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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

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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.

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

of a given cell population cannot be carried out at every process step, but rather following a period of expansion or differentiation, or both.

NOTE 3 Measurements of morphology, biomarker expression and biological activity are key metrics. Potency derived from biological activity is a more complex measurement than cell quality. It is the cells' response to external triggers (for instance, their ability to differentiate) and is expected to be related to the cells' therapeutic effect in patients.

NOTE 4 Based on the user's process, the user can define the in-process characterization and controls, and the final product (i.e. cells for therapeutic use) characterization and controls.

5.3 Performance parameters and correlation to cell quality attributes

The performance of cell processing equipment should be assessed by characterizing cells on defined metrics before and after processing through the equipment. The supplier can characterize a selection of different cell types, representative of cells for which the equipment is intended to be used. The user should validate the performance of the equipment in the context of its own process and cell type of choice.

The processing performance evaluation should include the cell viability, specific target cell yields, concentrations of recovered cells and the processing time in the equipment.

Assessments of recovered cells should take into account to assay the cell viability and critical quality attributes of cells for therapeutic use, including cell morphology, the degree of cell clumping, relevant cell surface markers such as phenotypic markers, and markers of cell activation. Assessment of recovered cells should also take into account tests for acute damage (such as apoptosis) or delayed cell damage (such as attachment efficiency and proliferative ability).

6 Components of the equipment system

6.1 Hardware

6.1.1 General

Cell processing hardware should be qualified for its intended use. Suppliers should ensure that specifications are met. Users should ensure that the integrity, quality and functionality of the cells for therapeutic use is not compromised as a result of hardware operation.

NOTE 1 Cell processing hardware refers to physical items or components of an equipment that are necessary for performing a specific field operation.

Users should identify backup hardware when only one device is in use by the laboratory or manufacturing site.

Each hardware, including that designated as backup hardware, should undergo qualification and validation before its first use which includes, but is not limited to, IQ, OQ and PQ.

NOTE 2 Qualification and validation of each hardware are also part of the process validation.

The user should establish and document an oversight of all hardware, including ensuring conformance with IQ/OQ, maintenance and calibration schedules and procedures.

6.1.2 Physical integrity

Physical integrity for processing equipment or instruments used in manufacturing cells for therapeutic use refers primarily to requirements around containment of potentially biohazardous material.

The physical integrity shall be validated after manufacturing and during transport of equipment to users as part of initial IQ.

NOTE International Safe Transit Association (ISTA) Procedure 2A is available as the basis of such validation[44].

6.1.3 Physical strength

The equipment's physical strength should be evaluated based on its intended use. Data on the breakage and leakage of device components should be provided by the supplier.

6.1.4 Packaging

Packaging for equipment should be validated by the supplier and should be suitable for the equipment and all components to maintain the physical integrity of the equipment during storage, shipping and handling.

Suppliers should conduct appropriate assessment and ensure the equipment's physical integrity including the use of suitable packaging materials.

6.1.5 Recovery of cells

There should be a risk-based approach in place to assess whether a strategy for the recovery of cells in the event of equipment failure is necessary. If the recovery of cells in the event of equipment failure is required, the process should be validated. If the validated process fails, the reason for failure should be assessed. Suppliers can recommend a procedure to ensure maximal recovery of cells and minimize the risk of contamination. The responsibility for applying these recommendations falls on the user.

6.1.6 Validation of performance qualification

The equipment's operation with defined parameters and range of operations should be validated and documented. Validation should be conducted under intended use conditions and worst-case scenarios, including both component testing and whole system testing.

If the equipment offers a range of operation, and can be changed by users, the associated parameters that can be changed should be clearly identified and the range of changes should be documented and validated by the user.

Access to particularly critical operations or applications should be protected, and only allowed to trained personnel. Electronic records produced during an operation should include the identifier of the process run as well as the identifier of the person responsible for its operation. A validated backup system should be provided to prevent loss of electronic data and records.

6.1.7 Physical evaluation of equipment and cell sample interaction

Equipment operation should not cause unintended damage to cells in terms of physical and chemical characteristics or the biological activity of cells. The supplier should implement safety measures, such as alarm, to prevent conditions that can cause damage to cells, such as excessive temperature and physical forces. If such conditions occur during the manufacturing of cells for therapeutic use, users need to assess potential damage to cells and potential risk of administration to patients, and shall document assessment results and actions in consequence.

6.1.8 Damage to cells

The operation of the cell processing equipment should not cause unintended physical damage to the cells. The supplier should demonstrate that controls are in place to prevent excessive temperatures or physical forces from occurring throughout the entire cell processing operation within the device. In case the equipment is not able to self-regulate the temperature, the temperature parameters of the equipment will rely on the appropriate control of the environment. The supplier should document the

proper temperature control of the environment recommended to the user as part of the intended use of the equipment.

Suppliers can provide technical and biological performance data to demonstrate that repeated operation of the device at the minimum and maximum operating conditions will not cause functional alteration or damage to the relevant cellular elements due to excessive heat production, pressures, centrifugal forces or fluid shear stresses throughout the entire flow path. The user shall validate the individual process in worst case conditions to determine the operational limits of the equipment in the context of an individual workflow.

Controls should also be in place to ensure that the flow path components during equipment operation are free of abrupt transitions, sharp edges, inadvertent clamping or kinks, which can damage cellular elements. These controls should be validated through evaluation of processed cells for therapeutic use covering a range of cell types that the equipment is intended to process.

Wherever practical, equipment validation should include assessments on cell viability and function according to a priori specifications.

6.1.9 Impact to clean room environment

Manufacturing equipment for cells for therapeutic use is often placed in a controlled clean room environment. Users shall determine the impact of the equipment on the "in operation" validation particle levels. Any additional computerized equipment (e.g. laptops) shall meet the relevant clean room requirements of the room that it is placed in, if possible. Appropriate cleaning or disinfection procedures should also be established and implemented for the equipment, as part of the cleaning validation.

NOTE See the ISO 14644 series[10] and the ISO 14698 series[11].

Likewise, suppliers for cell processing equipment should characterize the equipment to determine expected particulate burden. Observed particles should be characterized to identify the particulates (size and nature) and possible ingress routes of the particles into the equipment or cell process. Equipment should also be designed to be easy to clean and composed of detergent-resistant components.

6.1.10 Monitoring

Processes for manufacturing cells for therapeutic use can include patient-derived material intended for autologous use. These materials are often not easily replicable, and medical need can require urgent manufacture, making the impact of a sample loss extremely high. Monitoring equipment should facilitate the real-time identification of equipment failure so that users can initiate their prepared alternative patient care procedure plans. Real-time equipment monitoring is particularly important for devices such as incubators and bioreactors where the cell material is kept for long periods of time. For critical parameters, optimal values as well as minimal and maximal acceptance limits should be determined. Parameters of how frequently and a plan for ensuring that this monitoring occurs should be put into place (e.g. for incubators constant CO_2 monitoring systems to be calibrated every six months, no constant system CO_2 levels checked daily, or according to the manufacturer's specifications).

6.2 Equipment software for manufacturing of cells for therapeutic use

Software is an integral part of many equipment systems for the manufacturing of cells for therapeutic use. There are two types of software in an equipment system, i.e. software that controls multiple pieces of equipment that constitute to an equipment system (out of the scope of this document) and software embedded in a single equipment (equipment software). Equipment software working together with hardware shall be validated for its usage. The objective is to produce documented evidence, which provides a high degree of assurance that all parts of a system will consistently work correctly when

brought online. Validation of equipment software is often performed simultaneously with the IQ, OQ and PQ of corresponding equipment.

NOTE Good automated manufacturing practices (GAMP®)[1)] have guidelines for computer system validation and these guidelines recommend that users and suppliers work together, so that responsibilities regarding the validation process are understood. For users, GAMP® provides a documented assurance that a system is appropriate for the intended use before it goes "live." Suppliers can use GAMP® to test for avoidable defects in the supplied system to ensure that a good quality product leaves the facility. The GAMP® framework addresses how systems are validated and documented. Companies do not need to follow the same set of procedures and processes of a GAMP® framework to achieve validation and qualification levels that satisfy inspectors. Instead, GAMP® examines the systems development life cycle (SDLC) – a conceptual model that lays out the deliverable documents required by GAMP® – of an automated system to identify issues of validation, compliance and documentation.

Additional details on the risk-based approach which should be used to validate software that operates equipment is described in Reference [46].

6.3 Consumables

6.3.1 General

Any consumables that the cells come in contact with during the manufacturing process have the potential to generate impurities that can be carried over to the final cells for therapeutic use.

Consumable suppliers should carefully evaluate and document the potential for materials that come in contact with the cells or reagents to yield impurities or can cross link to proteins, growth factors, antibodies, etc.

For the use of disposable consumables, an approach should be explored where the detection of potential integrity or structural issues of pipes, tubing, vessels or containers before they cause a leak, spill or discharge into the processing environment is taken into account. In addition, secondary containment approaches should be investigated based on a risk assessment of the equipment and disposables.

6.3.2 Biocompatibility

The biocompatibility of all consumable materials that come into contact with the cells, either directly or indirectly, should be taken into account. Materials that come into direct contact with cells include but are not limited to sample collection and harvest bags, bioreactors, tubing for transfer of cells and direct-contact sensors. Materials that come into indirect contact with cells include but are not limited to storage and delivery vessels and transfer tubing. Materials that have been approved for direct medical use and materials that have documented biocompatibility should be used. Untested materials should be assessed with appropriate biocompatibility assays using a risk-based approach. Materials containing known allergens such as latex should be avoided wherever practical.

Further guidance for the determination of material biocompatibility is given in ISO 10993-1[4].

6.3.3 Toxicity of chemical sterilants

Clean-in-place and steam-in-place processes for consumables shall be validated for effective sterilization and removal of cleaning agent(s). The use of chemical sterilants can be avoided by using single-use systems. The potential toxicity of chemical sterilants used for consumables should be taken into account for using equipment pre-sterilized by the supplier versus conducting in-house cleaning and sterilization. Validation of the post-sterilant washing process shall be performed. This helps to ensure that chemical sterilants have been sufficiently removed prior to the introduction of any cell-contacting materials.

For liquid chemical sterilants, those to be removed easily by rinsing should be considered.

1) This trademark is provided for reasons of public interest or public safety. This information is given for the convenience of users of this document and does not constitute an endorsement by ISO.

Chemical sterilants should be chosen based on characteristics including toxicity, efficacy, kinetics of activity, material compatibility, ease and cost of use, and disposal process. Use of ICH Q3C class 1 and class 2 solvents should be avoided. A toxicity profile of the final product formulation of the germicide or the active ingredient(s), or both, should be acquired from the sterilant provider.

Further guidance for the chemical sterilants and sterilization procedures is given in ISO 14160[9].

6.3.4 Toxicity of extracted and leached materials

Extractable materials are chemical compounds that can be extracted from a manufacturing equipment consumable under extreme process conditions. Leachable materials are a subset of extractables that enter the manufacturing process stream under normal operating conditions and can be detectable in the final product. The potential for leaching of toxic compounds from the manufacturing process should be evaluated, especially for single-use processing units comprising plastic materials. Leachability should be assessed under a wide range of representative operating conditions including time, temperature, pH and representative media or buffer with maximal operating extraction propensities. Examples of potential leachable compounds include plasticizers and cyclic esters derived from adhesive materials. In addition, radiation-based sterilization can cause degradation of polymeric materials and form low-molecular mass compounds, which are potential sources of extractables. Therefore, a radiation-based sterilization process should be carefully carried out to avoid its impact on leachability.

Classes of potential leachable materials include:

a) volatile, semi-volatile and non-volatile organic compounds;

b) inorganic elements and ions.

In-process leachables (compounds released during the manufacturing process) are of particular concern in the manufacturing of cells for therapeutic use. Although direct risk to the patient can be minimized for in-process leachables, these chemical entities can directly impact the therapeutic cells' viability, integrity and effector function.

NOTE An investigation on disposable bags for cell culture media using Chinese hamster ovary (CHO) cells is reported in Reference [47].

The toxicity of leachables and in-process leachables shall be evaluated with regard to both effect on the patient and effect on the function of cells for therapeutic use. Patient safety threshold levels of known leachable compounds can be obtained[48][49], but additional studies can be needed to assess the cytotoxic levels.

Further guidance for the evaluation of consumables and extracted and leached materials is given in ISO 10993-1[4].

6.3.5 Particulates

Care should be taken to minimize particle introduction into equipment systems for manufacturing cells for therapeutic use. Cell processing consumables should not introduce excessive loads of non-cellular particles into the product as removal of foreign particles by terminal filtration is limited to those particles significantly larger than the cells, and removal of sub-visible particles by filtration is typically not possible.

The appropriate upper limit of particles in cells for therapeutic use can vary from product to product, and can depend on the nature and route of administration of the cells for therapeutic use, the size and materials of the contaminating particles, and the particles' potential impact on safety or cell efficacy.

The workflow for manufacturing cells for therapeutic use in closed systems greatly limits the impact of particulates external to the equipment on the product quality. Consumables should in this case possess suitable controls and barriers (such as air filters) to limit particles to an acceptable level for the intended use of the equipment. Users can then conduct a risk assessment based on the information provided by suppliers, and develop mitigation strategies.

Because the detection of particulates in the final drug product is confounded by the presence of cells, suppliers should implement appropriate controls in their manufacturing process to mitigate the risk of particle contamination or generation. As there is no specific standard or method developed for single-use technology or equipment for such a purpose, suppliers can rely on compendial methods with some modifications to test particulates. Testing for limits of subvisible and visible particles is described in compendial standards.

NOTE 1 Tests for the contamination of subvisible particles are described in harmonized documents including the ICH guideline and international, regional and national pharmacopeia[25][37][38][39][40].

NOTE 2 Tests for visible particulates in injections are described in Reference [41].

Particulate generation in a simulated use setting should be assessed. Particulate generation assessment at extremes of operational parameters or during prolonged equipment operation should also be performed.

6.3.6 Stability of disposable single-use components

Suppliers of single-use components that have direct contact with cellular material used in the manufacturing process shall provide estimates for expiration dates and shelf life according to validated testing protocols, including sterility maintenance tests and evaluations of key functional properties.

NOTE Guidance on accelerated aging relevant to the testing of single-use systems is provided in ASTM F1980-07(2007).

The integrity of single-use materials should be maintained throughout their use including shipping, set-up, process run and take-down when used as directed by suppliers. Suppliers should provide usage limits regarding temperature, pressure and chemical compatibility as appropriate for the device.

7 Documentation and notification of changes

7.1 Documentation

7.1.1 General

There should be sufficient documentation to describe the equipment, its intended use and the directions for its use, as well as the calibration and maintenance records.

The supplier should provide clear and concise instructions that delineate the technological features of the specific equipment and on how the equipment is intended to be used.

The intended use of the equipment should be compatible with the performance characteristics of the cells for therapeutic use for which it is intended to be used. If applicable, specific uses that are known to not be compatible with the equipment should also be documented.

The supplier shall provide equipment or equipment design specifications, and the range of operation (e.g. flow rates, pressures, centrifuge speeds, temperatures). If the equipment can be programmed by the user, a list of the programmable ranges should be provided.

There should be sufficient documentation to facilitate IQ, OQ and PQ of the equipment at the manufacturing site. A drug master file (DMF), or a similar document to support regulatory filing can be considered.

7.1.2 Documentation for off-the-shelf equipment or instruments

Documentation for off-the-shelf equipment or instruments should include:

a) functional specification;

b) process description;

c) acceptance test specifications [factory acceptance testing (FAT), site acceptance testing (SAT)];

d) acceptance test results (FAT, SAT);

e) user manual and technical manual, which should include as appropriate:

   1) operation method;

   2) cleaning method;

   3) maintenance method;

f) assembly drawing and bill of materials for mechanical installation;

g) specification sheet(s) for commercial products;

h) electrical schematics;

i) software programs;

j) description of planned preventive maintenance programs for the equipment/instrument and of the recording system;

k) qualification and calibration, including the recording systems and arrangements for computerized systems validation.

7.1.3 Custom-designed supplier documentation package for equipment or instruments

A custom-designed supplier documentation package for equipment or instruments should include:

a) functional specification;

b) process description;

c) acceptance test specifications (FAT, SAT);

d) acceptance test results (FAT, SAT);

e) user manual and technical manual, which should include as appropriate:

   1) operation method;

   2) cleaning method;

   3) maintenance method;

f) assembly drawing and bill of materials for mechanical installation;

g) specification sheet(s) for commercial products;

h) electrical schematics;

i) software programs.

8 Use and maintenance of equipment

8.1 Use of equipment

Users should determine a routine for the requalification or revalidation of the equipment on a risk basis that considers the criticality of the equipment to process and product quality. Users shall monitor equipment on a regular basis and should make adequate power backups available for all critical equipment. In addition, with upper and lower levels of performance specifications defined for critical

parameters, performance trending should be monitored by the user to act preventively before failure occurs. When real-time equipment monitoring is conducted, users should observe and document its trending, allowing the timely mitigation of risks for the cellular material.

Where sterile processing is claimed, the user should periodically validate the ability of the equipment and process to maintain sterility during aseptic process simulations or media fills.

If multiple lots or batches are processed in the same manufacturing area, users should carefully document and maintain traceability of cell samples. Line clearance procedures of equipment should be performed between lot or batch production as part of the procedures to limit contamination between batches.

In general, the use of disposable processing units or single-use systems is recommended. There should be a secondary containment approach implemented on the single-use processing equipment to appropriately manage any spills.

If changes to the operation of the equipment are made by the user, these changes should be within the functional range of the equipment as specified by the supplier and validated by the user (see 6.1.6). The supplier shall notify the user of any changes to the equipment, including equipment upgrades, changes of raw materials used in equipment manufacturing or changes of component suppliers. Potential risks associated with equipment changes shall be evaluated by the user based on the information provided by the supplier. Change controls should be performed for any changes that can affect the validated status of facilities, equipment and processes.

8.2 Maintenance of equipment

Users should maintain and calibrate critical cell processing equipment on a regular basis at the manufacturing facility. Users should keep maintenance records on file and affix notices of equipment calibration.

Suppliers can incorporate warning systems to indicate the need of periodic maintenance. The user should provide oversight of all equipment, including conformance with IQ or OQ, maintenance and calibration schedules, and procedures.

Users should perform regularly scheduled inspections, evaluations and testing by qualified personnel for critical parts in order to manage leak prevention. Inspections, evaluations and testing should be conducted on containers, associated piping, valves and appurtenances, and on other equipment and components with direct product contact that can be a source or cause of a failure of designed integrity. Activities can involve one or more of the following:

a) an external visual inspection of containers, piping, valves, appurtenances, foundations and supports;

b) a non-destructive testing (examination) to evaluate the integrity of certain containers;

c) additional evaluations, as needed, to assess the equipment's fitness for continued service.

The type of inspection programme and its scope will depend on site-specific conditions and the application of good engineering practices, and adherence to applicable industry standards or suppliers' requirements, or both. An inspection, evaluation and testing programme should specify the procedures, schedule or frequency, types of equipment covered, person(s) conducting the activities, and recordkeeping practices.