TECHNICAL SPECIFICATION

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In vitro diagnostic test systems — Qualitative nucleic acid-based *in vitro* examination procedures for detection and identification of microbial pathogens —

Part 1: General requirements, terms and definitions

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 —

Partie 1: Exigences générales, termes et définitions

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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 on the meaning of ISO specific terms and expressions related to conformity assessment, as well as information about ISO's adherence to the WTO principles in the Technical Barriers to Trade (TBT), see the following URL: Foreword — Supplementary information.

The committee responsible for this document is ISO/TC 212, *Clinical laboratory testing and in vitro diagnostic test systems*.

ISO/TS 17822 consists of the following parts, under the general title *In vitro diagnostic test systems — Qualitative nucleic acid-based in vitro examination procedures for detection and identification of microbial pathogens*:

— *Part 1: General requirements, terms and definitions*

— *Part 2: Quality practice guide for medical laboratories*

Introduction

Nucleic acid-based *in vitro* diagnostic examination procedures are now commonly used in laboratory medicine for the detection and identification of microbial pathogens. These examination procedures have become particularly valuable for the detection of infectious agents that are difficult to grow in culture. For a review of recent advances and current practices associated with *in vitro* diagnostic examination procedures based on nucleic acid-amplification and detection technology ("molecular diagnostics"), see References [38], [35], [36], [37], [39], [41], and [42].

ISO/TS 17822-1 defines concepts and establishes general principles for the design, development, and performance of qualitative nucleic acid-based *in vitro* diagnostic examinations for the detection and identification of microbial pathogens in human specimens.

Traditional PCR examination procedures typically consist of three steps: (1) sample preparation and nucleic acid extraction, (2) nucleic acid amplification, and (3) nucleic acid detection and identification. The analytical technology is continuing to evolve. Recent kinetic approaches ("real-time PCR") incorporate detection in the amplification step, and multiplex PCR includes the entire system in a cassette.

Due to the inherent complexity and unparalleled analytical sensitivity of nucleic acid-based examination procedures, special attention to their design, development, and use is required, including determination of analytical and clinical performance characteristics, documentation of instructions for use, design of medical laboratory facilities, implementation of appropriate quality assurance practices, verification of the performance characteristics by the medical laboratory in conditions of actual use, and risk management.

As with all *in vitro* diagnostic examination procedures, suitability of a nucleic acid-based examination procedure for its intended clinical uses must be demonstrated as part of the development process. Analytical performance characteristics must be determined and validated for the detection and identification of the target pathogen. Clinical performance characteristics must be determined and validated based on clinical evidence, including evaluation of the benefits and risks to patients. Instructions for use must be clearly documented and effective quality assurance procedures must be specified.

Prior to examination of patient specimens, satisfactory implementation of the examination procedure must be verified by the medical laboratory under conditions of actual use. In other words, the successful transfer of the validated examination procedure from the development laboratory or IVD manufacturer to the end-user medical laboratory must be demonstrated by objective evidence. Any modification of the examination procedure after this transfer may require validation that the analytical and/or clinical performance remains suitable for its intended uses, including reassessment of any risks that could be affected by the modification.

In vitro diagnostic test systems — Qualitative nucleic acid-based *in vitro* examination procedures for detection and identification of microbial pathogens —

Part 1: General requirements, terms and definitions

1 Scope

This Technical Specification is intended for

— IVD medical device manufacturers, medical laboratories, and research and development laboratories that develop nucleic acid-based qualitative *in vitro* diagnostic examination procedures for the detection and identification of microbial pathogens in human specimens, and

— medical laboratories that perform nucleic acid-based *in vitro* diagnostic examinations for the detection and identification of microbial pathogens in human specimens.

This part of ISO/TS 17822 does not apply to

— nucleic acid-based examinations that are not intended for *in vitro* diagnostic use, or

— quantitative nucleic acid-based *in vitro* diagnostic examination procedures.

2 Normative references

The following documents, in whole or in part, are normatively referenced in this document and are indispensable for its application. For dated references, only the edition cited applies. For undated references, the latest edition of the referenced document (including any amendments) applies.

ISO 13485:2003, *Medical devices — Quality management systems — Requirements for regulatory purposes*

ISO 14971:2007, *Medical devices — Application of risk management to medical devices*

ISO 15189:2012, *Medical laboratories — Requirements for quality and competence*

ISO 15190:2003, *Medical laboratories — Requirements for safety*

ISO 18113-1:2009, *In vitro diagnostic medical devices — Information supplied by the manufacturer (labelling) — Part 1: Terms, definitions and general requirements*

ISO 18113-2:2009, *In vitro diagnostic medical devices — Information supplied by the manufacturer (labelling) — Part 2: In vitro diagnostic reagents for professional use*

ISO 18113-3:2009, *In vitro diagnostic medical devices — Information supplied by the manufacturer (labelling) — Part 3: In vitro diagnostic instruments for professional use*

ISO 23640:2011, *In vitro diagnostic medical devices — Evaluation of stability of in vitro diagnostic reagents*

BIPM JCGM 200:2012, *International vocabulary of metrology — Basic and general concepts and associated terms (VIM), 3rd edition*

3 Terms and definitions

For the purposes of this document, the terms and definitions given in ISO 13485, ISO 14971, ISO 15189, ISO 18113-1, JCGM 200, and the following apply.

NOTE The terms and definitions given in ISO 18113-1 take precedence over other sources.

3.1
amplification product
amplicon
nucleic acid products created from a target amplification reaction

Note 1 to entry: Amplicons will be double-stranded DNA if created by a PCR reaction and will be primarily single-stranded RNA if created in a nucleic acid sequence-based amplification or transcription-mediated amplification reaction.

3.2
analytical performance
ability of an examination procedure to measure or detect a particular analyte

[SOURCE: GHTF/SG5/N 6:2012, 4.4.1, modified.]

Note 1 to entry: Analytical performance is determined from analytical performance studies used to assess the ability of an *in vitro* diagnostic examination procedure to measure or detect a particular analyte.

Note 2 to entry: Analytical performance characteristics can include analytical sensitivity, detection limit, analytical specificity (interference and cross-reactivity), trueness, precision, and linearity.

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

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

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

Note 2 to entry: Lack of analytical specificity in immunochemistry measurement procedures can be due to cross-reactivity (see ISO 18113-1:2009, A.3.12).

Note 3 to entry: Specificity of a measurement procedure should not be confused with clinical specificity (see ISO 18113-1:2009, A.3.16).

Note 4 to entry: JCGM 200:2008 uses the term selectivity for this concept instead of specificity.

Note 5 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.

3.4
annealing
process of hybridization of complementary strands of nucleic acid under specific conditions, for example, as in binding of a primer or a probe to the complementary target nucleic acid sequence

[SOURCE: ISO 22174:2005, 3.4.15]

3.5
clinical accuracy
diagnostic accuracy
(laboratory medicine) ability of an examination procedure to differentiate between patients who have a specific condition and those who do not have the condition

[SOURCE: CLSI EP29-A]

Note 1 to entry: Measures of clinical accuracy include clinical sensitivity and clinical specificity.

Note 2 to entry: Clinical accuracy is affected by the prevalence of the target disease or condition. With the same sensitivity and specificity, clinical accuracy of a particular examination procedure increases as the disease prevalence decreases.

3.6
clinical evaluation
(laboratory medicine) assessment and analysis of clinical evidence in order to verify the clinical safety and performance of an *in vitro* diagnostic examination procedure

[SOURCE: Based on GHTF/SG5/N2R8:2007]

3.7
clinical evidence
(laboratory medicine) all the information that supports the scientific validity and performance for a particular intended use

[SOURCE: GHTF/SG5/N 6:2012, 4.2, modified]

Note 1 to entry: Clinical evidence or data can include results of any clinical investigations or studies of the *in vitro* diagnostic examination procedure, results of relevant studies reported in the scientific literature, and published or unpublished reports of other clinical experience such as adverse events.

Note 2 to entry: Clinical evidence is used to support the labelling of an IVD medical device, including any claims made about the scientific validity and performance of the device or examination procedure

3.8
clinical performance
(laboratory medicine) ability of an *in vitro* diagnostic examination procedure to yield results that are correlated with a particular clinical condition or physiological state in accordance with the target population and intended user

[SOURCE: GHTF/SG5/N 6:2012, 4.4.2, modified]

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 Device 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.

3.9
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 particular disease or condition

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

Note 1 to entry: Also defined as percent positivity in samples 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 (FN), or 100 × TP/(TP + FN). This calculation is based on a study design where only one sample is taken from each subject.

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

3.10
clinical specificity
diagnostic specificity
(laboratory medicine) ability of an *in vitro* diagnostic examination procedure to recognize the absence of a target marker associated with a particular disease or condition

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

Note 1 to entry: Also defined as percent negativity in samples 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 is taken from each subject.

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

3.11
clinical utility
(laboratory medicine) usefulness of the results obtained from an *in vitro* diagnostic examination procedure and the value of the information to the patient and/or the broader population

[SOURCE: GHTF/SG5/N 6:2012, 4.7, modified]

Note 1 to entry: Clinical utility supports clinical decisions for patient management, such as effective treatment or preventive strategies.

3.12
complementary DNA
cDNA
single-stranded DNA that is complementary to a given RNA synthesized in the presence of reverse transcriptase to serve as a template for synthesis of DNA copies

3.13
contamination
introduction of an undesirable substance or matter

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

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 inconclusive due to measurement uncertainty.

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

[SOURCE: ISO 18113-1:2009, definition A.3.13]

3.15
denaturation
physical and/or (bio) chemical treatment which destroys or modifies the structural, functional, enzymatic, or antigenic properties of the analyte

[SOURCE: ISO 21572:2013, 3.1.6]

Note 1 to entry: Denaturation of DNA results in separation of double-stranded DNA into single-stranded DNA.

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

[SOURCE: ISO 22174:2005, 3.3.7]

3.17
detection limit
limit of detection
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

[SOURCE: JCGM 200:2008, 4.18, modified — notes deleted.]

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.

[SOURCE: ISO 22174:2005, 3.1.8]

3.18
deoxyribonucleic acid
DNA
polymer of deoxyribonucleotides occurring in a double-stranded (dsDNA) or single-stranded (ssDNA) form

[SOURCE: ISO 22174:2005, 3.1.2]

3.19
DNA polymerase for PCR
thermostable enzyme which catalyses repeated DNA synthesis

[SOURCE: ISO 22174:2005, 3.4.17]

3.20
DNA sequencing
determining the order of nucleotide bases (adenine, guanine, cytosine, and thymine) in a molecule of DNA

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

3.21
equipment qualification
verification through inspection, testing, and documentation that the correct equipment has been properly installed and performs according to pre-established specifications

3.22
external amplification control
control DNA added to an aliquot of the extracted nucleic acid in a defined amount or copy number serving as a control for amplification in a separate reaction

[SOURCE: ISO 22174:2005, 3.5.3.2]

3.23
forward work flow
unidirectional work flow
(laboratory medicine) principle of material/sample handling applied to ensure that the primary sample and the processed sample (including amplified DNA) remain physically segregated during the examination procedure

[SOURCE: ISO 24276:2006, modified]

3.24
hybridization
specific binding of complementary nucleic acid sequences under suitable reaction conditions

[SOURCE: ISO 22174:2005, 3.6.3]

3.25
identification
process of recognizing the unique attributes that identify a measurand

Note 1 to entry: In a nucleic acid-based identification examination, the process for determining that an isolate belongs to one of the established target nucleic acid sequences or organisms.

3.26
internal amplification control
DNA added to each reaction in a defined amount or copy number which serves as an internal control for amplification

[SOURCE: ISO 22174:2005, 3.5.3.1]

3.27
mastermix
mixture of reagents needed for PCR, except for the target DNA and the controls

[SOURCE: ISO 22174:2005, 3.4.18]

3.28
multiplex PCR
PCR reaction that uses multiple pairs of primers

[SOURCE: ISO 22174:2005, 3.4.11]

3.29
negative extraction control
extraction blank
control carried through all steps of the nucleic acid extraction procedure in the absence of a test sample

[SOURCE: ISO 22174:2005, 3.5.4]

3.30
negative PCR control
reaction performed with nucleic acid-free water without any PCR inhibitors

[SOURCE: ISO 22174:2005, 3.5.6]