TECHNICAL SPECIFICATION

ISO/TS 23565

First edition
2021-10

Biotechnology — Bioprocessing — General requirements and considerations for equipment systems used in the manufacturing of cells for therapeutic use

Biotechnologie — Bioprocédés — Exigences et considérations générales pour les systèmes d'équipement utilisés dans la fabrication de cellules à usage thérapeutique

Reference number
ISO/TS 23565:2021(E)

ISO copyright office
CP 401 • Ch. de Blandonnet 8
CH-1214 Vernier, Geneva
Phone: +41 22 749 01 11
Email: copyright@iso.org
Website: www.iso.org

Published in Switzerland

Contents

Page

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.*

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.

Biotechnology — Bioprocessing — General requirements and considerations for equipment systems used in the manufacturing of cells for therapeutic use

1 Scope

This document specifies minimum requirements and general considerations for equipment, consisting of hardware, software and consumables, used in the manufacturing of cells for therapeutic use. This includes equipment for processing cells for therapeutic use starting from cell isolation/selection, expansion, washing and volume reduction, from cell finish through to cryopreservation for the storage of cells for therapeutic use.

This document gives guidance on the design, use and maintenance of equipment and equipment systems to both suppliers and users from aspects including the target parties, i.e. supplier or user, and phase of involved task, i.e. design, use or maintenance.

This document is applicable to any unit operation system that is used, alone or in combination, for the manufacturing of cells for therapeutic use, meeting user requirements. It is applicable to devices used for the purpose of monitoring equipment status.

It does not apply to:

— processing equipment for cells for therapeutic use used at the point of care;

— devices used for analytical purposes;

— biosafety cabinets, general cell culture equipment (such as CO_2 incubators, etc.), and software to control multiple equipment systems or multiple unit operations.

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 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
batch
quantity of material regarded as a single unit, and having a unique reference

Note 1 to entry: Batch is primarily a processing term.

[SOURCE: ISO 15270:2008, 3.3]

3.2
cells for therapeutic use
product containing cells as the active substance

EXAMPLE A cell therapy medicinal product (allogenic, autologous, somatic, genetically modified), tissue engineered product.

Note 1 to entry: For the purpose of this document, "cells" mean human cells and tissues of autologous as well as allogeneic.

[SOURCE: ISO 21973:2020, 3.1, modified — The example has been replaced. Notes 2 and 3 to entry have been deleted.]

3.3
consumable
tubing, filter, culture vessel, bag or bottle used to transfer, culture or act as a container for the biologics or another consumable used in the production of *cells for therapeutic use* (3.2)

3.4
corrective action
action to eliminate the cause of a nonconformity and to prevent recurrence

Note 1 to entry: There can be more than one cause for a nonconformity.

Note 2 to entry: Corrective action is taken to prevent recurrence whereas *preventive action* (3.15) is taken to prevent occurrence.

[SOURCE: ISO 9000:2015, 3.12.2, modified — Note 3 to entry has been deleted.]

3.5
critical quality attribute
CQA
physical, chemical, biological or microbiological property or characteristic that is within an appropriate limit, range or distribution to ensure the desired quality and consistency of a cellular therapeutic product

Note 1 to entry: CQA is generally related to the clinical efficacy and safety of the product.

3.6
equipment
device or machine that performs a specific field operation

[SOURCE: ISO 11783-1:2017, 3.20, modified — Note 1 to entry has been deleted.]

3.7
equipment system
set of *equipment* (3.6) that act together in a common purpose of producing *cells for therapeutic use* (3.2)

3.8
impurity
constituent of the product not intended to be part of the final formulation

3.9
installation qualification
IQ
process of establishing by objective evidence that all key aspects of the process *equipment* (3.6) and ancillary system installation comply with the approved equipment specification

[SOURCE: ISO 11139:2018, 3.220.2, modified — "approved equipment specification" has replaced "approved specification".]

3.10
line clearance
removal (line purge) of everything associated with the prior production run

[SOURCE: ISO 15378:2017, 3.5.4, modified — Note 1 to entry has been deleted.]

3.11
lot
unit of production that, as far as practicable, consists of production units of a single type, class, size and composition, manufactured under the same conditions, and at substantially the same time

[SOURCE: ISO 24408:2005, 3.1]

3.12
monitoring
continuous or repeated checking, supervising, critically observing, measuring or determining the status of a system to identify variance from an expected performance level or baseline, intended to control the system

3.13
operational qualification
OQ
process of obtaining and documenting evidence that installed *equipment* (3.6) operates within predetermined limits when used in accordance with its operational procedures

[SOURCE: ISO 11139:2018, 3.220.3]

3.14
performance qualification
PQ
process of establishing by objective evidence that the process, under anticipated conditions, consistently produces a product which meets all the required product specifications

[SOURCE: ISO 11139:2018, 3.220.4, modified — “all the required product specifications” has replaced “all predetermined requirements”.]

3.15
preventive action
action to eliminate the cause of a potential nonconformity or other potential undesirable situation

Note 1 to entry: There can be more than one cause for a potential nonconformity.

Note 2 to entry: Preventive action is taken to prevent occurrence whereas *corrective action* (3.4) is taken to prevent recurrence.

[SOURCE: ISO 9000:2015, 3.12.1]

3.16
quality by design
QbD
systematic approach to development that begins with predefined objectives and emphasizes product and process understanding and process control, employing statistical, analytical and risk-management methodology in the design, development and manufacture of goods

3.17
risk-based approach
methodology that allows to prioritize activities based on a previous analysis of data

3.18
shelf life
specific time for which a product can be stored under recommended conditions and can maintain acceptable product quality

3.19
software
all or part of the programs, procedures, rules, and associated documentation of an information processing system

[SOURCE: ISO/IEC 2382:2015, 2121278, modified — Notes 1 to 3 to entry have been deleted.]

3.20
stability
characteristic of a material, when stored under specified conditions, to maintain a value(s) for stated property(ies) within specified limits for a specified period of time

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

3.21
sterility
state of being free from viable microorganisms

Note 1 to entry: In practice, no such absolute statement regarding the absence of microorganisms can be proven.

[SOURCE: ISO 11139:2018, 3.274]

3.22
supplier
entity who manufactures cell processing *equipment* (3.6) for a *user* (3.25)

3.23
toxicity
ability of a substance to produce an adverse effect upon a living organism

[SOURCE: ISO 472:2013, 2.767]

3.24
unit operation
defined part of a manufacturing process

[SOURCE: ISO 11139:2018, 3.309]

3.25
user
sponsor
therapeutic manufacturer
entity who makes use of cell processing *equipment* (3.6) for the manufacturing of *cells for therapeutic use* (3.2)

3.26
validation
confirmation, through the provision of objective evidence, that the requirements for a specific intended use or application have been fulfilled

[SOURCE: ISO 9000:2015, 3.8.13, modified — Notes 1 to 3 to entry have been deleted.]

4 General considerations

4.1 General

This document specifies minimum requirements and general considerations for equipment and equipment systems, used in the manufacturing of cells for therapeutic use. There are regulatory

guidance documents available for cell processing equipment. Documents on bioprocessing equipment used in biologics manufacturing are also available (see the Bibliography for examples).

NOTE In this document, the subject of a sentence that contains requirement(s) related to the supplier or the user, or both, of an equipment is the equipment itself. The subject of a sentence that contains requirement(s) related only to the supplier of an equipment is the supplier. The subject of a sentence that contains requirement(s) related only to the user of an equipment is the user.

In the manufacturing of cells for therapeutic use, various types of equipment systems are used for:

a) cell harvest or cell collection;

b) cell extraction or cell purification (e.g. centrifuge, biosafety cabinet);

c) cell cultivation or cell expansion or cell differentiation (e.g. bioreactors);

d) cell washing and volume reduction (e.g. automated washing devices);

e) final formulation or fill or finish;

f) cell storage (e.g. programmed freezer).

Equipment systems for manufacturing cells for therapeutic use generally comprise three distinct components that entail different approaches to quality assurance and risk management: hardware, software and consumables. A high level of assessment should encompass the whole equipment system as the sum of the individual components and together with the implications of upstream and downstream processes for the complete workflow.

Hardware and software should be qualified. Associated processes should be validated. The impact of the hardware to the cell product quality, as well as to the clean room environment, if applicable, should be assessed.

Software should be validated. A system should be in place to ensure accessibility control, traceability, data integrity and storage.

Consumables are important to ensure safety. As cellular products cannot be sterilized at the end of the production, they are produced under aseptic conditions. Equipment that utilizes single-use consumables such as tubing and collection bags should be used, as this can allow for processing to be performed in a lower-grade clean room space on a risk-based approach.

Where open processing steps are performed, a suitable operating environment is required. The user should determine the enclosure degree of equipment, based on operating the environment (e.g. clean level) and necessary requirements to maintain patient safety.

4.2 Incorporating equipment and testing into the manufacturing workflow of cells for therapeutic use

Carrying out the cell processing workflow generally requires a series of unit operations to be performed using different processing methods and equipment types.

In-process and release testing should be in place to ensure that each instrument or machine operates as intended.

NOTE For in-process tests or controlling (critical) process parameters, or both, it is generally accepted that the criteria are set based on QbD, if applicable. QbD focuses on the fact that quality is built into a product with an understanding of the product and process by which it is developed, and manufactured along with the knowledge regarding the risks involved in manufacturing the product and how best to mitigate those risks.

Successful incorporation of equipment into the manufacturing workflow of cells for therapeutic use includes the maintenance of sterility and integrity, which is achieved by using suitable environmental controls, connectors or closed systems, or multiples of these to maintain uniformity and exclude potential external contaminants.

The responsibility of assembling a workflow composed of different equipment pieces lies exclusively with the user. The supplier, however, should develop their products in a way that enables the construction of said workflow(s).

4.3 Unit operation equipment systems

Wherever practical, best practice should include the use of a closed system for each unit operation step.

When unit operations or systems are not fully closed, processing steps or the systems should be operated in appropriately designed facilities, biosafety cabinets or other suitable systems to reduce the potential for product contamination or adulteration, or both.

4.4 Connecting to upstream or downstream processing equipment, or both

When equipment needs to be connected to upstream or downstream processing equipment, suitable sterile connectors shall be used and operated in a manner that maintains sterility to minimize the risk of introducing contaminants into the process. The selection of connectors depends on the manufacturing environment and type of operation (closed system versus biosafety cabinet), and the nature, rate and volume of the transfer. Sterile connectors or tubing that can be sterile welded and sterile sealed, or both, should be used. Alternatively, qualified and sterile transfer bags with appropriate attachments and tubing should be used to transfer materials between unit operations.

Connectors should be designed by the supplier to be compatible and suitable for the designated task. Prior to using in manufacturing, the designer and the user shall verify that the connectors are compatible and suitable for the designated task as equipment and connectors do not necessarily come from the same supplier.

Consumable joint designs not validated by the supplier shall be validated by the user.

4.5 Monitoring and surveillance software

Suppliers of cell processing equipment should introduce means of monitoring critical parameters of the instrument and software applications. If the embedded software does not have the surveillance functionality, external software and hardware (e.g. pharma surveillance systems) should be connected by users to monitor errors or technical issues of the equipment.

Users of cell processing equipment should evaluate the need for monitoring while connecting different devices in a single workflow. Mitigation strategies based upon corrective action and preventive action should be in place to allow curbing the risk to the cells for therapeutic use in the event of equipment failure.

4.6 Impurity and toxicity contribution to final cells for therapeutic use

Any process-related impurities, such as leachables from equipment components with direct cell contact, can potentially be carried over to the final cells for therapeutic use. Suppliers as well as users should understand and acquire as much information as possible on impurities generated from each piece of processing equipment.

If downstream unit operations include washing the drug substance intermediates or drug product, certain risks associated with impurities from upstream processes can be mitigated.

Refer to 6.3.4 for the evaluation of consumables and extracted and leached materials.

4.7 Sterility and non-pyrogenicity

The qualification and maintenance of sterility and non-pyrogenicity of equipment to process cells for therapeutic use is of particular importance due to limited downstream processing steps for removal of pyrogens, lack of terminal sterile filtration, and the reduced window for microbial testing associated with cells for therapeutic use. Sterility and endotoxin certifications shall be obtained for all materials

for which suppliers have made a sterility claim. Sterile in place and clean in place techniques should be properties of multi-use devices.

The equipment should be designed and utilized in such a way that the number of in-process connections, such as tube welding, is minimized in order to reduce the risk of contaminations. The sampling frequency and technique should be assessed for the risk to compromise sterility and non-pyrogenicity (e.g. sanitization of the sample port with alcohol prior to entry can help to reduce the bioburden load). To minimize the risk of containment breach, closed systems should be assessed for integrity pre- or post-use, such as demonstration of pressure hold. Sterilizing grade filters should be assessed for integrity post-use.

Non-endotoxin pyrogens, including material-mediated pyrogens, should be considered, when applicable[43].

5 Equipment overall performance characteristics and evaluation

5.1 General

The equipment performance should be characterized, and performance data should be generated by suppliers, to demonstrate the intended use of the equipment with consistency. The equipment performance can be used as a frame of reference for users to select and qualify equipment.

5.2 Description of performance characteristics

Performance characteristics define the operational characteristics of the equipment in order to best specify how and which of the available equipment can accomplish the work. Robust statistical methodology should be in place to accept or reject a given validation of a biological process.

Performance characteristics are specific to the type of equipment and the role that it is intended to perform. Generally, performance characteristics of cell processing equipment include yields, processing efficiency, instrument response times, sensitivity and mechanical properties among others. Control levels of operating conditions such as temperature, air flow rate, pH of media or buffer should be considered when determining performance characteristics.

An assessment of properly functioning equipment shall be made based on the quality of the final product and shall be assessed by the user. Typically, end points of properly functioning equipment are measured by biological and functionality readouts of the cells for therapeutic use (quality of final product) prior to the lot release. These readouts encompass assays to determine the immunochemical, biochemical or molecular attributes of the product or multiples of these. More specifically, the attributes can include the following:

a) Cell recovery, which refers to the “total cell yield” after processing through the equipment. The value is defined as the ratio of the cell number after processing to the cell number before processing and is measured experimentally. It gives a measure of cells lost due to equipment operation, handling or operator error.

   NOTE 1 Cell recovery does not make an inference about viable (functional) cells.

b) Cell viability, which is a measure of viable cells. Viable cells demonstrate attributes of being alive (i.e. metabolic activity, replication ability or capacity to resume these functions). Measurements of cell viability immediately post-processing are typically conducted via viable cell counts.

   NOTE 2 Cell viability determination methods based on automated cell counting equipment or conventional cell counting methods such as manual dye-based assays or ATP assays are available. Characterization of equipment for these methods and characterization of process performance using these methods are independent activities.

c) Cell phenotype, which is one of the key performance metrics defining a cell product following equipment processing. Unlike cell viability and cell recovery the characterization of the phenotype