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

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Contents

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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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~~". "single cells" changed to~~". "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 ~~cell~~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, and transfer from packaging to an administration device if not directly administered from the packaging.

NOTE Examples of clinical facilities include hospitals and authorized infusion ~~centers~~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.

