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Biotechnology — Cell viability analytical methods —

Part 1: General requirements and considerations

Biotechnologie — Méthodes d'analyse de la viabilité cellulaire —

Partie 1: Exigences générales et considérations

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Foreword

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This document was prepared by Technical Committee ISO/TC 276, *Biotechnology*, Subcommittee SC 1, *Analytical methods*.

A list of all parts in the ISO 8934 series can be found on the ISO website.

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

Evaluation of cell viability is a fundamental measurement in biotechnology. Cell viability measurements are widely and routinely used in basic research, drug discovery, toxicity testing, manufacturing control and release testing for cell banks, biological products, and cellular therapeutic products. Cell viability can be important in ensuring the safety and efficacy of cellular therapeutic products, in determining cell dose and product potency in cellular therapeutic products, and in the manufacturing and control of cell-based products and products derived from cells.

A quantity value for cell viability can be determined through a broad range of analytical methods evaluating different attributes related to the viable state of the cell(s). Several biological properties, or attributes, serve as the targets for identifying the viable state of the cell(s), and can be used to determine the viability status of cells. Examples include observations of the cell's membrane integrity, metabolic activity, nuclear morphology, and a cell's ability to replicate. Cell viability can also refer to different quantities related to viable and non-viable cells including percent cell viability, viable cell concentration, and signals related to the viable state. There is also a wide range of instrumentation used in the measurement of cell viability, including image based, flow cytometry based, spectrophotometric, and electrical signal-based approaches. Given the wide range of analytical methods associated with cell viability, it is often challenging to compare cell viability results from different analytical methods without additional knowledge regarding the viable state attribute investigated or the analytical method that was conducted. In addition, different applications require the use of different cell viability analytical methods that are compatible with or relevant to the intended use. Although cell viability standards exist, these standards are either test method specific, test article specific, sector specific or region specific. Existing standards do not address the general need of establishing common terminology for cell viability, considerations for fit for purpose cell viability analytical method development and the reporting of cell viability measurement results.

This document establishes a common approach for defining fit for purpose cell viability analytical methods to facilitate common understanding between users of the standard. This document provides general concepts and terminology for cell viability measurements, provides considerations for measurement control strategies and validation strategies, and considerations for establishing cell viability analytical method standard operating procedures. This document also includes the establishment of a common framework for reporting cell viability measurements.

This document is intended for a broad and worldwide industry where the quality and viability of cells are critical for research and product development.

This part of the ISO 8934 series is focused primarily on mammalian cells.

Biotechnology — Cell viability analytical methods —

Part 1: General requirements and considerations

1 Scope

This document specifies the general requirements for cell viability analytical methods and for reporting cell viability. This document gives general guidelines for selecting and establishing fit for purpose cell viability analytical methods. This document specifies requirements for establishing standard operating procedures for cell viability analytical methods. This document also gives guidelines for managing sources of variability for cell viability measurements during pre-analytical, analytical, and post-analytical phases.

This document is applicable to cells in suspension, cells adhered to a substrate, and cells in complex matrices.

This document is primarily applicable to cell viability measurements of nucleated mammalian cells.

NOTE 1 Several sector/application-specific international and national standards for cell viability currently exist.

NOTE 2 When applicable, the user can consult existing standards when operating within their scope.

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
analytical method
investigative procedure for qualitatively or quantitatively measuring or assessing the presence, amount, or functional activity of a target entity (the analyte)

[SOURCE: ISO 23033:2021, 3.3]

3.2
analytical method matrix
set of two or more complementary *analytical methods* (3.1) to measure different aspects of a *quality attribute* (3.32)

[SOURCE: ISO 23033:2021, 3.7]

3.3
attribute
physical, chemical, biological, or microbiological property or characteristic

[SOURCE: ISO 20391-1:2018, 3.5]

3.4
attribute component
quantity used to derive a *quality attribute* (3.32)

[SOURCE: ISO 23033:2021, 3.9]

3.5
biological property
biological phenomenon that is evaluated to assess the *quality attribute* (3.32)

[SOURCE: ISO 23033:2021, 3.11]

3.6
bioprocessing monitoring mode
spatio-temporal position of a measurement device (i.e. sensor) or measurement process in relation to a bioreactor or vessel

3.7
calibration
operation that, under specified conditions in a first step, establishes a relation between the *quantity* (3.34) values with measurement uncertainties provided by measurement standards and corresponding indications with associated measurement uncertainties and, in a second step, uses this information to establish a relation for obtaining a measurement result from an indication

[SOURCE: ISO/IEC Guide 99:2007, 2.39, modified — Notes to entry deleted.]

3.8
cell concentration
cell count (3.9) per volume

Note 1 to entry: Typically used for cells in suspension.

[SOURCE: ISO 20391-1:2018, 3.6]

3.9
cell count
discrete number of cells

Note 1 to entry: Cell count is typically expressed as *cell concentration* (3.8) or area density.

[SOURCE: ISO 20391-1:2018, 3.7]

3.10
cell death
state of irreversible degeneration of vital cellular functions culminating in the loss of cellular integrity

Note 1 to entry: Definition based on Reference [5].

3.11
cell viability analytical method
investigative procedure for measuring or assessing the presence, amount, or functional activity of *viable cells* (3.53), non-viable cells, other category related to *viable state* (3.55), or ratio thereof

3.12
examinand
nominal property (3.27) intended to be examined

Note 1 to entry: Definition based on Reference [7].

3.13
examination
process of experimentally obtaining one or more values that can reasonably be attributed to a *nominal property* (3.27) together with any other available relevant information

Note 1 to entry: Definition based on Reference [7].

3.14
fit for purpose
in line with prearranged requirements for an *intended use* (3.17)

[SOURCE: ISO 20387:2018, 3.24, modified — Note to entry deleted.]

3.15
in-house reference material
non-certified material or substance, produced by one laboratory, one or more of whose property values are sufficiently homogeneous and well established to be used for the *intended use* (3.17)

Note 1 to entry: The use of in-house reference materials can include, but is not limited to, *validation* (3.51), *calibration* (3.7), monitoring of comparability, and potency and process evaluations.

[SOURCE: ISO 23033:2021, 3.24]

3.16
installation qualification
IQ
establishing by objective evidence that all key aspects of the process equipment and ancillary system installation adhere to the manufacturer's approved *specification* (3.45) and that the recommendations of the supplier of the equipment are suitably considered

[SOURCE: ISO 23033:2021, 3.25]

3.17
intended use

use for which a product, process, or service is intended according to the *specifications* (3.45), instructions or information or multiple of them provided by the manufacturer or user

[SOURCE: ISO 23033:2021, 3.26]

3.18
intermediate measurand
measurand (3.22) that is obtained as a part of the *analytical method* (3.1) where the *quantity value* (3.36) is utilized by the user of the *analytical method* (3.1) but not reported as a *quantity value* (3.36) for the reported measurand

3.19
intermediate precision
measurement precision under a set of intermediate *precision* (3.31) conditions

Note 1 to entry: The intermediate precision condition refers to the condition of measurement, out of a set of conditions that includes the same measurement procedure, same location, and replicate measurements on the same or similar objects over an extended period of time but can include other conditions involving changes (e.g. analyst or instrument).

[SOURCE: ISO/IEC Guide 99:2007, 2.23, modified — "measurement" was deleted from the term, note 1 to entry has been added.]

3.20
limit of detection
lowest amount of analyte in a *sample* (3.43) which can be detected but not necessarily quantitated as an exact value

[SOURCE: ISO 23033:2021, 3.29]

3.21
limit of quantitation
lowest amount of analyte in a *sample* (3.43) which can be quantitatively determined with suitable *precision* (3.31) and accuracy

Note 1 to entry: The limit of quantitation is a parameter of quantitative *analytical methods* (3.1) for low levels of compounds in *sample* (3.43) matrices and is used particularly for the determination of *impurities* (3.23) or degradation products or both.

[SOURCE: ISO 23033:2021, 3.30]

3.22
measurand
quantity (3.34) intended to be measured

[SOURCE: ISO/IEC Guide 99:2007, 2.3, modified — Notes to entry and examples deleted.]

3.23
measurement principle
phenomenon serving as a basis of a measurement

Note 1 to entry: The phenomenon can be of a physical, chemical, or biological in nature.

[SOURCE: ISO/IEC Guide 99:2007, 2.4, modified — Notes to entry and examples have been deleted.]

3.24
measurement target
intended object of measurement

Note 1 to entry: A measurement target can denote a feature or complex features of cells that is informative of cellular status or quality. The term is additional to the term analyte or *measurand* (3.22) in situations where the use of those terms is not appropriate or possible.

Note 2 to entry: A measurement target can include both a *measurand* (3.22) and *examinand* (3.12).

[SOURCE: ISO 23033:2021, 3.21, modified – Notes to entry added]

3.25
membrane integrity
ability of a cell membrane to generate or maintain gradients of the concentration of specific target molecules in solution

Note 1 to entry: Membrane integrity indicates metabolic activity of the cell but is not related to proliferation potential.

Note 2 to entry: The result of a membrane integrity test depends on the selected molecule.

3.26
metadata
data that define and describe other data

[SOURCE: ISO/IEC 11179-1:2023, 3.2.26]

3.27
nominal property
property of a phenomenon, body, or substance, where the property has no magnitude

Note 1 to entry: The nominal property is one for which only comparability by equivalence applies.

[SOURCE: ISO/IEC Guide 99:2007, 1.30, modified — Notes to entry and examples deleted.]

3.28
operational qualification
OQ
establishing by objective evidence process control limits and action levels which result in an *analytical method* (3.1) that meets all predetermined requirements

[SOURCE: ISO 23033:2021, 3.33]

3.29
performance criteria
required functionality and behaviour of the *test method* (3.49)

[SOURCE: ISO 23033:2021, 3.34]

3.30
performance qualification
PQ
establishing by objective evidence that the *analytical method* (3.1), under anticipated conditions, consistently meets all predetermined requirements

[SOURCE: ISO 23033:2021, 3.35]

3.31
precision
closeness of agreement between indications or measured *quantity* (3.34) values obtained by replicate measurements on the same or similar objects under specified conditions

Note 1 to entry: Precision is usually expressed numerically by measures of imprecision, such as standard deviation, variance, or coefficient of variation under the specified conditions of measurement.

Note 2 to entry: The 'specified conditions' can be, for example, *repeatability* (3.38) conditions of measurement, *intermediate precision* (3.19) conditions of measurement, or *reproducibility* (3.40) conditions of measurement.

Note 3 to entry: Measured *quantity value* (3.36) refers to the *quantity* (3.34) value representing a measurement result.

[SOURCE: ISO/IEC Guide 99:2007, 2.15, modified — Term “measurement precision” was deleted and Notes 3 and 4 to entry were deleted.]

3.32
quality attribute
physical, chemical, biological, or microbiological property or characteristic that is an indicator of the quality

[SOURCE: ISO 23033:2021, 3.38]

3.33
quality control material
QCM
reference material (3.37) used for quality control of a measurement

[SOURCE: ISO Guide 30: 2015, 2.1.22]

3.34
quantity
property of a phenomenon, body, or substance, where the property has a magnitude that can be expressed as a number and a reference

[SOURCE: ISO/IEC Guide 99:2007, 1.1, modified — Notes to entry and example were deleted.]

3.35
quantity formula
mathematical relation among *quantities* (3.34) in a given system of quantities, independent of measurement units

[SOURCE: ISO/IEC Guide 99:2007, 1.22, modified — notes and examples were deleted and term changed to "quantity formula".]

3.36
quantity value
value of a quantity
number and reference together expressing magnitude of a *quantity* (3.34)

[SOURCE: ISO/IEC Guide 99:2007, 1.19, modified — Notes to entry and examples were deleted.]

3.37
reference material
material, sufficiently homogeneous and stable with reference to specified properties, which has been established to be fit for its *intended use* (3.17) in measurement or in *examination* (3.13) of *nominal properties* (3.27)

[SOURCE: ISO/IEC Guide 99:2007, 5.13, modified — Notes to entry and examples deleted.]

3.38
repeatability
precision (3.31) of measurement under a set of repeatability conditions of measurement

Note 1 to entry: Repeatability conditions of a measurement refers to condition of measurement, out of a set of conditions that includes the same measurement procedure, same operators, same measuring system, same operating conditions and same location, and replicate measurements on the same or similar objects over a short period of time (see ISO 23033:2021, 3.41).

[SOURCE: ISO/IEC Guide 99:2007, 2.21, modified — Term “measurement repeatability” was deleted and Note 1 to entry was added.]

3.39
representative sample
sample (3.43) that accurately represents or reflects the *attributes* (3.3) of the system

Note 1 to entry: Generally intended to provide information on the system, often to serve as a basis for decision on the system or its production.

[SOURCE: ISO 23033:2021, 3.42]

3.40
reproducibility
precision (3.31) of measurement under reproducibility conditions of measurement

Note 1 to entry: Reproducibility conditions of measurement refer to the condition of measurement, out of a set of conditions that includes different locations, operators, measuring systems, and replicate measurements on the same or similar objects.

[SOURCE: ISO/IEC Guide 99:2007, 2.25, modified — Note to entry replaced and term “measurement reproducibility” modified.]

3.41
robustness
measure of a *test method* (3.49) capacity to remain unaffected by small, but deliberate variations in method parameters and provides an indication of its reliability during normal usage

[SOURCE: ISO 23033:2021, 3.44]

3.42
ruggedness
degree of *reproducibility* (3.40) of test results obtained by the analysis of the same *samples* (3.43) under a variety of normal test conditions

Note 1 to entry: Normal test conditions can include for example: different laboratories, different analysts, different instruments, different reagent lots, different analysis days, different elapsed times, different temperatures etc.

[SOURCE: ISO 23033:2021, 3.45]

3.43
sample
one or more parts taken from a system

[SOURCE: ISO 23033:2021, 3.46]

3.44
sensitivity
quotient of the change in an indication of a measuring system and the corresponding change in a value of a *quantity* (3.34) being measured

[SOURCE: ISO/IEC Guide 99:2007, 4.12, modified — Notes to entry deleted and term "sensitivity of a measuring system" revised.]

3.45
specification
document stating needs or expectations that are stated, generally implied or obligatory

3.46
specificity
characteristic of a *test method* (3.49) that expresses qualitatively and quantitatively its ability to detect or determine an individual analyte without interferences from accompanying species

[SOURCE: ISO 23033:2021, 3.48, modified – Note to entry deleted.]

3.47
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/TS 20399-1:2022, 3.17]

3.48
standard operating procedure
SOP
written procedure prescribed for repetitive use as a practice, in accordance with agreed-upon *specifications* (3.45) aimed at obtaining a desired outcome

[SOURCE: ISO 21899:2020, 3.22]

3.49
test method
technical procedure used with a specified *analytical method* (3.1)

[SOURCE: ISO 23033:2021, 3.52]

3.50
test sample
small aliquot of the *sample* (3.43) that is prepared for measurement in the method of interest

Note 1 to entry: Generally, test samples are representative of the *sample* (3.43) they are prepared from and are sometimes referred to as "representative test sample(s)".

[SOURCE: ISO 20391-2:2019, 3.1.35]

3.51
validation
confirmation, through the provision of objective evidence, that the requirements for a specific *intended use* (3.17) or application have been fulfilled

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

3.52
verification
confirmation, through the provision of objective evidence, that specified requirements have been fulfilled

[SOURCE: ISO 9000:2015, 3.8.12, modified — Notes to entry deleted.]

3.53
viability
quantity or quantities (3.34) associated with the *viable state* (3.55)*of* cells within a cell *sample* (3.43) , that is based on the measurement of a pre-selected *viable state attribute(s)* (3.56) that is (are) relevant to the *intended use* (3.17)

Note 1 to entry: The *viable state* (3.55) of cells can change over time and can be heterogeneous within a cell population. Thus, viability typically only represents the *viable state* (3.55) of a cell or of cells within a cell population at the time of measurement.

3.54
viable cells
cells within a *sample* (3.43) that have an *attribute* (3.3) or *attributes* (3.3) of being alive (e.g. metabolically active, capable of reproduction, possessed of intact cell membrane, or with the capacity to resume these functions) defined based on the *intended use* (3.17)

Note 1 to entry: Non-viable cells can be considered those cells within a *sample* (3.43) that do not exhibit an *attribute* (3.3) or *attributes* (3.3) of being alive based on the *intended use* (3.17).

[SOURCE: ISO 20391-1:2018, 3.29, modified — Note 1 to entry added.]

3.55
viable state
<of cells> condition of a cell(s) related to an *attribute(s)* (3.3) of being alive

Note 1 to entry: The viable state can be described by a spectrum of *attributes* (3.3) related to vital cellular function and *cell death* (3.10). *Attributes* (3.3) related to the viable state can include *membrane integrity* (3.25), metabolic activity, molecular markers of cell injury, proliferative capacity, cell adhesion, cell motility, mechanical integrity of the cell, reactivity to stimuli, cell or organelle morphology.

Note 2 to entry: Viable state can be applied to a single cell or a population of cells.

3.56
viable state attribute
physical, biochemical, or *biological property* (3.5) or characteristic that is an indicator of the *viable state* (3.55) of the cell(s)

Note 1 to entry: In some applications, viable state attribute is referred to as the *biological property* (3.5) of the *cell viability analytical method* (3.11).

4 Symbols and abbreviated terms

Abbreviated term or symbol	Description
AO	Acridine orange
ATP	Adenosine Triphosphate
CAR-T	Chimeric antigen receptor T Cells
CQA	Critical quality attribute
CRM	Certified reference material
DAPI	4',6-Diamidino-2-phenylindole
DMSO	Dimethyl sulfoxide
LDH	Lactate dehydrogenase
LoD	Limit of detection
LoQ	Limit of quantitation
MTS	3-(4,5-dimethylthiazol-2-yl)-5-(3-carboxymethoxyphenyl)-2-(4-sulfophenyl)-2H-tetrazolium
N_1	Viable cell count
N_t	Total cell count
N_0	Non-viable cell count
PBMC	Peripheral blood mononuclear cell
PI	Propidium iodide
PMT	Photomultiplier tube
QCM	Quality control material
RFU	Relative fluorescence units
RM	Reference material
SD	Standard deviation
SOP	Standard operating procedure
TUNEL	Terminal deoxynucleotidyl transferase dUTP nick end labeling
V	Viability, in %

5 General concepts of cell viability

5.1 General

Cell viability is a quantity associated with the viable state of cells and is based on the measurement of pre-selected viable state attributes that are selected based on the intended use.

NOTE 1 Cell viability is sometimes discussed in the context of cell vitality. Cell vitality can be considered a subset of cell viability where typically, vitality is a quantity(s) associated with viable cell state attributes that are not directly indicative of cell necrosis.

NOTE 2 Cell viability is sometimes discussed in the context of cell health where cell viability is referred to as a measure of cell health. Here the terminology of “cell health” is not used in order to avoid confusion with the pre-analytical condition of the cells (e.g. the condition of the organism at the time the cells were isolated, for example cells isolated from a “healthy” donor versus a “diseased donor). Cells from a diseased or “un-healthy” condition can still be viable and non-viable.

Cell viability can be important in determining cell dose and product potency in cellular therapeutic products, and in the control of manufacturing processes of cell-based products and products derived from cells.