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Biotechnology — Bioprocessing — General requirements for the design of packaging to contain cells for therapeutic use

Biotechnologie — Bioprocédés — Exigences générales pour la conception d'emballages destinés à contenir des cellules à usage thérapeutique

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Foreword

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The procedures used to develop this document and those intended for its further maintenance are described in the ISO/IEC Directives, Part 1. In particular, the different approval criteria needed for the different types of ISO documents should be noted. This document was drafted in accordance with the editorial rules of the ISO/IEC Directives, Part 2 (see www.iso.org/directives).

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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 276, *Biotechnology*.

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

Medicinal products containing cells as active substances, which are employed in cell therapy or gene therapy, are expected to deliver novel therapeutic value to patients who are currently untreated or under-treated. These products have potential capabilities to repair, replace or regenerate tissues affected by disease or injury. Development of such products is at the forefront of scientific innovation. Therefore, manufacturers of cells for therapeutic use are expected to maintain product quality throughout the product life cycle by continuously improving their ability to process cells with advanced technology.

Cells for therapeutic use are complex products, as compared with conventional pharmaceuticals. They are produced in a variety of culture systems, such as a system in which cells are suspended in a medium, or a system in which tissue formed by cells is immersed in a medium. At the point of their administration, various methods such as surgery or infusion are applied. In addition, special attention is taken in their storage and transportation, which is not always considered in conventional pharmaceuticals. This includes the need to store products in a precisely controlled, closed environment to prevent contamination by foreign substances (viruses, bacteria, mycoplasmas, etc.) at a certain temperature, such as culture environment or at a cryogenic temperature. Even with these complexities, it is indispensable to maintain the quality of cells for therapeutic use from manufacturing to usage.

Packaging is important for cells for therapeutic use to keep their quality. Therefore, a standard for packaging to contain cells for therapeutic use is necessary. Existing standards, such as ISO 3826-1, however, do not provide information for handling cells for therapeutic use.

This document provides general requirements to design packaging intended to contain cells for therapeutic use. It provides useful information for packaging suppliers to manufacture packaging with consideration given to the specific configurations needed for cells for therapeutic use. It is also useful for packaging users when they need to consult with packaging suppliers for custom-made packaging.

This document is intended to help packaging suppliers to design and manufacture packaging in consideration of enclosing, storage, transportation, and utilization processes of cells for therapeutic use. This document is also intended to help packaging users to design and employ packaging in consideration of the above-mentioned processes.

Biotechnology — Bioprocessing — General requirements for the design of packaging to contain cells for therapeutic use

1 Scope

This document specifies general requirements and considerations for the design of packaging used to contain cells for therapeutic use.

This document is applicable to packaging intended to contain the final products of cells for therapeutic use, as well as their starting and intermediate materials.

This document does not apply to:

a) receptacles used for processing cells in manufacturing processes, e.g. cell culture flask or bag;

b) shipping containers containing packages for transportation;

c) services that utilize packages, e.g. storage services.

NOTE 1 Examples of packaging, packages and shipping containers are illustrated in Annex A.

NOTE 2 The design of packaging includes processes to ensure that the designed packaging is manufactured to a required specification through trial manufacturing, testing and implementation of quality management.

NOTE 3 International, national or regional regulations or requirements can also apply to specific topics covered in this document.

2 Normative references

There are no normative references in this document.

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
cells for therapeutic use
product containing cells as the active substance

EXAMPLE Cell therapy medicinal product, tissue engineered product.

Note 1 to entry: The term “cells” refers to cells and *tissues* (3.12) for autologous, allogeneic and xenogeneic use.

Note 2 to entry: This term includes cells as starting materials and those cultured as intermediate materials of the product.

Note 3 to entry: The term “therapeutic use” includes clinical research, hospital exemption and testing use.

Note 4 to entry: Cells for therapeutic use are often used with additional components. Furthermore, they are sometimes shipped with a pre-treatment drug, concomitant drug or coping drug.

[SOURCE: ISO 21973:2020, 3.1, modified — Notes 2 and 3 to entry modified. Note 4 to entry added.]

3.2
package
packaging (3.3) with its contents

Note 1 to entry: The term "contents" includes the following:

a) cells or a *suspension of cells* (3.11), or both;

b) buffer or medium where a) is immersed;

c) additional components, e.g. cryopreserving agent, pre-treatment drug, concomitant drug, coping drug.

Note 2 to entry: Examples of packages are illustrated in Annex A.

[SOURCE: ISO 11683:1997, 3.3, modified — Notes 1 and 2 to entry added.]

3.3
packaging
form of receptacle intended to contain *cells for therapeutic use* (3.1)

Note 1 to entry: In the field of transportation, packaging can be considered as the primary receptacle.

Note 2 to entry: Examples of packaging are illustrated in Annex A.

3.4
packaging material
material used in *primary packaging* (3.7) and *secondary packaging* (3.8)

3.5
packaging supplier
entity who either manufactures or supplies, or both, *packaging* (3.3) for the *packaging user* (3.6)

3.6
packaging user
entity who makes use of *packaging* (3.3) for *cells for therapeutic use* (3.1)

Note 1 to entry: The packaging user includes the manufacturer of cells for therapeutic use and the provider of starting material, e.g. a cell bank, blood bank, clinical site.

Note 2 to entry: The term "packaging user" excludes clinical facilities and clinical workers.

3.7
primary packaging
packaging (3.3) that comes into direct contact with *cells for therapeutic use* (3.1)

Note 1 to entry: This term can be used in the singular form or the plural form.

Note 2 to entry: Primary packaging is designed to come into direct contact with additives, substrates or preservation solutions.

Note 3 to entry: The content of cells for therapeutic use can have various compositions, which can also be in close contact with the packaging.

3.8
secondary packaging
packaging (3.3) that contains one or more *primary packaging* (3.7)

Note 1 to entry: This term can be used in the singular form or the plural form.

Note 2 to entry: Secondary packaging can have single or multiple layer(s).

3.9
shipping container
type of container intended to contain and protect *packages* (3.2) during transportation

Note 1 to entry: Examples of shipping containers are illustrated in Annex A.

Note 2 to entry: A shipping container can have functionalities such as repeated use, temperature-regulation, gas composition-regulation and traceability.

3.10
storage container
part of container intended to protect *packages* (3.2) during storage

3.11
suspension of cells
individual cells or aggregates of cells dispersed in a liquid matrix

Note 1 to entry: The liquid matrix can include viscous or gel-like matrices.

[SOURCE: ISO 20391-2:2019, 3.1.6, modified — Term changed from "cell suspension". "individual cells" replaced "single cells" in the definition. Note 1 to entry added.]

3.12
tissue
organization of cells, cells and extra-cellular constituents, or extra-cellular constituents

[SOURCE: ISO 11139:2018, 3.303]

4 General strategy for packaging design

4.1 General

Cells for therapeutic use are stored and transported within packaging from the cell-supplying site to the manufacturing site, or from the manufacturing site to another manufacturing site, storage or clinical site. The cells are in direct contact with the packaging. Table 1 summarizes the general strategy for the design of packaging for cells for therapeutic use. Table 1 shows the factors that are important when using or manufacturing packaging for cells for therapeutic use. Table 1 also provides cross-references to the requirements for packaging, packaging design and applicable test methods given in this document for each factor.

Table 1 — General strategy for the design of packaging for cells for therapeutic use

Factor	Requirement of packaging	Packaging design	Applicable test methods
Configuration of cells for therapeutic use (see 4.2)	Not applicable	6.2	Not applicable
Process of containing cells for therapeutic use in packaging (see 4.3)	5.2	6.2, 6.3, 6.4	Not applicable
Disturbances in storage and transportation including contamination (see 4.4)	5.3.1	6.2, 6.3, 6.4, 6.5	8.2
Impact on external environment when cells for therapeutic use leak from packaging (see 4.5)	5.3.2	6.2, 6.3, 6.4	8.3
Interaction between cells for therapeutic use and packaging (see 4.6)	5.3.3	6.3, 6.5	8.4
Usability of packaging in clinical facilities (see 4.7)	5.4	6.2, 6.3, 6.4	8.5
Environmental load (see 4.8)	Not applicable	6.5	Not applicable

4.2 Configuration of cells for therapeutic use

4.2.1 General

One of the significant characteristics of cells for therapeutic use is that they have various configurations. Therefore, the configuration of cells for therapeutic use shall be taken into account when designing, manufacturing and using the packaging. In this document, the configuration of cells for therapeutic use is categorized into two types: suspension of cells (see 4.2.2) and tissue (4.2.3).

4.2.2 Suspension of cells

Since cells for therapeutic use in the category "suspension of cells" are dispersed in a medium in the packaging, the methods applied to administer this type of cells to patients in clinical facilities can be intravenous infusion, injection, catheter, etc. Examples of preparation work for administration at clinical facilities include dilution and removal of the storage solution used during storage and transportation, or transfer from packaging to an administration device, or both, if not directly administered from the packaging.

NOTE Examples of clinical facilities include hospitals and authorized infusion centres.

4.2.3 Tissue

Cells for therapeutic use, which maintain their organized structures by coexisting with biomaterials such as collagen and those supported by scaffold, are included in the category "tissue".

Tissue often has a function closer to that of a living body than individual or aggregated cells dispersed in a solution, and the function is often maintained by retaining the structure that resembles the tissue from which the cells are derived. Therefore, maintaining structural integrity and cell viability during storage and transportation shall be taken into account for the packaging design.

In addition, surgical treatment is generally the method used for administering this type of the cells to patients. Therefore, either packaging selection or design, or both, shall take into account the environment in which the cells are used in clinical facilities.

NOTE Tissue can include primary as well as artificially generated tissues, such as microtissues or other *in vitro* generated tissue-like structures.

4.3 Process of containing cells for therapeutic use in packaging

A suspension of cells shall be contained in the packaging together with the dispersion medium, such as a storage solution.

Tissue shall also be contained in the packaging with the dispersion medium, so that its structure is retained to ensure its effectiveness. In addition, the containing process of tissue using a support or biomaterial such as collagen as adjunct to the cells can be performed to maintain the structure.

4.4 Disturbances in storage and transportation including contamination

Disturbances in storage and transportation including contamination affect cell quality. Therefore, protection of the cells from influential disturbances shall be taken into account when designing packaging.

NOTE Cell quality can be ensured by demonstrating that the physical, chemical, biological or microbiological properties are within an appropriate limit, range or distribution.

4.5 Impact on external environment when cells for therapeutic use leak from packaging

When either cells for therapeutic use or their related contents, or both, leak out from the packaging, it can affect one or all of the external environment, workers or quality of the contents. Therefore, avoiding leakage shall be taken into account when designing packaging.

4.6 Interaction between cells for therapeutic use and packaging

The packaging user shall be aware that either the packaging material itself or its components, or both, can affect the cell quality of cells for therapeutic use.

4.7 Usability of packaging in clinical facilities

The packaging user shall be aware that the process of using cells for therapeutic use in clinical facilities can affect cell quality.

4.8 Environmental impact

Materials and processes that have a low environmental load should be applied to manufacture packaging where possible and meaningful.

5 Design for packaging

5.1 General

This clause describes in detail the issues to be taken into account for the strategies described in Clause 4.

Based on the issues, a risk assessment should be conducted that considers the characteristics of the target cells for therapeutic use, the relationship between the cells for therapeutic use and the packaging, and the packaging itself.

5.2 Enclosing process

5.2.1 Explanation of the enclosing process

The process to enclose cells for therapeutic use in primary packaging can affect the cell quality of such cells. Therefore, an enclosing process that does not impair cell quality shall be performed, and shall

take cell characteristics into account. The packaging shall be selected by the packaging user or supplied by the packaging supplier to the packaging user, taking the enclosing process into account.

During the enclosing process of the suspension of cells, there is a risk that shear stress or air bubbles can cause functional decline or cell death. Therefore, the process condition(s) shall be adjusted to avoid excessive stress to the cells and to prevent air bubbles mixing with the suspension of cells.

NOTE When the enclosing speed is set to be excessively slow in order to avoid applying stress and forming air bubbles, the operation time increases, which can result in cell function deterioration or cell death.

5.2.2 Packaging for the enclosing process

The packaging used for containing the cells shall be suitable for the enclosing process and shall maintain the cell quality.

Requirements for packaging shall be taken into account when applying the process to contain cells for therapeutic use in the packaging. Where ready-made packaging is employed, the packaging user should evaluate its impact by taking into account both the characteristics of the cells and the types of influences applied to the cells during the enclosing process, e.g. contact of cells to the packaging material. Where undesired influences are detected, the causes of the influences shall be eliminated by tailoring the enclosing process or changing the packaging employed.

The concept of packaging differs depending on the environment in which the enclosing process is performed, e.g. contained in a closed system using aseptic joining, in isolators or safety cabinets where foreign substances are controlled, or in an open environment.

The following factors shall be taken into account in the enclosing process:

a) the type of cells for therapeutic use (cells dispersed in solution or cells retaining their structure);

b) the temperature when enclosing;

c) the atmospheric composition when enclosing;

d) the cleanliness when enclosing;

e) cross-contamination (microorganisms, other cells from another batch or another production campaign);

f) the duration from the start to the end of the enclosing process;

g) the variation in cell number when subdividing;

h) the agents used to dilute the cells.

NOTE The above items can be interrelated.

5.3 Processes from enclosing to usage

5.3.1 Disturbances that affect cells for therapeutic use

The packaging user shall identify disturbances and shall establish the critical level for each identified item that affects cell quality. Moreover, the packaging user shall use packaging with sufficient protection against the identified disturbances and their critical level.

When the packaging user provides information about disturbances, the packaging supplier shall provide the packaging user with sufficient protection based on the provided information. For cases where the packaging supplier does not receive information about disturbances from the packaging user, the conditions of the disturbances shall be estimated and packaging that has sufficient protection capability for the estimated conditions shall be supplied. For cases where the packaging supplier cannot

disclose the level for identified disturbances to the packaging user, the packaging user shall ensure the packaging protection capability.

Disturbances can include:

a) force, including:

   1) force that causes deformation;

   2) vibration;

   3) impact;

   4) shear stress;

b) light;

c) temperature, including:

   1) cryogenic temperatures below –150 °C (e.g. mechanical freezing, immersion into liquid nitrogen or coexisting nitrogen gas);

   2) cryogenic temperatures below –60 °C (e.g. mechanical, dry ice);

   3) temperature change during freezing and thawing;

   4) temperature change or uneven temperature distribution, or both, during the shipment of unfrozen cells (e.g. 37 °C);

d) contamination, including:

   1) microbes such as bacteria, fungi algae, protozoa and viruses;

   2) particulates;

   3) gas and gas exchange, or the limitation of that (e.g. carbon dioxide or oxygen);

e) delay in shipment caused by unforeseen circumstances such as, but not limited to, custom delays.

5.3.2 Leakage

The packaging shall prevent the cells for therapeutic use, including the cell preservation solution and substrates that are enclosed in the packaging, from leaking from the packaging. Any leakage can affect cell quality, and can negatively influence the external environment.

The packaging shall also prevent external liquid from leaking inside to avoid contamination.

Custom-made packaging solutions shall undergo continual improvement cycles, which shall be used to ensure that the products to be packaged determine the packaging design.

5.3.3 Interactions between cells for therapeutic use and packaging

5.3.3.1 General

The interaction between the packaging material and its components and the enclosed cells shall not affect the quality of cells for therapeutic use. It is also important that packaging shall not affect the composition of the substances (e.g. medium and substrate) that play a key role in maintaining cell quality. Therefore, the interaction between cells for therapeutic use and packaging shall be taken into account when designing packaging, including but not limited to:

a) extractables/leachables;

b) adsorption of cells to packaging surface;

c) sterility, including:

   1) sterility of packaging;

   2) sterility barrier properties of packaging;

d) endotoxin(s);

e) insoluble matter and either foreign matter or insoluble particulate, or both;

f) cytotoxicity;

g) influence of biological products;

   EXAMPLE Animal-derived material that is used as plasticizer in some plastic resins.

h) mycoplasma;

i) adsorption of the content to the packaging material;

j) gas permeability;

k) container geometry.

5.3.3.2 Adsorption to packaging

The packaging can interact with cells for therapeutic use by adsorbing the cells and components of the solution in which cells are dispersed or placed onto the inner surface of the primary packaging material.

The packaging user should check whether adsorption can affect the cell quality. If it can, the packaging user should identify the factors related to the adsorption that influence cell quality and should establish the acceptable value range for each of the identified factors before selecting or ordering the primary packaging material.

When the packaging user intends to apply a custom-made packaging, the packaging user shall provide the packaging supplier with information regarding the identified adsorption-related factors and their individual acceptable value range. The packaging supplier shall evaluate the information and notify the packaging user about whether such information is sufficient for manufacturing the requested packaging. If the information is not sufficient, the packaging supplier and the packaging user shall discuss and determine whether additional information needs to be provided by the packaging user to the packaging supplier.

5.3.3.3 Other types of interactions

In addition to adsorption, the packaging can interact with cells for therapeutic use through the factors listed in 5.3.3.1.

The packaging user should check whether these factors can affect the cell quality. If they can, the packaging user should identify the factors that influence cell quality and should establish the acceptable value range for each of the identified factors before selecting or ordering the primary packaging material.

When the packaging user intends to apply a custom-made packaging, the packaging user shall provide the packaging supplier with information regarding the identified factors and their individual acceptable value range. The packaging supplier shall evaluate the information and notify the packaging user about whether such information is sufficient for manufacturing the packaging. If the information is not sufficient, the packaging supplier and the packaging user shall discuss and determine additional information that shall be provided by the packaging user to the packaging supplier.

5.4 Usage

The packaging should be compatible with either the method or process flow, or both, of the operation performed on the cells for therapeutic use in the clinical facility and manufacturing facility.

The packaging should be useable in the processes of work in the clinical facility and manufacturing facility so that it does not affect the following elements:

a) The cell quality.

b) The external environment (e.g. workers), as follows:

   1) The packaging user should apply the packaging, which has sufficient usability so that storage, transportation and operation in clinical facilities do not affect the cell quality of the cells and the external environment.

   2) The packaging supplier shall supply the packaging user with packaging that has the usability required by the packaging user. If the packaging supplier does not receive usability information from the packaging user, the packaging supplier should estimate the usability and manufacture the packaging based on the estimation.

c) The operating environment and situation, as follows:

   1) General:

      i) Packaging should be considered for the environment and situation in which cells for therapeutic use are administered.

   2) Opening method and location:

      i) Packaging should be considered for the flow of operation performed from the package reception to the package opening in manufacturing plants or clinical facilities, taking into account the work environment.

      ii) Packaging should be disinfected or decontaminated easily, considering the risk of contamination depending on the environment when opening the packaging. In addition, packaging should be considered for safety of workers who perform opening work in manufacturing plants and clinical facilities.

      NOTE 1 There is a special need to consider safety of workers when manipulating packaging for infectious samples.

      iii) In order to protect the quality and safety of the product as well as workers, packaging shall not permit the egress of product or ingress from the external environment under expected shipment and storage conditions.

   3) Conditions of storage or thawing, or both:

      i) Where cells for therapeutic use require freezing and thawing, packaging should be taken into account for the freeze–thaw process.

      ii) Packaging should allow the change in the temperature of its contents as uniformly as possible (e.g. upper part versus lower part of the packaging) during the freeze–thaw process in order to attain consistency of the performance of the cells enclosed.

iii) Packaging should allow appropriate thawing characteristics (e.g. rate, uniformity) to enable optimal functionality of the thawed product.

d) The number of cells remaining in the package, as follows:

1) Packaging should be designed to minimize the number of remaining cells when the cells are removed from the package, to prevent a reduction in cell numbers during subsequent manufacturing steps or administration.

e) The identifiability, as follows:

1) Packaging shall be designed to have sufficient size and shape to provide identification for the dedicated purpose.

NOTE 2 There are many ways to add identification information, e.g. label, barcode, integrated circuit (IC) chip.

f) The visibility, as follows:

1) Where a visual inspection of the enclosed cells is required, the packaging shall have transparency so that contaminants in the packaging substrate and storage solution can be confirmed. Whether the package is wholly or partially transparent depends on the manufacturer's requirements.

g) The container orientation stability, as follows:

1) Packaging shall be designed to maintain the desired orientation and prevent spillage of cells for therapeutic use during the process of removing.

NOTE 3 Orientation stability can be necessary when tissue is taken out from the package and applied to the patient.

6 Implementing packaging design

6.1 General

Packaging shall be designed based on the strategies, requirements and considerations described in Clauses 4 and 5.

Packaging shall be designed taking into account the shape (see 6.2), layers (see 6.3), ports (see 6.4) and packaging materials (see 6.5).

6.2 Shape

The shape of the packaging is an important factor to maintain the performance of the cells for therapeutic use. When the packaging shape is not suitable for the enclosed cells, the disturbances listed in 5.3.1 a) can affect the cells during storage and transportation. The shape of the packaging should be determined by taking into account the following factors during storage, transportation and reconditioning (e.g. washing, medium change, mixing, thawing):

a) the outer dimension of the shipping container, the storage container, or the equipment and container for freezing, thawing and storage, or combination of them, as applicable;

b) the inner dimension of the shipping container, the storage container, or the equipment and container for freezing, thawing and storage, or combination of them, as applicable;

c) the number of packages that can be placed in the shipping container, the storage container, or the equipment and container for freezing, thawing and storage, or combination of them, as applicable.

In addition, the handling efficiency during storage and transportation should be taken into account.

6.3 Layers

Packaging design should be optimized by taking the factors described in 4.2 to 4.8 into account so that the cell qualities of the enclosed cells for therapeutic use are not affected. Therefore, in order to protect the cells for therapeutic use from the affecting factors, the packaging structure shall be determined in terms of layer(s). The packaging structure can be designed as single-layered primary packaging or a multi-layered structure composed of two or more layers including secondary packaging, providing the cell quality is not affected. Primary packaging is especially important for the cell quality because it is in direct contact with the contents. Where the packaged cells need to retain their structure, support for maintaining their structure can be introduced in the primary packaging.

6.4 Ports

For a suspension of cells, the packaging shall have one or more ports as part of its structure, taking into account the reduction of disturbances that affect cells for therapeutic use (see 5.3.1), the inhibition of leakage during storing and transportation (see 5.3.2), the operating environment, and the situation for both enclosing and use (see 5.4). Examples for the use of the ports include, but are not limited to:

a) a sterile connection when a sterile connection device is used;

b) a filtered vent to keep the pressure for removal of the cells for therapeutic use by injection;

c) the addition of diluted solution keeping cleanliness.

6.5 Packaging materials

Packaging materials shall be selected to reduce the disturbances described in 5.3.1 and the interactions with cells for therapeutic use described in 5.3.3. Where the packaging is composed of only a single material, it is easier to predict the impact on the cells for therapeutic use. When the packaging materials are made of plastic, the influence of the materials on the cells for therapeutic use shall be taken into account.

The environmental impact of the packaging materials should be taken into account throughout the entire life cycle, including use and disposal processes.

Examples of perspectives to take into account include, but are not limited to:

a) procurement of sustainable packaging materials;

b) application of easily recyclable single materials (mono-materials);

c) reduction of carbon dioxide and similar environmentally damaging gas emissions throughout the life cycle of the packaging manufacturing process, use and disposal.

6.6 Communication between packaging supplier and packaging user

The general approach for the packaging supplier and the packaging user to determine the packaging for the intended purpose should be as follows:

a) the packaging supplier produces ready-made packaging that fulfils the requirements given in Clause 5 according to their knowledge on the types of cells for therapeutic use;

b) the packaging user selects the appropriate packaging for the intended purpose from the ready-made packaging;

c) if there is no appropriate ready-made packaging, the packaging user clarifies the user-requirement specification and asks the packaging supplier to supply custom-made packaging;

The packaging supplier shall design custom-made packaging based on the packaging user's requirements.

7 Quality management

The packaging shall be designed so that a quality management system (QMS) can be implemented during the manufacture of such packaging.

NOTE ISO 9001 and ISO 13485 are examples of relevant QMS standards.

In order to apply a packaging fitting for the cells for therapeutic use, the packaging user shall be aware of, and be updated when available on, the factors described in 4.2 to 4.8 that can affect cells for therapeutic use and the measures that are used to preserve their stability and performance, including the preservation solution and the support board.

8 Examples of test methods

8.1 General

Test methods for packaging to evaluate the requirements described in Clause 5 are listed in 8.2 to 8.5. The following methods can be used to perform the tests required for intended purpose.

8.2 Test methods related to disturbance

Prevention of contamination:

— ISO 291

8.3 Test methods related to leakage

8.3.1 Liquid leak from packaging:

— ISO 291

8.3.2 ISO 3826-1:2019, external force:

— ISO 291

— ISO 2248

8.4 Test methods related to interaction between cells for therapeutic use and packaging

8.4.1 Ensuring sterility:

— ISO 11135

— ISO 11137-1:2006, ISO 11137-1:2006/Amd.1:2013, ISO 11137-1:2006/Amd.2:2018

— ISO 17665-1

8.4.2 Endotoxin:

— ISO 3826-1

— ISO 8536-4

— European Pharmacopoeia, 10th Edition[23]: 2.6.14. *Bacterial Endotoxins*

— US Pharmacopeia, 43rd Edition[24]: <85> *Bacterial Endotoxins Test*

— Japanese Pharmacopoeia, 17th Edition[25]: 4.01 *Bacterial Endotoxins Test*

NOTE The above-listed pharmacopeias provide test methods for endotoxins. Current good manufacturing processes (cGMPs) do not necessarily provide concrete test methods.

8.4.3 Insoluble matter and either foreign matter or insoluble particulate, or both:

— ICH Q4B Annex 3[22]

— European Pharmacopoeia: 10th Edition[23]: 2.9.19. *Particulate contamination: sub-visible particles*

— US Pharmacopeia, 43rd Edition[24]: <788> *Particulate Matter in Injections*

— Japanese Pharmacopoeia, 17th Edition[25]: 6.06 *Foreign Insoluble Matter Test for Injections*

8.4.4 Extractables and leachables:

— ISO 10993-18

— European Pharmacopoeia, 10th Edition[23]: 3.2.2 *Plastic Containers and Closures for Pharmaceutical Use*, Supplement 6.6 Dissolution Test for Solid Dosage Forms

— US Pharmacopeia, 43rd Edition[24]: <1> *Injections "Volume in Containers"*; <1663> *Assessment of Extractables Associated with Pharmaceutical Packaging/Delivery Systems;* <1664> *Assessment of Drug Product Leachables Associated with Pharmaceutical Packaging/Delivery Systems*

— Japanese Pharmacopoeia, 17th Edition[25]: 6.05 *Test for Extractable Volume of Parenteral Preparations*

8.4.5 Cytotoxicity:

— ISO 10993-5

8.4.6 Mycoplasma:

— European Pharmacopoeia, 10th Edition[23]: 2.6.2. *Mycobacteria*

— US Pharmacopeia, 43rd Edition[24]: <63> *Mycoplasma Tests*

— Japanese Pharmacopoeia, 17th Edition[25]: *General Information, Mycoplasma Testing for Cell Substrates used for the Production of Biotechnological/Biological Products*

8.5 Other test methods

8.5.1 Transparency:

— ISO 3826-1

— European Pharmacopoeia, 10th Edition[23]

— US Pharmacopeia, 43 Edition[24]

— Japanese Pharmacopoeia, 17th Edition[25]: 7.02 Test Methods for Plastic Containers 1.4. Transparency test

8.5.2 Water vapour and gas permeability:

— European Pharmacopoeia, 10th Edition[23]: 3.1.6 Polypropylene for Containers and Closures for Parenteral/Ophthalmic

— US Pharmacopeia, 43rd Edition[24]: <671> *Containers — Performance Testing for Plastic Containers*

— Japanese Pharmacopoeia, 17th Edition[25]: 7.02 *Test Methods for Plastic Containers*

8.5.3 Period of self-standing:

— The packaging does not collapse when placed against the horizontal plane.

8.5.4 Strength of protective cover for the area of administration (if applicable):

— The packaging shall be placed lid side up and the heat seal and wire are attached to the grips of the tension tester. A tensile load shall be applied until the lid is completely removed from the container, and the load and the amount of movement during this time is measured. An example of protective cover is illustrated as a cap in Figure A.1, a) "packaging".

8.5.5 Other physiochemical properties:

— ISO 10993-19