INTERNATIONAL STANDARD

ISO 17822

First edition
2020-11

In vitro diagnostic test systems — Nucleic acid amplification-based examination procedures for detection and identification of microbial pathogens - Laboratory quality practice guide —

Part :
Laboratory quality practice guide

Systèmes d'essai pour diagnostic in vitro — Modes opératoires d'examen in vitro qualitatifs fondés sur l'acide nucléique pour la détection et l'identification d'agents pathogènes microbiens — Guide pratique sur la qualité dans les laboratoires —

Partie : Guide pratique de qualité au laboratoire

Reference number
ISO 17822:2020(E)

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Published in Switzerland

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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 212, *Clinical laboratory testing and in vitro diagnostic test systems.*

This first edition of ISO 17822 cancels and replaces ISO/TS 17822-1:2014, which has been technically revised. The main changes are as follows:

— Clause 4 has been updated and merged from ISO/TS 17822-1:2014.

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

Nucleic acid amplification-based tests (NAATs) are now commonly used in in vitro diagnostic (IVD) tools in laboratory medicine for the detection, identification and quantification of microbial pathogens. The NAAT result is influenced by all steps of the entire diagnostic workflow (i.e. pre-examination, examination, post-examination). Therefore, this document considers all critical aspects of the entire diagnostic workflow when designing, developing and implementing and using a specific microbial pathogen NAAT examination.

NAAT examinations include PCR technology as well as other amplification-based technologies such as, but not limited to, loop-mediated isothermal amplification (LAMP), transcription-mediated amplification (TMA) and strand displacement amplification (SDA).

This document covers the implementation of commercially available IVD(s) into the medical laboratory routine use as well as the design, development and implementation of laboratory developed tests (LDT).

This document will address the additional specific considerations, requirements and recommendations for the detection of microbial pathogens with sampling, nucleic acid extraction, genetic heterogeneity and the laboratory containment category which is required.

Due to high analytical sensitivity of nucleic acid-based examination procedures, special attention to their design, development and use is required. This includes verification of analytical and validation of clinical performance characteristics.

In this document, the following verbal forms are used:

— “shall” indicates a requirement;

— “should” indicates a recommendation;

— “may” indicates a permission;

— “can” indicates a possibility or a capability.

In vitro diagnostic test systems — Nucleic acid amplification-based examination procedures for detection and identification of microbial pathogens - Laboratory quality practice guide —

Part :
Laboratory quality practice guide

1 Scope

This document describes the particular clinical laboratory practice requirements to ensure the quality of detection, identification and quantification of microbial pathogens using nucleic acid amplification tests (NAAT).

It is intended for use by laboratories that develop, and/or implement and use, or perform NAAT for medical, research or health-related purposes. This document does not apply to the development of in vitro diagnostic (IVD) medical devices by manufacturers. However, it does include verification and validation of such devices and/or the corresponding processes when implemented and used by the laboratories.

2 Normative references

The following documents are referred to in the text in such a way that some or all of their content constitutes requirements of this document. For dated references, only the edition cited applies. For undated references, the latest edition of the referenced document (including any amendments) applies.

ISO 15189, *Medical laboratories — Requirements for quality and competence*

ISO 15190, *Medical laboratories — Requirements for safety*

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
accuracy
closeness of agreement between a test result or measurement result and the true value

Note 1 to entry: In practice, the accepted reference value is substituted for the true value.

Note 2 to entry: The term “accuracy”, when applied to a set of test or measurement results, involves a combination of random components and a common systematic error or bias component.

Note 3 to entry: Accuracy refers to a combination of trueness and precision.

[SOURCE: ISO 3534-2:2006]

3.2
amplification product
amplicon
specific *DNA* (3.17) fragment produced by a DNA-amplification technology, such as the *polymerase chain reaction (PCR)* (3.34)

[SOURCE: ISO 13495:2013, 3.3.1]

3.3
analytical specificity
specificity
capability of a measuring system, using a specified measurement procedure, to provide measurement results for one or more *measurands* (3.28) which do not depend on each other nor on any other quantity in the system undergoing measurement

Note 1 to entry: Lack of analytical specificity is called analytical interference (see ISO 18113-1:2009, A.3.2[21]).

Note 2 to entry: Specificity of a measurement procedure should not be confused with clinical specificity (SOURCE: ISO 18113-1:2009, A.3.16[21]).

Note 3 to entry: VIM; JCGM 200; 2012[22] uses the term selectivity for this concept instead of specificity.

Note 4 to entry: For qualitative and semiquantitative examination procedures, analytical specificity is determined by the ability to obtain negative results in concordance with negative results obtained by the reference method.

[SOURCE: ISO 18113-1:2009, A.3.4]

3.4
biorisk
probability or chance that a particular adverse event (in the context of this document: accidental infection or unauthorized access, loss, theft, misuse, diversion or intentional release), possibly leading to harm, will occur

[SOURCE: WHO Biorisk management , Laboratory biosecurity guidance , September 2006]

3.5
biosafety
describes the containment principles, technologies and practices that are implemented to prevent the unintentional exposure to pathogens and toxins, or their accidental release

[SOURCE: WHO Biorisk management Laboratory biosecurity guidance September 2006]

3.6
biosecurity
set of preventive measures and actions to reduce the risk of intentional or unintentional transmission of infectious diseases

Note 1 to entry: Biosecurity encompasses the prevention of the intentional removal (theft) of biological materials from laboratories.

Note 2 to entry: These preventive measures are a combination of systems and practices implemented in laboratories against the use of dangerous pathogens and toxins for malicious use to prevent the spread of these biological agents.

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

Note 1 to entry: according to US Code of Federal Regulations, calibration is a process of testing and adjusting an instrument or test system to establish a correlation between the measurement response and the concentration or amount of the substance that is being measured by the test procedure (modified from 42CFR 493.1218)[20].

[SOURCE: VIM; JCGM 200; 2012]

3.8
certified reference material
CRM
reference material (RM) (3.41) characterized by a metrologically valid procedure for one or more specified properties, accompanied by a *RM* (3.41) certificate that provides the value of the specified property, its associated uncertainty, and a statement of metrological traceability

Note 1 to entry: The concept of value includes a nominal property or a qualitative attribute such as identity or sequence. Uncertainties for such attributes may be expressed as probabilities or levels of confidence.

Note 2 to entry: Metrologically valid procedures for the production and certification of *RMs* (3.41) are given in, among others, ISO 17034[17].

Note 3 to entry: ISO/IEC Guide 99:2007[19] has an analogous definition.

[SOURCE: ISO Guide 30, 2.1.2]

3.9
clinical performance
<laboratory medicine> ability of an in vitro diagnostic examination procedure to yield results that are correlated with a specific clinical condition or physiological state in accordance with the target population and intended user

Note 1 to entry: Although sometimes referred to as diagnostic performance or clinical validity; clinical performance is the harmonized term endorsed by the Global Harmonization Task Force (GHTF) and its successor, the International Medical Devices Regulators Forum (IMDRF).

Note 2 to entry: Evaluation of clinical performance often relies on the outcome of other types of clinical examinations to define "true positive or true negative" results.

[SOURCE: GHTF/ SG5/N 6:2012, 4.4.2, modified — medical device has been changed to — examination procedure and particularly has been changed to — specific.]

3.10
clinical sensitivity
diagnostic sensitivity
<laboratory medicine> ability of an in vitro diagnostic examination procedure to identify the presence of a target marker associated with a specific disease or condition

Note 1 to entry: Also defined as percent positivity in *samples* (3.44) where the target marker is known to be present.

Note 2 to entry: Diagnostic sensitivity is expressed as a percentage (number fraction multiplied by 100), calculated as 100 × the number of true positive values (TP) divided by the sum of the number of true positive values (TP) plus the number of false negative values (FP), or 100 × TP/(TP + FN). This calculation is based on a study design where only one *sample* (3.44) is taken from each subject.

Note 3 to entry: The target condition is defined by criteria independent of the examination procedure under consideration.

[SOURCE: ISO 18113-1:2009, A.3.15]

3.11
clinical specificity
diagnostic specificity
<laboratory medicine> ability of an in vitro diagnostic examination procedure to recognise the absence of a target marker associated with a specific disease or condition

Note 1 to entry: Also defined as percent negativity in *samples* (3.44) where the target marker is known to be absent.

Note 2 to entry: Clinical specificity is expressed as a percentage (number fraction multiplied by 100), calculated as 100× the number of true negative values (TN) divided by the sum of the number of true negative plus the number of false positive (FP) values, or 100 × TN/(TN + FP). This calculation is based on a study design where only one *sample* (3.44) is taken from each subject.

Note 3 to entry: The target condition is defined by criteria independent of the examination procedure under consideration.

[SOURCE: ISO 18113-1:2009, A.3.16]

3.12
complementary DNA
cDNA
single-stranded *DNA* (3.17) that is complementary to a given *RNA* (3.42) and synthesized in the presence of reverse transcriptase to serve as a *template* (3.47) for synthesis of *DNA* (3.17) copies

3.13
contamination
introduction of an undesirable substance or matter

3.14
cut-off value
quantity value used as a limit to identify *samples* (3.44) that indicate the presence or the absence of a specific disease, condition or *measurand* (3.28)

Note 1 to entry: Defines which measurement results are reported as positive and which are reported as negative.

Note 2 to entry: Measurement results near the cut-off value can be considered inconclusive.

Note 3 to entry: The selection of the cut-off value determines the *clinical specificity* (3.11) and *clinical sensitivity* (3.10) of the examination.

3.15
denaturation
physical and/or chemical treatment which results in the separation of nucleic acid double helices

Note 1 to entry: denaturation of *DNA* (3.17) results in separation of double-stranded *DNA* (3.17) into single-stranded *DNA* (3.17).

[SOURCE: ISO 21572:2013, 3.1.6 — modified, term "denaturation of proteins" has been changed to "denaturation", and " the POI or" has been deleted. Note 1 to entry has been added.]

3.16
deoxyribonucleoside triphosphate
dNTP
solution containing dATP, dCTP, dGTP, dTTP and/or dUTP

[SOURCE: ISO 22174:2005, 3.3.7]

3.17
DNA
deoxyribonucleic acid
polymer of deoxyribonucleotides occurring in a double-stranded (dsDNA) or single-stranded (ssDNA) form

[SOURCE: ISO 22174:2005, 3.1.2]

3.18
DNA polymerase for PCR
thermostable enzyme which catalyses repeated *DNA* (3.17) synthesis

[SOURCE: ISO 22174:2005, 3.4.17]

3.19
DNA sequencing
determining the order of nucleotide bases (adenine, guanine, cytosine, and thymine) in a molecule of *DNA* (3.17)

Note 1 to entry: Sequence is generally described from the 5' end.

3.20
hybridization
specific binding of complementary *nucleic acid* (3.32) sequences under suitable reaction conditions

[SOURCE: ISO 22174:2005, 3.6.3]

3.21
inhibition
reduction of amplification or interference with detection process that can lead to false negative results or reduced quantity

3.22
interfering substances
endogenous or exogenous substances in clinical specimens/*samples* (3.44) that can alter an examination result

[SOURCE: ISO 20186:2019-1, 3.15 modified]

3.23
inhouse assay
laboratory developed test
LDT
type of in vitro diagnostic test that is designed, manufactured and used within a single laboratory

Note 1 to entry: Inhouse assay/LDT needs to be validated for its intended use before putting into service.

3.24
linearity
ability of a method of analysis, within a certain range, to provide an instrumental response or results proportional to the quantity of *nucleic acid target sequence* (3.46) to be determinded in the laboratory *sample* (3.44)

Note 1 to entry: In the case of qPCR, the quantification cycle (also termed cycle threshold or crossing point) is inversely proportional to the quantity of nucleic acid target sequence. (3.46).

Note 2 to entry: The term linearity is frequently linked with the linear range of the method and refers to the ability of a method to give a response or result that is directly propotional to the concentration of the nucleic acid target sequence (3.46).

[SOURCE: ISO 16577:2016, 3.92 modified — Notes 1 and 2 to entry added; 'quantity of analyte' replaced with 'quantity of the *nucleic acid target sequence*' (3.46).]

3.25
limit of detection
LOD
measured quantity value, obtained by a given measurement procedure, for which the probability of falsely claiming the absence of a component in a material is *β*, given a probability α of falsely claiming its presence

Note 1 to entry: The term analytical sensitivity is sometimes used to mean detection limit, but such usage is now discouraged. See ISO 18113-1:2009, A.2.7 and A.2.8 for further information.

Note 2 to entry: In a nucleic acid-based identification examination, the lowest concentration or content of the target organism per defined amount of matrix that can be consistently detected under the experimental conditions specified in the method.

Note 3 to entry: In molecular methods and quantitative molecular methods, the lowest concentration of measurand that can be consistently detected (typically, in >95 % of samples (3.44) tested under routine clinical laboratory conditions) and in a defined type of *sample* (3.44).

Note 4 to entry: This concentration must yield an assay value that can be reproducibly distinguished from values obtained with *samples* (3.44) that do not contain the measurand.

[SOURCE: ISO 18113-1:2009, A.3.14, modified — new notes to entry added.]

3.26
limit of quantification
LOQ
lowest concentration or quantity of the *nucleic acid target sequence* (3.46) per defined volume that can be measured with reasonable statistical certainty consistently under the experimental conditions specified in the method

Note 1 to entry: Generally expressed in terms of the signal or measurement (true) value that will produce estimates having a specified coefficient of variation (CV).

[SOURCE: ISO 16577:2016, 3.91, modified — replaced, content of the analyte of interest' with 'quantity of the *nucleic acid target sequence* (3.46)', 'amount of matrix' with 'volume' and 'relative standard deviation (RSD)' with 'coefficient of variation (CV)'.]

3.27
mastermix
mixture of reagents needed for nucleic acid amplification, except for the target *DNA* (3.17) and the controls

[SOURCE: ISO 22174:2005, 3.4.18]

3.28
measurand
quantity intended to be measured

[SOURCE: VIM; JCGM 200; 2012]

EXAMPLE 1 Quantity of gene target measured by *PCR* (3.34) is influenced by the *amplicon* (3.2) size of the *PCR* (3.34) assay and fragment size of the *template* (3.47) (~<amplicon size).

EXAMPLE 2 *Denaturation* (3.15) of *DNA* (3.17) in a *sample* (3.44) into ssDNA influences quantification by dPCR as the two strands are partitioned separately.

Note 1 to entry: The specification of a measurant requires knowledge of the kind of quantity, including any relevant component, and the chemical entities involved.

Note 2 to entry: In the second edition of the VIM and in IEC 60050-300:2001, the measurand is defined as the 'particular quantity subject to measurement'.

