SLOVENSKI STANDARD
kSIST-TS FprCEN/TS 17747:2022

01-januar-2022

Molekularne diagnostične preiskave in vitro - Specifikacije za predpreiskovalne procese za eksosome in druge zunajcelične vezikle v vensko polni krvi - DNK, RNK in proteini

Molecular in vitro diagnostic examinations - Specifications for pre-examination processes for exosomes and other extracellular vesicles in venous whole blood - DNA, RNA and proteins

Molekularanalytische in-vitro-diagnostische Verfahren - Spezifikationen für präanalytische Prozesse für Exosomen und andere extrazelluläre Vesikel im venösen Vollblut - DNA, RNA und Proteine

Analyses de diagnostic moléculaire in vitro - Spécifications relatives aux processuses préanalytiques pour exosomes et autres vésicules extracellulaires dans le sang total veineux - ADN, ARN et protéines

Ta slovenski standard je istoveten z: **FprCEN/TS 17747**

ICS:

11.100.10	Diagnostični preskusni sistemi in vitro	In vitro diagnostic test systems

kSIST-TS FprCEN/TS 17747:2022 **en,fr,de**

TECHNICAL SPECIFICATION

SPÉCIFICATION TECHNIQUE

TECHNISCHE SPEZIFIKATION

FINAL DRAFT
FprCEN/TS 17747

November 2021

ICS 11.100.10

English Version

Molecular in vitro diagnostic examinations - Specifications for pre-examination processes for exosomes and other extracellular vesicles in venous whole blood - DNA, RNA and proteins

Analyses de diagnostic moléculaire in vitro - Spécifications relatives aux processuses préanalytiques pour exosomes et autres vésicules extracellulaires dans le sang total veineux - ADN, ARN et protéines

Molekularanalytische in-vitro-diagnostische Verfahren - Spezifikationen für präanalytische Prozesse für Exosomen und andere extrazelluläre Vesikel im venösen Vollblut - DNA, RNA und Proteine

This draft Technical Specification is submitted to CEN members for Vote. It has been drawn up by the Technical Committee CEN/TC 140.

CEN members are the national standards bodies of Austria, Belgium, Bulgaria, Croatia, Cyprus, Czech Republic, Denmark, Estonia, Finland, France, Germany, Greece, Hungary, Iceland, Ireland, Italy, Latvia, Lithuania, Luxembourg, Malta, Netherlands, Norway, Poland, Portugal, Republic of North Macedonia, Romania, Serbia, Slovakia, Slovenia, Spain, Sweden, Switzerland, Turkey and United Kingdom.

Recipients of this draft are invited to submit, with their comments, notification of any relevant patent rights of which they are aware and to provide supporting documentation.

Warning : This document is not a Technical Specification. It is distributed for review and comments. It is subject to change without notice and shall not be referred to as a Technical Specification.

EUROPEAN COMMITTEE FOR STANDARDIZATION
COMITÉ EUROPÉEN DE NORMALISATION
EUROPÄISCHES KOMITEE FÜR NORMUNG

CEN-CENELEC Management Centre: Rue de la Science 23, B-1040 Brussels

Ref. No. FprCEN/TS 17747:2021 E

Contents

Page

European foreword

This document (FprCEN/TS 17747:2021) has been prepared by Technical Committee CEN/TC 140 “In vitro diagnostic medical devices”, the secretariat of which is held by DIN.

This document is currently submitted to the Vote on TS.

Introduction

Molecular *in vitro* diagnostics has enabled a significant progress in medicine. Further progress is expected by new technologies analysing profiles of nucleic acids, proteins, and metabolites in human tissues and body fluids. However, the profiles of these molecules can change drastically during the pre-examination process, including the specimen collection, transport, storage and processing.

Consequently, this makes the outcome from diagnostics or research unreliable or even impossible because the subsequent examination might not determine the real situation in the patient but an artificial profile generated during the pre-examination process.

Besides cell free circulating nucleic acids, circulating tumour cells (CTCs) and other rare cells, exosomes and other extracellular vesicles represent another key component of liquid biopsies. Therefore, there is a strongly increasing interest in research and emerging diagnostics in exosomes and other extracellular vesicles.

The pre-examination process described in this document results in enriched extracellular vesicles (EV) (e.g. exosomes) or DNA, RNA and proteins isolated therefrom.

New additional extracellular vesicles can be released and existing extracellular vesicles can be lost after blood collection, thus changing the overall EV DNA/RNA/protein profiles. Also, different anticoagulants in different types of blood collection tubes can influence the release of EVs from different cells present in blood, including those from platelets. Further factors can influence the post collection changes of the entire blood EV composition, such as storage and transport temperature and duration, centrifugation parameters, etc.

Standardization of the entire workflow from the specimen collection to the EV surface protein and isolated DNA, RNA and protein examination from EVs is therefore needed. Studies have been undertaken to determine the important influencing factors. This document draws upon such work to codify and standardize the steps of EV surface protein examination and of DNA, RNA and protein examination from EVs 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.

1 Scope

This document gives guidelines on the handling, storage, processing and documentation of venous whole blood specimens intended for DNA, RNA and protein examination from exosomes and other extracellular vesicles during the pre-examination phase before a molecular examination is performed. This document covers specimens collected in venous whole blood collection tubes.

The pre-examination process described in this document results in isolated DNA, RNA and proteins from enriched exosomes and other extracellular vesicles.

This document is applicable to molecular *in vitro* diagnostic examinations performed by medical laboratories. It is also intended to be used by health care institutions including facilities collecting and handling specimen, laboratory customers, *in vitro* diagnostics developers and manufacturers, biobanks, institutions and commercial organizations performing biomedical research, and regulatory authorities.

Different dedicated measures are taken during the pre-examination phase for venous whole blood circulating cell-free RNA (ccfRNA) examination and for venous whole blood circulating cell-free DNA (ccfDNA) examination, both without prior enrichment of exosomes and other extracellular vesicles. These are not described in this document but are covered in EN ISO 20186-3, *Molecular in vitro diagnostic examinations — Specifications for pre-examination processes for venous whole blood — Part 3: Isolated circulating cell free DNA from plasma* and CEN/TS (WI 00140134), *Molecular in vitro diagnostic examinations — Specifications for pre-examination processes for venous whole blood — Isolated circulating cell free RNA from plasma*.

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

ISO 15190, *Medical laboratories — Requirements for safety*

ISO/TS 20658, *Medical laboratories — Requirements for collection, transport, receipt, and handling of samples*

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:

— ISO Online browsing platform: available at http://www.iso.org/obp

— IEC Electropedia: available at https://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. 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
analyte
component represented in the name of a measurable quantity

[SOURCE: ISO 17511:2020, 3.2 — Deleted Example.]

3.3
blood collection set
intravenous device specialized for venipuncture, consisting of a stainless steel beveled needle and tube (tubing) with attached plastic wings and fitting connector

Note 1 to entry: The connector attaches to an additional blood collection device, e.g. a blood collection tube.

3.4
blood collection tube
tube used for blood collection, usually with a vacuum which forces blood from the vein through the needle into the tube

3.5
closed system
non-modifiable system provided by the vendor including all necessary components for the examination (i.e. hardware, software, procedures and reagents)

3.6
deoxyribonucleic acid
DNA
polymer of deoxyribonucleotides occurring in a double-stranded (dsDNA) or single-stranded (ssDNA) form

[SOURCE: EN ISO 22174:2005, 3.1.2]

3.7
deoxyribonuclease
DNase
enzyme that catalyzes the degradation of DNA into smaller components

3.8
examination
analytical test
set of operations having the object of determining the value or characteristics of a property

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

[SOURCE: ISO 15189:2012, 3.7, modified — Term and definition are used here without the original notes; an additional term was added.]

3.9
examination manufacturer
analytical test manufacturer
entity that manufactures and/or produces a specific analytical test

Note 1 to entry: For the purpose of this document, an EV DNA, RNA and protein examination manufacturer is meant.

3.10
examination performance
analytical test performance
analytical 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.

[SOURCE: EN ISO 20184-1:2018, 3.4]

3.11
extracellular vesicle
EV
particle naturally released from the cell that are delimited by a lipid bilayer and cannot replicate, i.e. does not contain a functional nucleus

EXAMPLE Exosomes, endosomes, oncosomes, apoptotic bodies

[SOURCE: [1]]

3.12
EV stabilizer
chemical formulation that increases the stability of EVs, including the overall EV populations, their cargo (e.g. DNA, RNA and proteins) and EV surface proteins in a specimen or sample

3.13
interfering substance
endogenous or exogenous substances in clinical specimens/samples that can alter an examination result

Note 1 to entry: Examples of endogenous substances are blood components and acidic polysaccharides.

Note 2 to entry: Examples of exogenous substances are talc and anticoagulant.

3.14
needle holder
barrel used in routine venepuncture procedures to hold the blood collection tube in place and to protect the phlebotomist from direct contact with blood

Note 1 to entry: Examples of endogenous substances are blood components and acidic polysaccharides.

Note 2 to entry: Examples of exogenous substances are talc and anticoagulant.

3.15
pre-examination processes
preanalytical phase
preanalytical workflow
pre-examination phase
processes 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 laboratory, storage, isolation of analytes, and end when the analytical examination begins

Note 1 to entry: The pre-examination phase includes preparative processes, e.g. RNA isolation procedures, which influence the outcome of the intended examination.

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

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

3.17
proficiency testing
evaluation of participant performance against pre-established criteria by means of interlaboratory comparisons

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

3.18
protein
type of biological macromolecules composed of one or more chains with a defined sequence of amino acids connected through peptide bonds

3.19
ribonucleic acid
RNA
polymer of ribonucleotides occurring in a double-stranded or single-stranded form

[SOURCE: EN ISO 22174:2005, 3.1.3]

3.20
ribonuclease
RNase
enzyme that catalyses the degradation of RNA into smaller components

3.21
room temperature
temperature in the range of 18 °C to 25 °C

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

[SOURCE: EN ISO 20166-1:2018, 3.22]

3.22
sample
one or more parts taken from a primary sample

[SOURCE: ISO 15189:2012, 3.24, modified — Example has been removed.]

3.23
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

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

3.24
storage
prolonged interruption of the pre-analytical workflow of a sample or analyte respectively, or of their derivatives, under appropriate conditions in order to preserve their properties

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

[SOURCE: EN ISO 20184-1:2018, 3.21, modified — Example has been removed.]

3.25
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 have been omitted.]

3.26
venous whole blood
blood collected after directly puncturing a vein, usually with a needle and syringe, or other collection device