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In vitro diagnostic medical devices — Multiplex molecular testing for nucleic acids —

Part 1: Terminology and general requirements for nucleic acid quality evaluation

Dispositifs médicaux de diagnostic in vitro — Tests moléculaires multiplex pour les acides nucléiques —

Partie 1: Terminologie et exigences générales pour l'évaluation de la qualité des acides nucléiques

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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*.

A list of all parts in the ISO 21474 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.

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Introduction

The first generation of in vitro diagnostics (IVD) medical devices for nucleic acid-based molecular tests have been focused on detection or quantitation of a single nucleic acid sequence (e.g., viral RNA, mRNA or genomic DNA) within a clinical specimen. By comparison, a multiplex molecular test simultaneously measures multiple nucleic acid sequences of interest in a single reaction. The development and clinical use of multiplex IVD medical devices are rapidly expanding with technological advances and new elucidation of the clinical significance of many biomarkers.

The measurement of multiple analytes of interest in a clinical specimen is generally performed by the following successive (or simultaneous) steps. After specimen collection, transport and storage, nucleic acids are extracted, with or without a subsequent purification procedure. The nucleic acid is then quantified, and its quality evaluated (if necessary), diluted (if necessary) and subjected to multiplex molecular test(s). Multiplex molecular tests in current clinical use detect DNA or RNA targets using various techniques, such as multiplex PCR examinations, microarrays, mass array or massive parallel sequencing-based methodologies.

Although quality aspects of nucleic acids for single target molecular analysis (such as singleplex PCR) has been described[1][2], this cannot necessarily be applied to multiplex molecular tests. Due to the inherent competition for more than one nucleic acid target in a multiplex assay, these assays are usually more sensitive to the isolated nucleic acid quality and quantity than single target assays. The variability of each specimen in biological, physical and chemical properties can influence the performance of multiplex assays to a larger degree than single target assays, potentially leading to unreliable results and hampering patient care. Thus, sample quality evaluation should require additional considerations for multiplex molecular tests.

The collection, transport and preparation of specimens for medical laboratory use has been addressed in national and international efforts in general including ISO/TS 20658 “Medical laboratories—Requirements for collection, transport, receipt and handling of samples”[3], “Guideline for the Quality Management of Specimens for Molecular Methods; The Procurement, Transport, and Preparation of Specimens” (Japan, JCCLS)[4] and “Guideline for the Quality Management of Specimens for Molecular Methods (Part 2) New Technologies and Sample Quality Control (Japan, JCCLS)”[5], and more specifically for different biological specimen types in the series of ISO 20166, 20184, and 20186[6][7][8].

This document describes the terminology and general quality requirements for nucleic acid used in multiplex molecular tests, in order to ensure reproducible performance of such tests.

NOTE Guidelines, requirements, and performance criteria laid down in this document, are intended to ensure that comparable, accurate and reproducible results are obtained in different laboratories.

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In vitro diagnostic medical devices — Multiplex molecular testing for nucleic acids —

Part 1: Terminology and general requirements for nucleic acid quality evaluation

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1 Scope

This document provides the terms and general requirements for the evaluation of the quality of nucleic acids as the analytes for multiplex molecular tests, which simultaneously identify two or more nucleic acid target sequences of interest. This document is applicable to all multiplex molecular methods used for examination using in vitro diagnostic (IVD) medical devices and laboratory developed tests (LDTs). It provides information for both qualitative and quantitative detection of nucleic acid target sequences.

This document is intended as guidance for multiplex molecular assays that detect and/or quantify human nucleic acid target sequences or microbial pathogen nucleic acid target sequences from human clinical specimens. This document is applicable to any molecular in vitro diagnostic examination performed by medical laboratories. It is also intended to be used by laboratory customers, in vitro diagnostics developers and manufacturers, biobanks, institutions and commercial organizations performing biomedical research, and regulatory authorities. This document is not applicable to metagenomics.

NOTE An examination procedure developed for a laboratory's own use is often referred to as a "laboratory developed test", "LDT", or "in-house test".

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

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 http://www.iso.org/obp

— IEC Electropedia: available at http://www.electropedia./org

3.1
accuracy
closeness of agreement between a measured quantity value and a true quantity value of a measurand

Note 1 to entry: The term accuracy, when applied to a set of test results, involves a combination of random components and a common systematic error or bias component (ISO 3534-2:2006, 3.3.1).

[SOURCE: ISO/IEC Guide 99:2007, 2.13, modified — "NOTE 1", "NOTE 2" and "NOTE 3" have been deleted, and new "Note 1 to entry" has been added.]

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