SLOVENSKI STANDARD
SIST-TS CEN/TS 16826-3:2018

01-september-2018

Molekularne diagnostične preiskave in vitro - Specifikacije za predpreiskovalne procese za hitro zamrznjena tkiva - 3. del: Izolirani DNA

Molecular in vitro diagnostic examinations - Specifications for pre-examination processes for snap frozen tissue - Part 3: Isolated DNA

Molekularanalytische in-vitro-diagnostische Verfahren - Spezifikationen für präanalytische Prozesse für schockgefrorene Gewebeproben - Teil 1: Isolierte DNA

Tests de diagnostic moléculaire in vitro - Spécifications relatives aux processus préanalytiques pour les tissus à congélation rapide - Partie 3: ADN isolé

Ta slovenski standard je istoveten z: **CEN/TS 16826-3:2018**

ICS:

11.100.10	Diagnostični preskusni sistemi in vitro	In vitro diagnostic test systems

SIST-TS CEN/TS 16826-3:2018 **en**

TECHNICAL SPECIFICATION

SPÉCIFICATION TECHNIQUE

TECHNISCHE SPEZIFIKATION

CEN/TS 16826-3

July 2018

ICS 11.100.10

English Version

Molecular in vitro diagnostic examinations - Specifications for pre-examination processes for snap frozen tissue - Part 3: Isolated DNA

Tests de diagnostic moléculaire in vitro - Spécifications relatives aux processus préanalytiques pour les tissus à congélation rapide - Partie 3: ADN isolé

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EUROPEAN COMMITTEE FOR STANDARDIZATION
COMITÉ EUROPÉEN DE NORMALISATION
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CEN-CENELEC Management Centre: Rue de la Science 23, B-1040 Brussels

Ref. No. CEN/TS 16826-3:2018 E

Contents

Page

European foreword

This document (CEN/TS 16826-3:2018) has been prepared by Technical Committee CEN/TC 140 “In vitro diagnostic medical devices”, the secretariat of which is held by DIN.

Attention is drawn to the possibility that some of the elements of this document may be the subject of patent rights. CEN shall not be held responsible for identifying any or all such patent rights.

CEN/TS 16826 consists of the following parts:

— *Molecular in vitro diagnostic examinations — Specifications for pre-examination processes for snap frozen tissue — Part 1: Isolated RNA*;

— *Molecular in vitro diagnostic examinations — Specifications for pre-examination processes for snap frozen tissue — Part 2: Isolated proteins*;

— *Molecular in vitro diagnostic examinations — Specifications for pre-examination processes for snap frozen tissue — Part 3: Isolated DNA*.

According to the CEN/CENELEC Internal Regulations, the national standards organisations of the following countries are bound to announce this Technical Specification: Austria, Belgium, Bulgaria, Croatia, Cyprus, Czech Republic, Denmark, Estonia, Finland, Former Yugoslav Republic of Macedonia, France, Germany, Greece, Hungary, Iceland, Ireland, Italy, Latvia, Lithuania, Luxembourg, Malta, Netherlands, Norway, Poland, Portugal, Romania, Serbia, Slovakia, Slovenia, Spain, Sweden, Switzerland, Turkey and the United Kingdom.

Introduction

Molecular *in vitro* diagnostics, including molecular pathology, has enabled a 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 of these molecules can change during specimen collection, transport, storage, and processing, thus making the outcome from diagnostics or research unreliable or even impossible because the subsequent examination assay will not determine the situation in the patient but an artificial pattern generated during the pre-examination process. Therefore, a standardization of the entire process from specimen collection to the 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.

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. Therefore, it is essential to take special measures to minimize the described DNA changes and modifications for subsequent examination.

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.

1 Scope

This document 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 examination 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.

EN ISO 15189:2012, *Medical laboratories — Requirements for quality and competence (ISO 15189:2012, Corrected version 2014-08-15)*

EN ISO/IEC 17020:2012, *Conformity assessment — Requirements for the operation of various types of bodies performing inspection (ISO/IEC 17020:2012)*

ISO 15190, *Medical laboratories — Requirements for safety*

3 Terms and definitions

For the purposes of this document, the terms and definitions given in EN ISO 15189 and the following apply.

ISO and IEC maintain terminological databases for use in standardization at the following addresses:

- IEC Electropedia: available at http://www.electropedia.org/
- ISO Online browsing platform: available at http://www.iso.org/obp

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. Tissues are heterogeneous and therefore cannot be aliquoted.

Note 2 to entry: The definition is derived from the 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: EN ISO 17511:2003, 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 of interest

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

3.5
cold ischemia
condition after removal of the tissue from the body until its stabilization or fixation

3.6
diagnosis
identification of a health or disease state from its signs and/or symptoms, where the diagnostic process can involve examinations 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

3.7
DNA
deoxyribonucleic acid
polymer of deoxyribonucleotides occurring in a double-stranded (dsDNA) or single-stranded (ssDNA) form

[SOURCE: EN ISO 22174:2005, 3.1.2]

3.8
DNase
deoxyribonuclease
enzyme that catalyzes the degradation of DNA into smaller components

3.9
examination
analytical test
set of operations having the object of determining the value or characteristics of a property

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

[SOURCE: EN ISO 15189:2012, 3.7, modified — The term and definition are used here without the original notes.]

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

3.11
homogeneous
uniform in structure and composition

3.12
interfering substance
endogenous substance of a specimen/sample or exogenous substance (e.g. stabilization solution) that can alter an examination result

3.13
pre-examination process
preanalytical phase
preanalytical workflow
process that start in chronological order, from the clinician's request and include the examination request, preparation and identification of the patient, collection of the primary sample(s), transportation to and within the medical or pathology laboratory, isolation of analytes, and ends when the analytical examination begins

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

[SOURCE: EN ISO 15189:2012, 3.15, modified — An additional term was added and details were adjusted to the scope of this document.]

3.14
primary sample
specimen
discrete portion of a body fluid, breath, hair or tissue taken for examination, study or analysis of one or more quantities or properties assumed to apply for the whole

[SOURCE: EN ISO 15189:2012, 3.16, modified — The term and definition are used here without the original notes.]

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

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

3.16
room temperature
for the purposes 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.

3.17
sample
one or more parts taken from a primary sample

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

3.18
stability
ability of a sample 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 for the purpose of this document is DNA.

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

3.19
storage
prolonged interruption of the preanalytical workflow of a sample or analyte respectively, or of their derivatives e.g., stained sections or tissue blocks, under appropriate conditions in order to preserve their properties

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

3.20
validation
confirmation, throughout 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: EN ISO 9000:2015, 3.8.13, modified — Note 1 and Note 3 were not taken over.]

3.21
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.

[SOURCE: EN ISO 9000:2015, 3.8.12, modified — Note 1 and Note 2 were not taken over.]

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.

3.22
warm ischemia
condition before the tissue is removed from the body, but where it is deprived of its normal blood supply

3.23
workflow
series of activities necessary to complete a task

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 EN ISO 15189:2012, 4.2, 5.4.4, 5.4.6 or EN ISO/IEC 17020:2012, Clause 8 and 7.2. The requirements on laboratory equipment, reagents, and consumables according to EN ISO 15189:2012, 5.3 shall be followed; EN ISO 15189:2012, 5.5.1.2 and 5.5.1.3 and EN ISO/IEC 17020:2012, 6.2 can also apply.

All steps of a diagnostic workflow can influence the final analytical test result. Thus, the entire workflow including biomolecule stability and sample storage conditions shall be verified and validated. Workflow steps which cannot always be controlled (e.g. warm ischemia) shall be documented. A risk assessment of non-controllable workflow steps including their potential impact on the analytical test performance shall be performed and mitigation measures shall be established to enable the required analytical test performance.

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 [6]. However, DNA methylation patterns may change in response to ischemia. [7] 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 [6].

Safety requirements on specimen transport and handling shall be considered (see EN ISO 15189:2012, 5.2.3 and 5.4.5 and ISO 15190).

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.

If a commercial product is not used in accordance with the manufacturer's instructions, responsibility for its validation, verification, use and performance lies with the user.

5 Outside the laboratory

5.1 Specimen collection

5.1.1 General

For the collection of the specimen, the requirements (e.g. disease condition, specimen size) for the intended molecular examination (see also Clause 6) should be considered.

See also EN ISO 15189:2012, 5.4.4.

5.1.2 Information about the specimen donor/patient

The documentation shall include the ID of the specimen donor/patient, which can be in the form of a code.

The documentation should include, but is not limited to:

a) the relevant health status of the specimen donor/patient (e.g. healthy, disease type, concomitant disease, demographics (e.g. age and gender);