. AMs present additional risks including the possibility of transmission of adventitious agents or the introduction of biological impurities. The AM user should make use of a risk-based approach to the selection of essential AMs. Attention should be drawn to the latest information, including, for example, guidance and regulatory documentation that can provide a good guide to the selection of appropriate sources of biological AMs.	Is the material derived from a source that reduces the risk of contamination with adventitious agents? For example, Reference [26] provides updated information on bovine material from non-TSE countries. Can the AM be replaced with another that has a lower risk profile? For example, porcine-derived trypsin replaced by recombinant trypsin, with a viral safety profile. Does the AM have a documented viral safety profile?

Table 2 *(continued)*

Factor	Key requirements and recommendations	Key questions
Manufacture	AM users should seek the maximum level of information related to the manufacturing process applied to a biological AM. For example, it can be that an AM is not of biological origin, but its manufacturing process can still have involved the use of a material of biological origin.	Is the AM manufactured in a dedicated facility, for example, to minimize possible cross contamination? If the AM is not manufactured in a dedicated facility, what measures are taken to avoid contamination by the manufacture of other AMs, for example, line clearance, facility cleaning, storage of other AMs? If the AM is not used in a dedicated facility, what safeguards are in place to avoid the cross contamination of that material? For example, line clearance procedures, cleaning. Have biological materials been used in the manufacturing process for the AM? If a recombinant protein was used, was it manufactured using a mammalian or bacterial expression system? If an AM was manufactured using animal-derived components or if the AM is animal-derived, have steps been implemented to reduce potential pathogens? If so, have these steps been validated?
Testing	The principles outlined in ICH Q5A(R1) 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 can be subject to batch variation. The correlation between assays or tests and user protocols should be established.	What characterization is carried out on the biological AM to show identity, purity and performance levels? If applicable, has the supplier of the AM performed adequate viral inactivation steps/safety testing before its release? Does the AM have a documented viral safety profile?
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. Information on the traceability of the components of the AM shall be documented and auditable to ensure viral safety of the AM.	Does the supplier have a record of the AM and of all of its components that ensures the risk control of the AM? In particular, are those AMs, components and sub-components of biological origin traceable to their source? Is the AM manufactured under a quality management system? If so, is the quality management system appropriate to ensure the safety and performance of the AM?

Table 2 *(continued)*

Factor	Key requirements and recommendations	Key questions
Continuity of supply	Once an AM has been identified, the AM supplier shall ensure that it can meet the requirements for the consistent and reliable supply of that AM. Any failure on their part to supply the requisite AM at the requisite level of quality can have a negative impact on the manufacture of a cell or gene therapy. The AM user shall evaluate the extent to which alternative suppliers of an AM can be considered as equivalent. Qualification of biological functionality can be necessary as well as AM quality. Where the AM of suitable quality is not commercially available, and cannot be effectively qualified, it can be manufactured either in-house or under contract, and under relevant controls with equivalent traceability. However, the AM user shall weigh the consistency of supply against the ability (in terms of cost and time) of full AM quality control (QC) that can be provided by purchase through an AM supplier.	What alternatives are available should an AM no longer be available? What characterization is necessary to ensure that an alternative AM can be considered as equivalent? If a suitable alternative is not available, can the AM be manufactured in-house? Is the supplier willing to sign a supply contract? What is the grade of the material offered? See also the examples of recognized quality declarations used by AM suppliers of AMs used in the manufacture of cellular therapeutic product given in Table E.1. Is the supplier constrained by sourcing? Are lead times stated? Are there special handling considerations of the AM to ensure function? Are there containment requirements to ensure sterility of process? Are there risks associated with addition of the AM in the process, either up-stream or down-stream, i.e. container, sterility of process, stability of AM?

6.2 Mitigation of risk

6.2.1 Scientific approach

Once an AM of biological origin has been purchased from the AM supplier, the responsibility for ensuring the fitness for purpose of the AM lies solely with the AM user. Due to this reason, the AM user should take into account a number of factors when using an AM in the processing or manufacture, or both, of a cellular therapeutic product.

Table 3 contains a list of factors that shall be taken into account by AM users to mitigate risks associated with AMs of biological origin, irrespective of the grade or quality standard that is claimed by the AM supplier.

Table 3 — Factors, key recommendations and considerations, and key questions for the mitigation of risks associated with biological materials used in the manufacture of cellular therapeutic products

Factor	Key recommendations and considerations	Key questions
Verification for the specific application or process in question	A single AM can be used in multiple different and often complex manufacturing processes (e.g. complex relationship between enzymes make extrapolation for other application difficult without a design of experiments approach) to generate many different cellular therapeutic products. For example, certain cytokines or growth factors, or both, are present in a wide variety of cell culture processes and products. The AM user should not assume that an AM suitable for one step in the manufacturing process is suitable for other steps in the process. For this reason, the AM user should take into account verification studies that measure the effects of the biological AM on final product quality, when applied to a particular process.	What are the specific risks and impacts on the final cell or gene therapy product quality if the AM is not fit for purpose? Where is the AM used in the manufacturing process and is it segregated from other components during manufacture? What sterilization or other decontamination measures have been applied? Is the AM manufactured under a specific quality system to meet a particular quality standard? What is the type and tissue source of the human material? What level of donor testing was carried out? In what country does the donor reside? Did the donation and procurement of the material follow regulatory requirements, e.g. donor consent?
Testing and characterization	A biological AM that does not present a direct safety risk can 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 certificate of analysis (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 AM user to characterize each batch of the incoming material. For analytical test methods with direct implications to safety and final product quality, these methods should be validated from the outset. All test 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 or 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 cell or gene therapy product cannot be identified and sequestered? What performance metrics need to be ensured between batches? What characterization of the product is carried out, e.g. release tests or specifications? Are there any animal components in the AM, and if so what type? What viral testing was carried out on the AM and have any viral clearance steps been carried out? If bovine material is present, have any steps been taken to minimize the risk of TSE transmission?

6.2.2 Supplier audit and questionnaires

One method of increasing the AM user's confidence in the quality of an AM is through an AM supplier audit. The AM supplier audit provides the AM 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 AM supplier is operating to a certified quality management system (QMS), this can provide further assurances to the AM user that a system of record keeping is being maintained and procedures are in place to ensure a state of control. These audits are used to assess the entire manufacturing process, the shipment and distribution procedures, along with any testing procedures. For each test carried out by the AM supplier (e.g. in process testing, final QC testing), a standard

operating procedure shall be in place along with an associated training record for each member of staff that carries out the test in question.

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

Before undertaking an audit of an AM supplier, the AM user can submit a questionnaire to the AM supplier that contains a number of key questions that allows the AM user to evaluate the suitability and quality of the AM in question.

The AM supplier questionnaire can be used to extract information related to the AM in question and shall 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 AM supplier regarding quality. Table 2 and Table 3 contain sample questions that the AM user can include in an AM supplier questionnaire.

If using bovine serum, the AM user shall check for specific guidelines on the use of bovine serum in the manufacture of cellular therapeutic product.

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

6.2.3 Risk assessment

The AM user can use the information provided by the AM 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.

Performing a risk assessment can be a resource intensive activity and prioritization of the highest risks should be made. Users should employ appropriate risk assessment tools (e.g. quality function deployment) to apply risk scoring. A risk assessment shall be made as part of a wider risk management procedure, encompassing identification, evaluation (i.e. likelihood to occur), control and review measures.

The AM user shall determine the acceptable level of risk and 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 shall be justified using a robust scientific rationale.

Risk assessments 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.

7 AM characteristics and quality attributes

7.1 AM components, identity and purity

7.1.1 General

The supplier should aim to produce the AM consistently according to an agreed specification. Analytical methods should be compendial, where appropriate. Non-compendial methods should be validated by the supplier.

7.1.2 Identity and quantity of component(s)

The AM supplier shall clarify the identity of each component for AMs that consist of chemically defined component(s). The AM supplier shall also clarify all identified molecular components and their relative concentrations for products that are mixtures of several components. The AM supplier shall determine relevant information regarding the variation of lots and the general acceptable range. The AM supplier and the AM user shall perform a suitably specific identity test. There are cases where the user needs to develop a different test if the supplier's test is not sufficiently specific for their application.

Where possible, all chemical components should meet relevant compendial requirements.

If the identity of all substances cannot be defined or disclosed, or both, then the AM should be assessed by its activity.

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

The AM supplier shall prepare a certificate of origin (CoO) for animal-derived material(s). Information documented should include the country of origin. Information can also include a health statement for the animal, herd or colony from which the component was derived, and evidence documenting absence of pathogens (e.g. viral clearance tests, sterility tests).

For human-derived materials, viral panel testing is required. The AM user shall be aware of relevant requirements in the country of use.

7.1.3 Purity and impurity

For AMs consisting of a single component that has been isolated or purified, or both, the purity of that component within such AMs should be defined and measured by the AM supplier and provided to the AM user. For AMs that consist of multiple components, the purity of active components in such AMs should be defined, measured and documented. For AMs from ill-defined biological materials (e.g. culture supernatants that contain collagenase activity), the activity that can affect the performance of such biological materials in the cell manufacturing process should be assessed and the effect of any substance that can cause an adverse response (e.g. endotoxin) shall be evaluated.

If an AM is produced in multiple lots, tests for the purity on such AM shall be completed for each lot. 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.

Impurities shall be identified and documented, as applicable. Tests to measure impurities and acceptable limits shall be established, as applicable.

If available, the AM supplier should report suitable tests so that the AM user can qualify its cellular therapeutic product for the purpose of detecting residuals of the AM.

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

The AM supplier should 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, as applicable.

The inclusion of evidence for consistency should be taken into account for AMs containing unknown or undisclosed components.

Proprietary information can be provided directly to the regulatory authority (e.g. through a master file or as a specific response to a specific query in a regulatory support file). The decision about what

information should be shared between the AM supplier and the AM user should be discussed and agreed upon by both parties entering this partnership.

If proprietary information on a component(s) of an AM is shared with the AM user, the AM user is responsible for determining whether the material is suitably consistent regarding such component(s) and should undertake studies to confirm this. These studies can include but are not limited to tests for contaminants, sterility, endotoxin, viruses, mycoplasma, pH and osmolarity.

If the AM supplier claims the AM is sterile, the method of sterilization should be documented and shared with the user.

7.2 AM storage and stability

7.2.1 General

The AM supplier shall provide sufficient information on the proper storage conditions for the AMs as well as the description of the assays used to determine the stability of the product corresponding stability information associated with those storage conditions.

The AM supplier should report any addition of stabilizers.

The AM user shall verify and test the performance in storage conditions for the intended use.

7.2.2 Stability and storage conditions

The AM supplier shall conduct stability testing to determine the shelf life for all AM forms and recommended storage conditions. Stability indicating parameters can be determined through following the principles of ICH Q1 and ICH Q5C as appropriate. Type and suitability for appropriate tests can be determined using ICH Q1 and ICH Q5C.

The AM supplier shall provide the AM user with the following information on stability and storage:

a) the manufacturing date;

b) the expiration date or shelf life;

NOTE Shelf life for each freezing temperature range (laboratory or deep freezer) and shelf life in refrigerator after thawing can be provided, if applicable.

c) the stability at a single temperature or several individual temperatures, as applicable;

d) the stability for each available AM form;

e) the recommended measures in case of exposure to other relevant detrimental environmental parameters such as exposure to intense light or vibration.

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

An AM's activity/performance shall remain consistent during storage through the duration of the AM's shelf life under appropriate recommended storage conditions.

The AM supplier shall provide the recommendations for storage conditions. Exemplary conditions are:

— the temperature;

— the exposure to light;

— the humidity;

— the pH sensitivity;

— the susceptibility to shaking;

— the susceptibility to oxidation/reduction.

If the AM is delivered in a different form or state than the form or state that it is used (e.g. reconstituted, thawed, aliquoted), the appropriate storage conditions for alternative forms or states shall be recommended, together with stability data, if available, by the AM supplier. The procedure for reconstitution shall be provided by the AM supplier, and changes associated with reconstitution in terms of stability and other properties communicated to the AM user.

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

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

— a maximum recommended number of freeze–thaw cycles;

— if applicable, shelf life in each freezing temperature range (e.g. laboratory freezer or deep freezer);

— if applicable, shelf life in refrigerator after thawing.

8 AM manufacturing and biosafety

8.1 Quality management system

Manufacturers of AM shall implement a QMS. Manufacturers of AM shall undergo regular audits (see 6.2.2). The AM supplier shall implement a nonconformity process to be audited by AM users. Such process shall include plans for implementing effective corrective actions, i.e. actions to eliminate the cause of nonconformity and to prevent recurrence, and timely remediation for identified critical issues.

NOTE ISO 13485 and ISO 9001 are baseline examples of a relevant QMS. It is important to assess whether meeting the requirements in existing management system standards including ISO 9001 and ISO 13485 are sufficient on a case-by-case basis.

Typical elements of a QMS are:

a) general principles;

b) manufacturing facility, environment;

c) manufacturing supply ability, delivery and the supply system;

d) manufacturing record-keeping systems;

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

f) education and training records;

g) safety management;

h) supplier management;

i) equipment management;

j) programme on materials used to produce AM, which includes keeping traceability records of these materials.

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

8.2 Manufacturing process

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

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

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

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. The use of antibiotics in manufacture is strictly controlled to limit environmental impact growing antibiotic resistance.

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

Particulates should be minimized as far as possible. Where possible, steps should be included to remove them. When available, measurement and quantity of particulates in the AM should be provided.

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

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

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

8.3 Container and closure systems

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

Containers and closure systems should be sterile. When possible, single use containers are recommended. Extractable potentials should be provided for the container of choice to AM users.

8.4 Animal and human-derived components

Risk assessment for animal-derived components should begin early in the cellular therapeutic product development process. Assessment of risk for animal-derived components are based on the risk for the intended use.

Points of view when defining animal-derived component free (ADCF) include:

a) product ingredients: the AM does not contain any materials from animal or human source as its components (e.g. cell culture media with no animal or human components as the main component of the AM but uses recombinant proteins);

b) production history: AM is produced without the use of any materials from an animal or human source.

NOTE There are documents that provide advice on developing a risk-based AM qualification framework, see ISO 13022, ICH Q9, USP <1043> and References [27] and [28].

For AMs from an animal or human source, traceability shall be established, strictly followed and documented. The use of searchable and rapidly retrievable information from a database and the

exchange of information in an electronic format is recommended. There is a standard format available, see ASTM E3077. All components shall be screened for relevant diseases according to the source of the materials. A CoO that includes the registration of an establishment where materials were collected as well as any relevant testing and documented results shall be kept by the AM supplier and made available, as necessary.

For AMs that contain animal-derived component(s) or human-derived component(s), or both, such component(s) shall be identified and documented. When an AM includes components which cannot be disclosed, a statement whether the AM includes animal-derived component or human-derived component, or both, shall be available to the AM user.

AM that are produced from human-derived starting materials should be obtained from licensed facilities. Such AMs shall be tested and documented by the collection sites.

8.5 Safety to cells and humans

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

The AM supplier shall provide the AM user with information on how sterility testing for and sterilization of the AM were performed and validated, and on what number of units and the level of sterility assurance were provided.

NOTE Such information is important for the AM user to establish the safety and sterility of the cellular therapeutic product, as it cannot be sterilized.

The AM user should perform additional testing to demonstrate safety to cells and humans. The AM user should evaluate the effect of the AM on cell characteristics, if necessary. Depending on the risks of AMs, such tests include but are not limited to the following:

a) cell proliferation;

b) genotoxicity;

c) cytotoxicity;

d) cell plasticity;

e) cell migration;

f) cell morphology;

g) gene expression;

h) chromosomal stability;

i) any other appropriate tests.

9 AM performance

9.1 General

AM performance testing can be done by the AM supplier and the AM user. Generally, the AM supplier does such testing to demonstrate the general performance of the AM, while the AM user does such testing for the purpose of the intended use of the AM.

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

The AM supplier should include performance testing data when small variations across components have the potential to cause measurable changes to the AM interaction with cells when available (e.g. in the case of complex cell culture media or serum).

In addition, in the case where the exact component identity and concentration is not known or cannot be disclosed, performance testing by the AM user can be used as an alternative method to demonstrate the consistency of the cellular therapeutic product.

9.2 Quality and testing

The AM user should assess AMs under a qualification framework that reflects the level of risk presented by that material.

The AM user should qualify the AM comprehensively throughout the development of cell and gene therapy products and should include in the product qualification an assessment of the material source, identity, purity, biological safety and overall suitability of the specific material. The AM user can have an opportunity for a risk-based approach to reduce suitability testing with appropriate justification, such as if the AM supplier is qualified and there is justification and routine assessment of the product.

The AM user shall also qualify an AM supplier, where their QMS and materials testing programmes shall be audited.

NOTE UPS <1043> provides advice on developing a risk-based AM qualification framework.

Where possible, highly qualified materials with a demonstrable quality specification should be adopted as AMs.

9.3 Qualification activity

The AM user should select the right AM(s) for use in manufacturing processes of cellular therapeutic products, and the right AM suppliers.

The AM user should implement a staged approach to AM that achieves a balance between the competing demands of risk mitigation and cost of goods containment at the various stages of the cell and gene therapy product development.

The AM user shall develop a specification for each AM to ensure its consistency and performance of the manufacturing process for a cellular therapeutic product. The AM user shall validate methods and assays for the testing used to develop such specifications. Guidelines for proper validation can be found in: ISO 5725-1, ISO 5725-2, ISO 5725-3, ISO 5725-4, ISO 5725-5, ICH Q2(R1) and ISO/IEC 17025.

If the AM user intends to use the AM outside of the AM supplier's specifications, the AM user shall qualify the AM for their intended storage, specifications and shelf life.

If process modifications for the AM or cellular therapeutic product are implemented, the risk assessment procedure can require reassessing the new practices and shall have communications between relevant parties.

The AM user's QC programme, such as good manufacturing practice (GMP), shall validate the ongoing quality performance of each AM in its intended application through an established and implemented qualification plan. A typical QC strategy should also cover:

a) the management of incoming material through receipt, segregation, inspection and release (prior to use);

b) quality and supply agreements put into place between AM supplier and AM user;

c) an ongoing assessment of lot-to-lot variability and analysis of impact on final product;

d) the vendor auditing and certification;

e) the CoA verification testing;

f) policies and practices for dealing with out-of-specification materials;

g) a stability programme (test results can be provided by AM supplier);

h) sampling considerations (e.g. sample plan backup in case of need for investigation);

i) archival sample storage;

j) the CoO (if applicable);

k) shipping and storage conditions (shipping shall be validated).

The AM user should define, document and implement quality control strategies for cellular therapeutic product manufacturing within a management system that meets the requirements of this document.

9.4 Performance assay

The AM supplier shall design and validate performance assays to demonstrate the effect of the AM on cells, or demonstrate lot-to-lot consistency, or both. Assays can include those that measure normal cell functions (e.g. cell survival, proliferation) or those that measure more specific cell identity and function (e.g. cell specific gene expressions or a performance assay of a cellular function).

The AM user should select performance assays based on the intended use of the AM. The AM supplier should provide the AM user with adequate details of the assay to assess whether the performance data generated from the assay is applicable to their use of the AM.

9.5 Performance assay results

Results from performance assays for intended use shall be documented by the AM user. Results for general performance assays performed by the AM supplier can also be provided to the AM user. The results, when available, should be provided in a manner that enables appropriate selection of AMs or fit-for-purpose, or both.

The result demonstrating the AMs lot-to-lot consistency can be provided upon request. The performance assay results can include:

a) the quantified result;

b) the distribution of lots within an acceptable range;

c) the uncertainty in the assay result when biological assays are used.

The AM supplier and the AM user should determine 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.

10 AM documentation

10.1 General

As AMs are intended for manufacturing cellular therapeutic products under this document, AM suppliers shall provide the AM user with such information by using the label or the catalogue, or both, e.g. “intended for use in manufacturing of cellular therapeutic products or gene therapy products”.

NOTE Suitability for use of an AM is basically determined by the AM user.

10.2 Reporting requirements

The AM supplier shall report sufficient information on quality assessment data to allow common understanding of the data and to enable data comparison. Information should include, but is not limited to:

a) the raw data;

b) the processed data;

c) scale(s) for quantitative or relative data;

d) benchmark to known/reference value(s);

e) the metadata (detailing sample, procedures, conditions, etc.);

f) the results from control strategies (to provide confidence for the performance of assay);

g) the product performance;

h) the stability;

i) QC;

j) the analytical testing methods.

The AM supplier is responsible for providing the CoAs and CoOs. The AM supplier shall be aware that the information provided by the AM supplier is assessed by the AM user and that there are cases in which the AM supplier needs to assist in audits by the AM user with detailed information. Information provided by the AM supplier can also be used to allow the AM user to subscribe and get any updated information from the AM supplier, if any new information becomes available. It is recommended that the AM supplier and the AM user should come to an agreement about what data should be shared through discussion and mutual agreement in advance, which should be captured in a quality agreement.

GMP for AMs shall be followed by commercialization stages. A GMP framework reinforces the partnership between the AM supplier and the AM user.

A safety data sheet (SDS) shall be provided for all substances and mixtures, e.g. following the criteria for physical, health or environmental hazards described in Reference [29], and for all mixtures which contain components 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 can apply depending on the country or region into which the AM is being supplied.

Reporting elements for AM shall include:

— a title (e.g. “Quality Report” or “Material Certificate”);

— AM ID, cell descriptors from which AM is derived (e.g. cell type, lot number or identifier, date of manufacture source);

— the name and address of the production facility, and the location where activities referred to in the report were carried out, if different from the address of the production facility;

— the date of issue of the report in a standard format in accordance with the ISO 8601-1;

— unique identification of the report (such as a serial number), and on each page an identification to ensure that the page is recognized as a part of the report, and a clear identification of the end of the report;

— the biological material identification or specific properties (if there is a biological source for AMs);

— the description of the test method(s) including sensitivity and specificity of the test method(s) and release criteria;

— the testing results with, where appropriate, the units of measurement;

NOTE The units of measurement can be SI units or other units that are defined for the purpose of reporting.

— unexpected observations.

In addition, reporting elements for an AM can include:

— relevant quality information of the AM and associated data;

— the storage conditions;

— the expiration date.

10.3 Certificate of analysis

The AM supplier shall issue a CoA for an AM. When there is a requirement to replace an AM during development, in order to make that change, an equivalent replacement AM should be sought, which has both scientific and regulatory implications.

NOTE A CoA allows comparison between AMs in order to make an informed decision in these replacements. This emphasizes the need for robust characterization of AM. Considerations for the characterization of AM are provided in Annex D.

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

a) The identity:

— Methods for identification should be as specific as possible (e.g. N-terminal protein sequence identification or appropriate identity test for an IP protected material such as cell culture media).

b) The 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) The 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 or validated tests with sufficient quantities to meet the applicable requirements, or both. The tests can include sterility, endotoxin, mycoplasma and adventitious viruses depending on the materials and the potential safety.

e) The performance/biological activity:

— Where an AM typically performs a biological function, the biological activity should be measured in a functional assay. The activity can be expressed as a specific activity. The assay should be calibrated against a recognized international standard when available, e.g. World Health Organization, and have a meaningful acceptable range defined. Where not available, biological

activity measurements should include relevant and reliable tests and the limitations of the tests well understood.

f) Biochemical properties.

g) The osmolality.

h) The pH.

10.4 Additional certificates

10.4.1 Certificate of origin

The AM supplier shall manage the supply chain of all materials and be able to provide certificates of origin, particularly for materials of animal or human origin, including serum, trypsin, milk and other biological fluids or derivatives. Details shall be included in the CoO such as the ADCF information described in 8.4.

10.4.2 Certificate of compliance

If available, the AM supplier can provide documentation to support claims of compliance to quality systems or standards.

10.4.3 Certificate of irradiation

If available, the AM supplier can provide a CoI, when applicable (for irradiated materials or other viral reduction steps, such as foetal bovine serum).

11 Managing changes to components

11.1 Impact of changes to components

There are cases in which the AM supplier needs to make changes to the AM if there is a need to ensure the quality of the cell-based therapeutic product is maintained. The need for consistency of quality of an AM is emphasized if an AM supplier:

a) changes their manufacturing process (including composition of the biological AM);

b) ceases manufacture;

c) changes the manufacturing site.

A framework for addressing changes in the AM can be found in ICH Q12.

Certain changes to the process or composition of biological AMs used at any stage during the development can impact the quality of the cellular therapeutic product. This can impact the validity of previous studies undertaken before the change.

The AM supplier shall classify the significance of each change and whether it requires notification to the AM user. For example, the regulatory frameworks in certain countries have clear change reporting categories for AMs (critical, major, minor, etc.) and not all changes are deemed reportable. Changes in biovigilance process to AMs that impact the quality, safety or efficacy of the final biological product shall be reported. The changes to be reported are generally more flexible during the development than commercialization.

11.2 Measures for managing changes to components

In the event of a change being made to AM (e.g. changes in the AM manufacturing process, composition, or container, closure system, or both), the AM supplier shall notify the AM users of such change as soon

as possible or with sufficient lead-time before changes are affected. The AM supplier and the AM user should make a quality agreement to capture this requirement.

Equally, the AM user shall identify and qualify an alternative AM supplier of the biological AM, as the preferred AM supplier can cease its manufacture. As such, the quality agreement executed by the AM user shall have a clear clause relating to continuity of supply.

The AM user shall have a suitable documentation to allow comparability studies to be carried out with a replacement or modified biological AM. The AM user should incorporate clauses into the original agreement with the AM supplier of the biological AM in question, mandating that, if changes to the manufacturing process for that AM are to occur, sufficient notice shall be given by the AM supplier of the biological AM to the AM user and the notice period required.

Annex A
(informative)

Decision chart of AMs

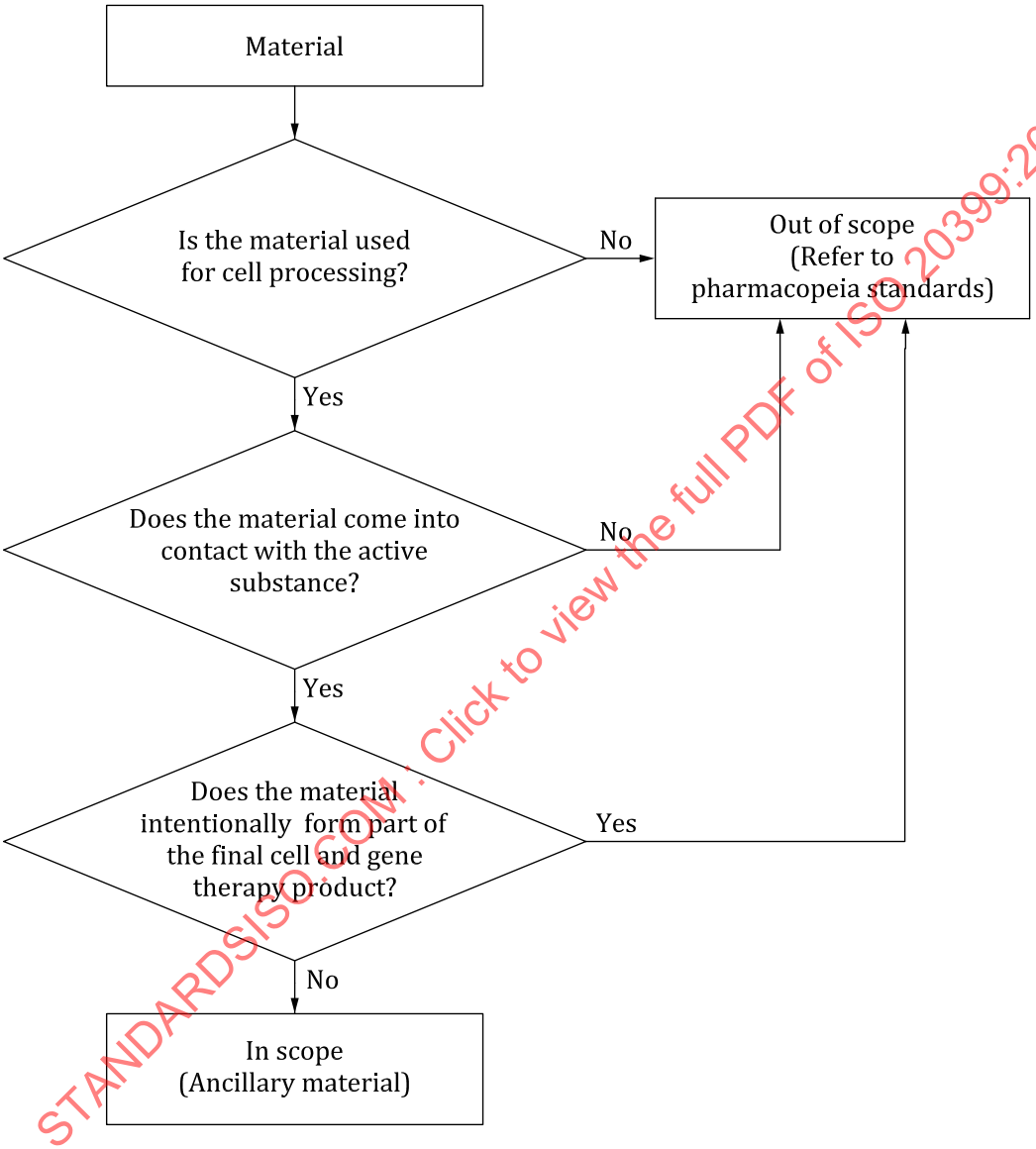


Figure A.1 — Decision chart that indicates whether or not a material is in scope of this document

For the purposes of this document, AMs include, but are not limited to, the following items:

a) reagents;

b) anticoagulants;

c) cytokines;

d) growth factors;

e) enzymes;

f) antibodies;

g) serum (human or bovine);

h) buffered solutions;

i) culture media;

j) dishes (coated with biological material);

k) beads (coated with biological material);

l) cryoprotectants (agents for cryopreservation);

m) activation agents/reagents.

n) non-mammalian cell, (e.g. insect cell, bacterial cell);

o) plasmid;

p) viral vector.

For the purposes of this document, AMs do not include the following items:

— cells that are starting materials, intermediates or final form of a cellular therapeutic product;

— feeder cells;

— additives used post bioprocessing;

— scaffolds;

— non-biological consumables (e.g. beads, dishes, tissue culture flasks, bags, tubing, pipettes, needles);

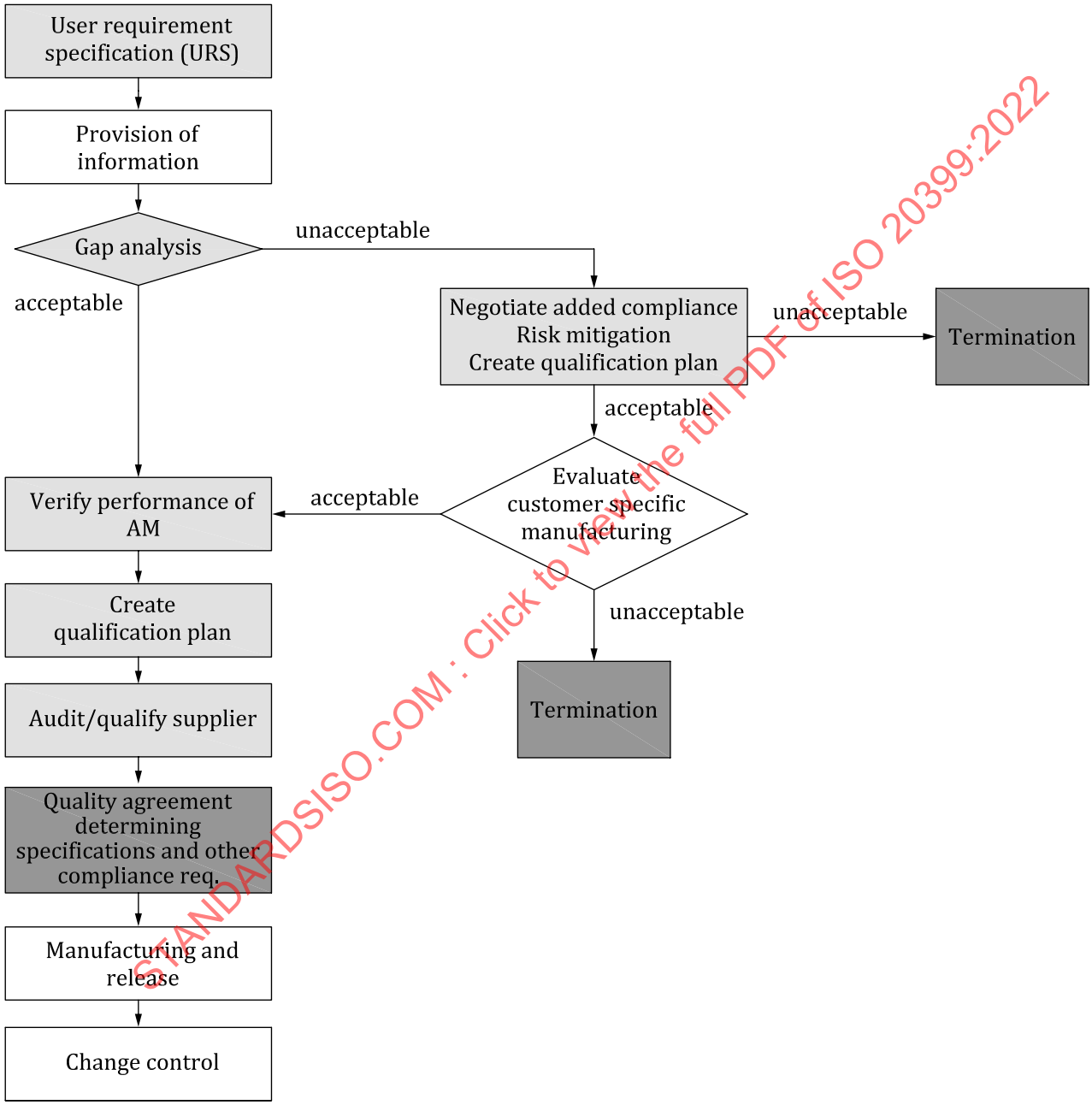
— other plasticware that come into contact with the cell or tissue;

— apparatus;

— instruments.

Annex B
(informative)

Example workflow from AM supplier to AM user



Key

- activity by AM supplier
- activity by AM user
- activity by AM supplier and AM user

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