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Molecular in vitro diagnostic examinations — Specifications for pre-examination processes for frozen tissue —

Part 3: Isolated DNA

Analyses de diagnostic moléculaire in vitro — Spécifications relatives aux processus préanalytiques pour les tissus congelés —

Partie 3: ADN extrait

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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).

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 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,* in collaboration with the European Committee for Standardization (CEN) Technical Committee CEN/TC 140, *In vitro diagnostic medical devices*, in accordance with the Agreement on technical cooperation between ISO and CEN (Vienna Agreement).

A list of all parts in the ISO 20184 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

Molecular in vitro diagnostics, including molecular pathology, has enabled significant progress in medicine. Further progress is expected with new technologies analysing nucleic acids, proteins, and metabolites in human tissues and body fluids. However, integrity and profile of these molecules can change during specimen collection, transport, storage, and processing. As a consequence the outcome from diagnostics or research can become unreliable or even impossible because the subsequent examination assay might not determine the real situation in the patient but instead, an artificial profile which is generated during the pre-examination process.

DNA integrity in tissues can change during processing and storage. Modifications of the DNA molecules can impact the validity and reliability of the examination test results. It is essential to take special measures to minimize the described DNA changes and modifications for subsequent examination.

Therefore, a standardization of the entire process from specimen collection to DNA examination is needed. Studies have been undertaken to determine the important influencing factors. This document draws upon such work to codify and standardize the steps for frozen tissue with regard to DNA examination in what is referred to as the pre-examination phase.

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.

Molecular in vitro diagnostic examinations — Specifications for pre-examination processes for frozen tissue —

Part 3: Isolated DNA

1 Scope

This document specifies requirements and gives recommendations for the handling, storage, processing, and documentation of frozen tissue specimens intended for DNA examination during the pre-examination phase before a molecular examination is performed.

This document is applicable to molecular in vitro diagnostic examinations including laboratory developed tests performed by medical laboratories and molecular pathology laboratories that evaluate DNA isolated from frozen tissue. 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.

Tissues that have undergone chemical stabilization pre-treatment before freezing are not covered in this document.

NOTE International, national, or regional regulations or requirements can also apply to specific topics covered in this document.

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 terms and definitions given in ISO 15189 and the following 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
aliquot
portion of a larger amount of homogenous material, assumed to be taken with negligible sampling error

Note 1 to entry: The term is usually applied to fluids. Solid tissues are heterogeneous and therefore cannot be aliquoted.

[SOURCE: Compendium of Chemical Terminology Gold Book. International Union of Pure and Applied Chemistry. Version 2.3.3., 2014; the PAC, 1990,62,1193 (Nomenclature for sampling in analytical chemistry (Recommendations 1990)) p. 1206; and the PAC 1990, 62, 2167 (Glossary of atmospheric chemistry terms (Recommendations 1990)) p. 2173.]

3.2
ambient temperature
unregulated temperature of the surrounding air

3.3
analyte
component represented in the name of a measurable quantity

[SOURCE: ISO 17511:2020, 3.2, modified — The example was not taken over.]

3.4
analytical test performance
accuracy, precision, and sensitivity of a test to measure the *analyte* (3.3) of interest

Note 1 to entry: Other test performance characteristics such as robustness, repeatability can apply as well.

3.5
biobanking
process of acquisitioning and storing, together with some or all of the activities related to collection, preparation, preservation, testing, analysing and distributing defined biological material as well as related information and data

[SOURCE: ISO 20387:2018, 3.6]

3.6
cold ischemia
condition after removal of the tissue from the body until its stabilization or fixation

[SOURCE: ISO 20184-2:2018, 3.5]

3.7
diagnosis
identification of a health or disease state from its signs and/or symptoms, where the diagnostic process can involve *examinations* (3.10) and tests for classification of an individual's condition into separate and distinct categories or subclasses that allow medical decisions about treatment and prognosis to be made

[SOURCE: ISO 20184-2:2018, 3.6]

3.8
DNA
deoxyribonucleic acid
polymer of deoxyribonucleotides occurring in a double-stranded (dsDNA) or single-stranded (ssDNA) form

[SOURCE: ISO 22174:2005, 3.1.2]

3.9
DNase
deoxyribonuclease
enzyme that catalyzes the degradation of *DNA* (3.8) into smaller components

[SOURCE: ISO 20184-1:2018, 3.8]

3.10
examination
analytical test
set of operations with the object of determining the value or characteristics of a property

Note 1 to entry: Processes that start with the isolated *analyte* (3.3) and include all kinds of parameter testing or chemical manipulation for quantitative or qualitative examination.

[SOURCE: ISO 15189:2012, 3.7, modified — Notes to entry 1 to 3 have been removed. Note 1 to entry has been added and "analytical test" has been added as a preferred term.]

3.11
grossing
gross examination
inspection of pathology specimens with the bare eye to obtain diagnostic information, while being processed for further microscopic *examination* (3.10)

[SOURCE: ISO 20184-1:2018, 3.10]

3.12
homogeneous
uniform in structure and composition

[SOURCE: ISO 20184-1:2018, 3.11]

3.13
interfering substance
endogenous substance of a *specimen* (3.18)/*sample* (3.17) or exogenous substance (e.g. stabilization solution) that can alter an *examination* (3.10) result

[SOURCE: ISO 20184-1:2018, 3.12]

3.14
pre-examination process
preanalytical phase
preanalytical workflow
process that starts in chronological order, from the clinician's request and include the *examination* (3.10) request, preparation and identification of the patient, collection of the *primary sample(s)* (3.18), transportation to and within the medical or pathology laboratory, isolation of *analytes* (3.3), and ends when the analytical *examination* (3.10) begins

Note 1 to entry: The pre-examination phase includes preparative processes that influence the outcome of the intended *examination* (3.10).

[SOURCE: ISO 15189:2012, 3.15, modified — An additional term was added and more detail was included.]

3.15
proficiency test
evaluation of participant performance against pre-established criteria by means of inter-laboratory comparisons

[SOURCE: ISO/IEC 17043:2010, 3.7, modified — The term and definition are used here without the original notes.]

3.16
room temperature
for the purpose of this document, temperature in the range of 18 °C to 25 °C

Note 1 to entry: Local or national regulations can have different definitions.

[SOURCE: ISO 20184-1:2018, 3.19]

3.17
sample
one or more parts taken from a *primary sample* (3.19)

[SOURCE: ISO 15189:2012, 3.24, modified — The example was not taken over.]

3.18
specimen
primary sample
discrete portion of a body fluid, breath, hair or tissue taken for *examination* (3.10), study or analysis of one or more quantities or properties assumed to apply for the whole

[SOURCE: ISO 20184-1:2018, 3.14]

3.19
stability
ability of a *sample* (3.17) material, when stored under specified conditions, to maintain a stated property value within specified limits for a specified period of time

Note 1 to entry: The *analyte* (3.3) for the purpose of this document is *DNA* (3.7).

[SOURCE: ISO Guide 30:2015, 2.1.15, modified — The words "reference material" were replaced by "sample material".]

3.20
storage
maintenance of biological material under defined and standardized conditions for the intended use

Note 1 to entry: Long-term storage typically occurs in laboratory archives or in biobanks.

3.21
validation
confirmation, through the provision of objective evidence, that the requirements for a specific intended use or application have been fulfilled

Note 1 to entry: The term "validated" is used to designate the corresponding status.

[SOURCE: ISO 9000:2015, 3.8.13, modified — Note 1 and Note 3 were not taken over.]

3.22
verification
confirmation, through provision of objective evidence, that specified requirements have been fulfilled

Note 1 to entry: The term "verified" is used to designate the corresponding status.

Note 2 to entry: Confirmation can comprise activities such as:

— performing alternative calculations,

— comparing a new design specification with a similar proven design specification,

— undertaking tests and demonstrations, and

— reviewing documents prior to issue.

[SOURCE: ISO 9000:2015, 3.8.12, modified — Note 1 and Note 2 to entry have been deleted; Note 3 to entry has been renumbered as Note 1 to entry; new Note 2 to entry has been added.]

3.23
warm ischemia
condition before the tissue is removed from the body, but where it is deprived of its normal blood supply

[SOURCE: ISO 20184-1:2018, 3.25]

Note 1 to entry: Disruption of normal blood supply varies significantly case by case. Therefore, warm ischemia duration and its effects depend on individual cases and it also can depend on the anatomy of the arterial blood supply.

3.24
workflow
series of activities necessary to complete a task

[SOURCE: ISO 20184-1:2018, 3.26]

4 General considerations

For general statements on medical laboratory quality management systems and in particular on specimen collection, reception and handling (including avoidance of cross contaminations) see ISO 15189, ISO/IEC 17025 or ISO/IEC 17020. The requirements on laboratory equipment, reagents, and consumables according to ISO 15189 shall be followed; ISO/IEC 17025 and ISO/IEC 17020 can also apply.

All steps of the pre-examination, examination and post-examination processes (i.e. the entire workflow) can influence the diagnosis or research study results. Thus, this entire workflow shall be specified, verified and validated during the development of the examination. This includes specifically all pre-examination process steps such as the examination request, preparation and identification of the patient, collection of the primary sample(s), transport to and within the medical laboratory, storage and isolation of analytes. Workflow steps which cannot always be controlled (e.g. warm ischemia) shall be documented.

In contrast to RNA or proteins, DNA in tissue is relatively stable during warm and cold ischemia. Changes of DNA sequence or copy numbers (e.g. comparative genomic hybridization (CGH) profiles) due to longer warm and cold ischemia durations are unknown[9]. However, DNA methylation profiles may change in response to ischemia[10]. The duration until the specimen is frozen should be kept as short as possible in order to avoid enzymatic degradation of DNA. The duration before freezing shall be documented and the temperature before freezing should be documented[9].

During the design and development of a DNA based examination, a risk assessment shall be performed (see also ISO 14971). Mitigation measures for eliminating or reducing identified risks shall be established where required for ensuring the performance of the examination.

Safety requirements on specimen transport and handling shall be considered as given in ISO 15189 and ISO 15190. International, national, or regional regulations or requirements can also apply.

During the whole pre-examination process, precautions shall be taken to avoid cross contamination between different specimens/samples, e.g. by using single-use material whenever feasible or appropriate cleaning procedures between processing of different specimens/samples.

Where the examination manufacturer has specified instructions for pre-examination steps, these shall be followed. When, for justified reasons (e.g. unmet patient needs), a commercial product is not used in accordance to the manufacturer's instructions, responsibility for its validation, verification, use and performance lies with the user.

For general considerations on specimen collection, transport, receipt, and handling, see ISO 20658 and ISO 20387.