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General requirements of tissue-engineered medical products

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Contents

Page

Foreword ..... **iv**
Introduction ..... **v**
1 Scope **1**
2 Normative references **1**
3 Terms and definitions **1**
4 General requirements for tissue-engineered medical products **4**
5 Materials **6**
5.1 General 6
5.2 Starting materials 6
5.2.1 Cells and tissues 6
5.2.2 Scaffolds and other substances 7
5.3 Ancillary materials 7
5.4 Excipients 8
6 Manufacturing process **8**
7 Characterization and control strategy **8**
8 Developmental studies **9**
9 Container closure system **9**
10 Transportation **10**
Bibliography **11**

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).

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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 150, *Implants for surgery*, Subcommittee SC 7, *Tissue-engineered medical products*.

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

Advances in the field of biological sciences have made possible the generation of a new type of medical product that when administered to the human body, may repair, replace, regenerate or enhance the function of impaired tissues or organs.

Extensive experience acquired through the administration of living human cells has yielded solid knowledge about the quality requirements and the risks associated with their use.

However, the development of tissue-engineered medical products (TEMPs) that are not simply obtained from a human donor or by separating living tissues, but rather are grown from various cell sources and are manipulated during manufacture to meet the medical needs of the patient, introduces new challenges with regard to quality requirements and risk management for the benefit of patients.

TEMPs utilizing human material are quite diverse but share a set of common quality requirements for their safe use. These kinds of products require special attention for contamination control, such as infectious agents transmitting disease (e.g. hepatitis, HIV, TSE) and harmful chemicals, unintended decomposition or degradation induced by inappropriate handling at any stage of the manufacturing process, tumorigenic potential, induction of an immunogenic reaction in the recipient, traceability of cells, critical materials, and the final product are key to product quality and its safe use.

This document has been developed with the objective of assisting interested parties, such as manufacturers and regulators, establish suitable quality parameters and specifications for the final TEMPs as well as cells, critical materials, processing steps and appropriate controls ensuring the safety of TEMPs.

General requirements of tissue-engineered medical products

1 Scope

This document specifies general requirements for tissue-engineered medical products (TEMPs), which are used in regenerative medicine. With regard to safety, this document outlines requirements for materials, manufacture, quality control, and unintentional biological effects elicited by TEMPs. This document does not address requirements for clinical trials and efficacy.

This document is not applicable to tissue-engineered products used for diagnosis, *ex-vivo* testing or extracorporeal treatments of patients (e.g. dialysis with TEMP components). TEMPs containing viable xenogenic cells, genetically modified cells, or cells derived from abnormal cells or tissues (e.g. cancerous tissues) are also excluded from the scope. The combination of TEMPs with medical devices, with the exception of scaffolds comprised of synthetic and/or naturally-derived (e.g. animal sourced) materials, is also excluded from the scope.

NOTE International, national or regional regulations or requirements, or the Pharmacopeia 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 13022, *Medical products containing viable human cells — Application of risk management and requirements for processing practices*

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

ISO/TS 20399-2, *Biotechnology — Ancillary materials present during the production of cellular therapeutic products — Part 2: Best practice guidance for ancillary material suppliers*

ISO/TS 20399-3, *Biotechnology — Ancillary materials present during the production of cellular therapeutic products — Part 3: Best practice guidance for ancillary material users*

ISO 22442-1, *Medical devices utilizing animal tissues and their derivatives — Part 1: Application of risk management*

ISO 22442-2, *Medical devices utilizing animal tissues and their derivatives — Part 2: Controls on sourcing, collection and handling*

ISO 22442-3, *Medical devices utilizing animal tissues and their derivatives — Part 3: Validation of the elimination and/or inactivation of viruses and transmissible spongiform encephalopathy (TSE) agents*

ISO/TR 22442-4, *Medical devices utilizing animal tissues and their derivatives — Part 4: Principles for elimination and/or inactivation of transmissible spongiform encephalopathy (TSE) agents and validation assays for those processes*

3 Terms and definitions

For the purposes of this document, the following terms and definitions 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/

3.1
active substance
substance comprised of manipulated cells, engineered tissues and/or other materials in the finished TEMP which has biological activity for its intended use

3.2
allogenic
cells, tissues, and organs in which the donor and recipient are genetically separate individuals of the same species

[SOURCE: ASTM F2312-11:2020, Clause 4, modified — alternative terms have been removed.]

3.3
autologous
cells, tissues, and organs in which the donor and recipient is the same individual

[SOURCE: ASTM F2312-11:2020, Clause 4, modified — alternative terms have been removed.]

3.4
bioactive agent
agent (e.g. peptide or protein) produced by (and purified from) naturally occurring or recombinant organisms, tissues or cell lines or synthetic analogs of such molecules

3.5
cellular therapeutic product
administration of cells to repair, modify or regenerate the recipient's cells, tissues, and organs or their structure and function, or both

[SOURCE: ASTM F2312-11:2010, Clause 4, modified — term has been modified from "cell therapy".]

3.5.1
cell line
progeny of a primary culture after the first subculture

Note 1 to entry: A cell line may be finite or continuous.

3.6
excipient
material that is present in the *TEMP* (3.18) administered to a patient, other than the active substance(s)

EXAMPLE Cryopreservation components.

3.7
finished TEMP
final formulated TEMP in its immediate container closure

3.8
genetically modified
having an altered or modified genetic material

[SOURCE: ASTM F2312-11:2020, Clause 4]

3.9
lifespan
period during which something exists

[SOURCE: ISO 19108:2002, 4.1.21]

3.10
medical device
instrument, apparatus, implement, machine, appliance, implant, reagent for *in vitro* use, software, material or other similar or related article, intended by the manufacturer to be used, alone or in combination, for human beings, for one or more of the specific medical purpose(s) of:

— diagnosis, prevention, monitoring, treatment or alleviation of disease;

— diagnosis, monitoring, treatment, alleviation of or compensation for an injury;

— investigation, replacement, modification, or support of the anatomy or of a physiological process;

— supporting or sustaining life;

— control of conception;

— disinfection of medical devices;

— providing information by means of *in vitro* examination of specimens derived from the human body; and

— does not achieve its primary intended action by pharmacological, immunological or metabolic means, in or on the human body, but which can be assisted in its intended function by such means

[SOURCE: ISO/IEC Guide 63:2019, 3.7]

3.11
medical product
medicinal product (drug), biological product, medical device or a combination of these

[SOURCE: ISO 13022:2012, 3.4]

3.12
ancillary material
AM
material that comes into contact with the TEMP during manufacturing, but is not intended to be part of the final product formulation

Note 1 to entry: AMs exclude non-biological consumables (e.g. tissue culture flasks, bags, tubing, pipettes, needles) and other plasticware that comes into contact with the TEMP or its components, but include consumables which have a biological component (e.g. coated dishes or beads).

Note 2 to entry: AMs exclude cells (e.g. feeder cells).

Note 3 to entry: In some cases, AM is described as raw material.

[SOURCE: ISO/TS 20399-1:2018, 3.1]

3.13
regenerative medicine
process of repairing, replacing, or regenerating human cells, tissues or organs to restore or establish normal function

[SOURCE: PAS 84:2012, 2.266]

3.14
scaffold
support or structural component or delivery vehicle, or matrix, consisting of synthetic and/or naturally-derived material(s), for modulating the biological properties (including, but not limited to, adhesion, migration, proliferation, differentiation) or transport of administered and/or endogenous cells and/or binding/transport of bioactive agents

[SOURCE: ASTM F2312-11:2020, Clause 4]

3.15
starting material
cells, tissues and/or additional substances, e.g. scaffolds, biomaterials, bioactive agents, which constitute the intended integral components of a TEMP

3.16
tissue
aggregation of specialized cells united in the performance of one or more particular function(s)

[SOURCE: ASTM F2312-11:2020, Clause 4]

3.17
tissue engineering
discipline that combines the principles of engineering and biology to obtain biological substitutes intended to regenerate, replace, modify, repair, or restore the function of tissues and organs

3.18
tissue-engineered medical product
TEMP
medical product consisting of manipulated cells and/or engineered tissues, with or without a synthetic and/or naturally-derived scaffold, that repairs, modifies, replaces, restores, or regenerates the recipient's cells, tissues, or organs or their structure and function, or both

[SOURCE: ASTM F2312-11:2020, Clause 4]

3.19
xenogenic
cells, tissues, and organs in which the donor and recipient belong to different species

[SOURCE: ASTM F2312-11:2020, modified — alternative terms have been removed.]

3.20
validation
confirmation, through the provision of objective evidence, that the requirements for a specific intended use or application have been fulfilled

Note 1 to entry: The objective evidence needed for a validation is the result of a test or other form of determination such as performing alternative calculations or reviewing documents.

Note 2 to entry: The word "validated" is used to designate the corresponding status.

Note 3 to entry: The use conditions for validation can be real or simulated.

[SOURCE: ISO 9000:2015, 3.8.13]

4 General requirements for tissue-engineered medical products

A TEMP may contain manipulated cells and/or engineered tissues, with or without a synthetic and/or naturally-derived scaffold as defined in 3.14. The quality control of any components and the finished TEMP shall be performed at the manufacturing processes and entire lifespan. The following aspects should be considered when defining the critical quality parameters for TEMPs and are discussed in further detail in this document:

— The presence of adventitious agents shall be minimized.

— The presence of deleterious excipients shall be minimized.

— The TEMP manufacturing process shall be adequately controlled and validated.

— Any necessary cell manipulation shall be assessed for tumorigenic potential.

— Materials that can cause severe harm to the patient by eliciting an immunogenic reaction should be excluded.

— The traceability of cells, critical materials and the final product is key to product quality and safe use of the TEMP.

— The TEMP shall elicit the intended therapeutic effect.

Due to the complex nature of TEMPs, a risk-based approach should be applied to determine the extent of manufacturing information, non-clinical and clinical data to be included in the technical documentation relating to the quality control, safety, and efficacy of the TEMP when used as intended.

NOTE Non-clinical data encompasses specifically both pre-clinical (animal) and *in vitro* data.

The risk management should be conducted according to ISO 13022:2012, Clause 4 and shall cover the entire development of the TEMP. Risk factors to be considered include, but are not limited to, the cell origin (autologous vs. allogenic) and cell type (e.g. primary cells or cell lines) and extent of their processing, the ability of the cells to proliferate and/or differentiate, the ability of the TEMP to initiate and sustain an immune response, the combination of cells with bioactive agents and/or structural materials (e.g. scaffold materials), the mode of administration and intended use, and the origin and quality (e.g. purity) of process materials. Relevant experience (i.e. available non-clinical and clinical data) with other similar types of TEMPs can also be considered in the risk analysis.

A description of the traceability system that the marketing authorization holder, sponsor and/or investigator intends to establish and maintain shall be provided. The finished TEMP and its starting materials, excipients, and ancillary materials, including all substances coming into contact with the active substance(s), should be traceable through sourcing, manufacturing, packaging, storage, transport, and delivery to the clinical site where the product is administered.

Also refer to ISO 13022:2012, Annex I. In the processing of TEMPs, reduction of the potential for intrinsic and extrinsic contamination of the finished TEMP should be considered.

A description of the chemical and physical characteristics and functional performance of the TEMP and a description of the TEMP manufacturing methods shall be provided. The interaction and compatibility between cells and/or tissues and the structural components as well as the interaction and compatibility between the TEMP and host tissue, i.e. biocompatibility, shall be described.

Figure 1 shows a graphic representation of the risk management process for TEMPs.

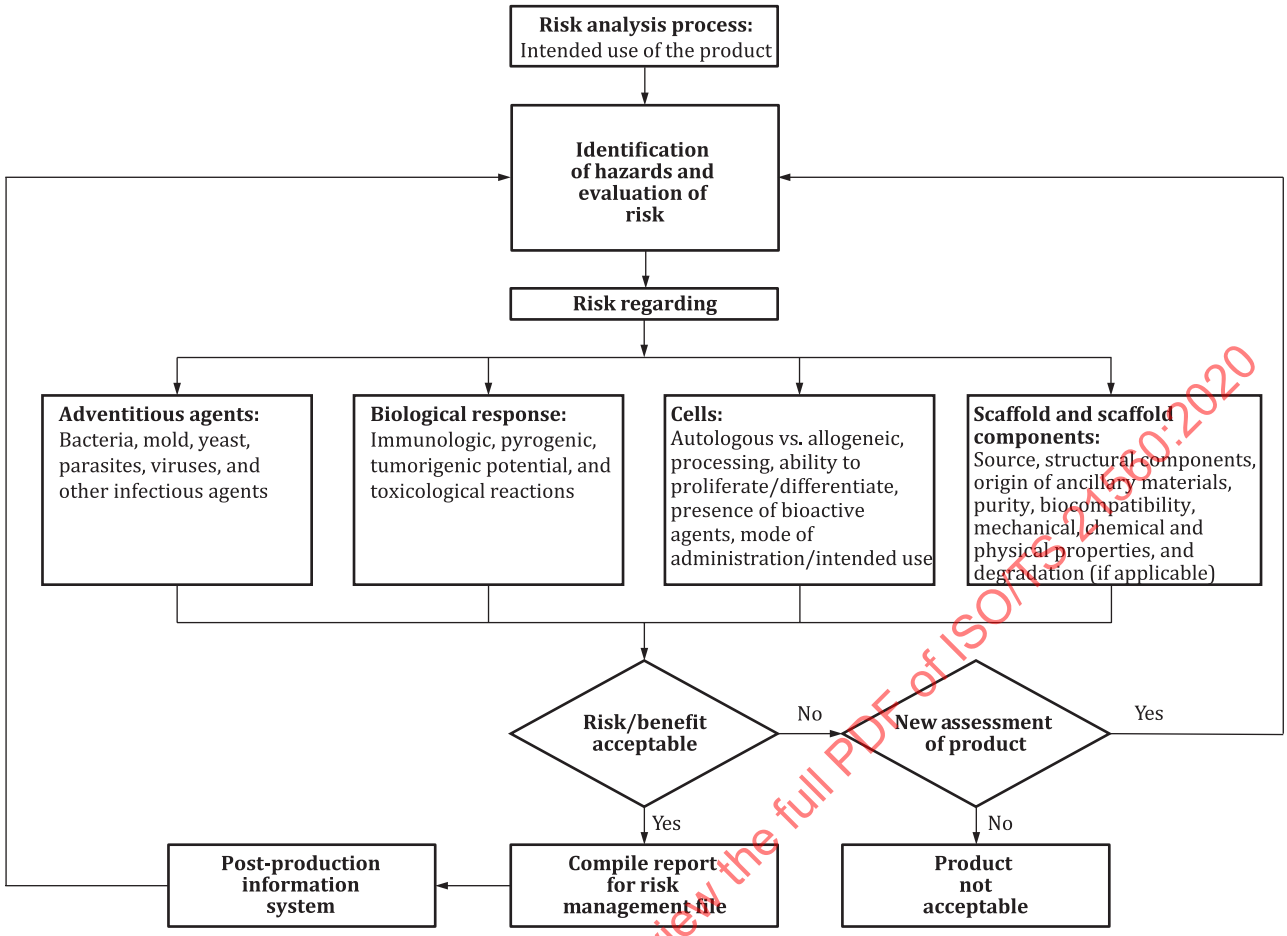

Figure 1 — Graphic representation of the risk management process for TEMPs (adapted and modified from ISO 13022:2012, Annex B)

5 Materials

5.1 General

For all materials used in the manufacturing of TEMPs, including starting materials, ancillary materials, and excipients, the acceptance criteria shall be defined for their suitability for their intended use and shall be evaluated through risk-based assessments prior to use. For all materials derived from human and animal origin, the stringent sourcing requirements shall be also adequately defined according to their intended use and shall be in compliance with ISO 13022 and ISO 22442-2.

5.2 Starting materials

5.2.1 Cells and tissues

Cells used for TEMPs may include primary cells or cells lines.

For cells or tissues of autologous or allogenic origin, summary information shall be provided on donor qualification (e.g. screening and testing), donation, procurement, tissue origin and cell type, and precautions taken to prevent the spread of the transmissible agents. Pooling of cells from different donors shall be justified, and the risk analysis shall address the possibility that the pooling of allogenic cell populations may increase the risk of undesired immunological responses in the recipient as well as transmission of infectious agents. If it is necessary to pool cells from different donors, the pooling strategies and measures to ensure traceability shall be described.

A master cell bank (MCB) and working cell bank (WCB) may be established for the manufacture of TEMPs. For cells obtained from a well-defined cell-banking system, summary information shall be provided on the history, source, derivation, materials used during derivation, culture and storage, and their characterization.

The characterization and testing of cells include, but are not limited to, cell count, viability, identity (e.g. phenotype, genotype or other markers), purity (e.g. identification and qualification of contaminating cells), adventitious agents (e.g. microbial, mycoplasma, virus, and prion), endotoxins, potency (e.g. relevant activity, cell maturation), karyology, tumorigenicity and suitability for the intended use. The genetic and phenotypic stability of the cells should also be demonstrated.

NOTE 1 Cellular therapeutic product technologies can be applied in tissue engineering to generate TEMPs.

NOTE 2 The requirements of ISO 13022 (section 4 and Annexes) apply for the human cellular part of the product.

NOTE 3 The requirements of ISO 20387 (all parts) apply for biobanking.

5.2.2 Scaffolds and other substances

Scaffolds and other substances, such as bioactive agents, that are used to construct or constitute engineered tissues or that are combined with cells to form the final formulated TEMP shall be considered starting materials.

For scaffolds, summary information on the safety, suitability, and biocompatibility shall be provided. The physical, mechanical, chemical, degradation (as applicable), and biological properties of the scaffold shall be taken into account. The testing regimen of scaffolds shall also be described and justified. For scaffolds that fall under the definition of a medical device, biocompatibility should be conducted in accordance with ISO 10993-1.

For other substances, such as bioactive agents and chemical substances used as a starting material, information on the origin, manufacturing, grade, safety, purity, potency, and suitability for the TEMP shall be provided. The chemical and biological properties or activities (e.g. the effects on the cells or tissues) shall be taken into account. The testing regimen shall concentrate on the aforementioned parameters. For those agents that are not approved or regulated as drugs or biologics, pre-clinical data should be taken into account and the interaction with cells and/or tissues and any *in vivo* effects should be studied.

NOTE The use of an approved drug is recommended, if applicable.

For animal-derived substances, e.g. scaffold, information on the source of animals (such as geographical origin, animal husbandry, age), specific acceptance criteria, measures to prevent and monitor infections in the source/donor animals, testing of the animals for infectious agents, including vertically transmitted microorganisms and viruses, and evidence of the suitability of the animal facilities shall be provided. Additionally, the viral safety shall be considered in the risk assessment and shall be in compliance with the ISO 22442-3.

5.3 Ancillary materials

Ancillary materials as defined in 3.12 are materials used during the manufacturing process for the purposes of cellular growth, differentiation, selection, maturation, or other critical manufacturing steps. Examples include culture media, additives (e.g. fetal bovine serum, growth factors, cytokines, monoclonal antibodies, antibiotic), digestion enzymes (e.g. trypsin, collagenase), cell separation or purification agents. Such materials are not intended to be components of the final TEMP and are intended to be removed.

Summary information shall be provided, including the list of all the ancillary materials used in specific manufacturing steps, species origin, supplier, the quality and grade (e.g. clinical grade), manufacturing condition (e.g. GMP-manufactured) and the concentration used in the specific manufacturing steps. The testing regimen of ancillary materials shall be described and justified in terms of identity, purity,

sterility, functionality or bioactivity and absence of adventitious agents. Further, the acceptance criteria for each ancillary material shall be defined. Any materials of animal origin used as ancillary material shall be in compliance with the ISO 22442 series.

For ancillary materials presenting potential toxicities to the recipient, the acceptance criteria limits shall be defined and controlled by sensitive and quantitative assays in the manufacturing processes or in the finished TEMPs. The analysing procedures to be used shall be described and fully validated.

Relevant standards, such as ISO 20399 series shall be considered. A cellular therapeutic product(s) may be incorporated in the processing of TEMPs. As such, ancillary materials can have implications with regard to the safety and effectiveness of a cellular therapeutic product and consequently, the finished TEMP. Appropriate control of ancillary materials is determined by a risk-based approach.

5.4 Excipients

Information on excipients present in the finished TEMP shall be provided, including a list of all excipients, their source, concentration, qualification and a rationale for the use of each excipient. The interaction(s) between the cells or tissues with the excipients should be characterized. Information demonstrating that materials meet standards appropriate for their intended use shall be provided.

For excipient(s) used for the first time in a TEMP in humans or administered via a novel route of administration, full details of manufacture, characterization, and controls, with cross references to supporting safety data, both non-clinical and clinical, shall be provided. A document containing the detailed validated processes for chemical, pharmaceutical, and biological characterization shall be provided.

For each excipient, the specifications and their justifications shall be detailed. The analytical procedures shall be described and fully validated.

6 Manufacturing process

The manufacturing process shall be validated to ensure lot/batch and process consistency, proper differentiation status and functional integrity of cells, tissues, and finished TEMP throughout manufacturing and transport up to the moment of administration of the TEMP. If cells are grown directly inside or on a scaffold, information shall be provided on the validation of the cell culture process with respect to cell growth, function and integrity of the construct.

For the processing of TEMPs, one should consider reducing the potential for an increase of intrinsic contamination of the product and avoiding extrinsic contamination of the product. Starting materials for the production of TEMPs can contain contaminants not normally considered during the processing of medical devices and drug products. Special consideration for the prevention, removal or inactivation of such contaminants during processing of TEMPs can be required where indicated by process risk assessment. For the control of microbial risk during processing of cells, tissues and finished products, ISO 18362 may be referenced. Unintended decomposition or degradation of the TEMP induced by inappropriate handling at any stage of the manufacture process shall be avoided.

7 Characterization and control strategy

For each TEMP, a characterization and control strategy shall be established which should cover each step of the product manufacturing including the control for the materials used, in-process and the finished TEMP. The parameters, e.g. critical quality attributes, starting materials and other materials used, manufacturing processes, intended use, and risk evaluation shall be considered in measuring and ensuring the desired product quality.

The characterization and control of materials, including the starting materials, the ancillary materials and excipients, have been described in Clause 5. For the finished TEMP, the viability, lifespan, growth, differentiation of cells in the TEMP and the potential of the migration of cells into the surrounding tissue shall be investigated (e.g. imaging techniques such as PET scan). When applicable, the extracellular

