SLOVENSKI STANDARD
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Molekularne diagnostične preiskave in vitro - Specifikacije za predpreiskovalne procese za hitro zamrznjena tkiva - 2. del: Posamični RNA

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

Molekularanalytische in-vitro-diagnostische Verfahren - Spezifikationen für präanalytische Prozesse für gefrorenes Gewebe - Teil 1: Isolierte RNS

Tests de diagnostic moléculaire in vitro - Spécifications relatives aux processus préanalytiques pour les tissus à congélation rapide - Partie 1: ARN extrait

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

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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.

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Foreword

This document (FprCEN/TS 16826-1:2015) 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 Formal Vote.

Introduction

Molecular *in vitro* diagnostics has enabled a significant progress in medicine. Further progress is expected by new technologies analysing signatures of nucleic acids, proteins, and metabolites in human tissues and body fluids. However, the profiles and/or integrity of these molecules can change drastically during primary sample collection, transport, storage, and processing thus making the outcome from diagnostics or research unreliable or even impossible because the subsequent analytical assay will not determine the situation in the patient but an artificial profile generated during the pre-examination process. Therefore, a standardisation of the entire process from primary sample collection to RNA analysis is needed. Studies have been undertaken to determine the important influencing factors. This Technical Specification draws upon such work to codify and standardize the steps for frozen tissue with regard to RNA analysis in what is referred to as the preanalytical phase.

1 Scope

This Technical Specification recommends the handling, documentation and processing of frozen tissue specimens intended for RNA analysis during the preanalytical phase before a molecular assay is performed. This Technical Specification is applicable to molecular *in vitro* diagnostic examinations (e.g., *in vitro* diagnostic laboratories, laboratory customers, *in vitro* diagnostics developers and manufacturers, institutions and commercial organisations performing biomedical research, biobanks, and regulatory authorities).

RNA profiles in tissues can change significantly before and after collection and can change differently in different donors' / patients' tissues.

Therefore, it is essential to take special measures to minimize the described profile changes and modifications within the tissue for subsequent RNA analysis.

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

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.

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

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 15189:2012 and the following terms and definitions apply.

3.1
ambient temperature
unregulated temperature of the surrounding air

3.2
analytical phase
processes that start with the isolated analyte and include all kind of parameter testing or chemical manipulation for quantitative or qualitative analysis

3.3
cold ischemia
condition after removal of the tissue from the body until its stabilization or fixation

3.4
pre-examination processes
preanalytical phase
preanalytical workflow
processes that start, in chronological order, from the clinician's request and include the examination request, preparation and identification of the patient, surgical procedure, collection of the primary sample(s), temporary storage, transportation to and within the analytical laboratory, aliquotting, retrieval, isolation of analytes, and end when the analytical examination begins

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

Note 1 to entry: The preanalytical phase may include preparative processes that may influence the outcome of the intended examination.

3.5
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 is used here without the original notes.]

3.6
quantitative RNA profile
RNA profile
amounts of the individual RNA molecules that are present in a sample and that can be measured in the absence of any losses, inhibition and interference

3.7
RNA
ribonucleic acid
polymer of ribonucleotides occurring in a double-stranded or single-stranded form

[SOURCE: EN ISO 22174:2005, 3.1.3]

3.8
room temperature
temperature which is defined as 18 °C to 25 °C for the purposes of this document

3.9
sample
one or more parts taken from a primary sample

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

3.10
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 30:1992, 2.7]

Note 1 to entry: The measured constituent for the purpose of this document is RNA.

3.11
warm ischemia
warm Ischemia is the condition where the tissue is deprived of its normal blood supply containing oxygen and nutrients while the tissue is at body temperature

4 General considerations

For general statements on primary sample collection and handling (including avoidance of cross contaminations) see EN ISO 15189:2012, 5.4.4, 5.2.6. Consumables including kits shall be verified before use in examination (see EN ISO 15189:2012, 5.3.2.3); EN ISO 15189:2012, 5.5.1.2 and 5.5.1.3 can also apply.

As all steps of a diagnostic workflow can influence the final analytical performance, the entire workflow comprising the preanalytical steps, including information on biomolecule stability and storage conditions, and analytical steps should be verified and validated (see EN ISO 15189).

The stability of the specific quantitative RNA profile(s) of interest should be investigated throughout the entire preanalytical workflow prior to the development and implementation of an analytical test.

Before tissues stabilized by freezing, quantitative RNA profile can change e.g., by gene induction, gene down regulation and RNA degradation. These effects depend on the warm and cold ischemia times and the ambient temperature before freezing. In addition, the described effects can vary in different donors' / patients' tissues.

Generally, the longer the warm and cold ischemia times and the higher the ambient temperature before freezing the tissue specimen, the higher is the risk that changes in the RNA profile can occur.

NOTE Intraoperative warm ischemia can result in more pronounced changes of RNA profiles than during postoperative cold ischemia. RNA profiles can also vary, depending on the origin and type of tissue, the underlying disease, the surgical procedure, the drug regime, and drugs administered for anaesthesia or treatment of concomitant disease and on the different environment conditions after the tissue removal from the body.

As warm ischemia cannot be easily standardized, its time and duration should be documented. When it is not possible to avoid cold ischemia, its time of onset, duration shall be documented and temperatures of the specimen transport container's surroundings should be documented. Where the specimen is transported to another facility for freezing, the transport duration shall be documented and the ambient conditions should also be documented.

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

During the whole preanalytical workflow precautions shall be taken to avoid cross contamination between different samples.

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

5 Outside the laboratory

5.1 Primary tissue collection manual

5.1.1 Information about the primary sample donor

The documentation should include, but is not limited to:

a) the primary donor / patient ID, which can be in the form of a code;

b) the health status of the primary sample donor (e.g., healthy, disease type, concomitant disease);

c) the information about routine medical treatment and special treatment prior to tissue collection (e.g., anaesthetics, medications, surgical or diagnostic procedures (e.g., biopsy device used for the collection));

d) the start of ischemia within the body (warm ischemia) by documenting the ischemia-relevant vessel ligation/clamping time point (usually arterial clamping time).

5.1.2 Information on the primary tissue sample

The documentation shall include, but is not limited to:

a) the time point when tissue is removed from the body;

b) the description of tissue type, tissue condition (e.g., diseased, unaffected by the disease) and organ of origin, including references to any marking applied in the operating theatre made by surgeon, radiologist or pathologist;

c) the documentation steps described under 6.3, if freezing is performed outside the laboratory.

5.1.3 Information on the primary tissue sample processing

The following steps shall be performed:

1. the documentation of any additions or modifications to the primary sample after removal from the body (e.g., labelling for the orientation of the specimen (e.g., ink-marking, stitches), incision(s));

2. the selection and use of transport containers and packages (e.g., cooling box, box for storing and transportation, vacuum packaging);

3. the selection and use of stabilisation procedures (e.g., cooling methods) for transport;

NOTE 1 Accidentally freezing and thawing the tissue (e.g., by using cool packs in a wrong manner) will lead to RNA degradation when the tissue thaws thereafter. It can also impact the morphological characterisation.

NOTE 2 This step can be omitted, if the specimen is directly frozen (see 6.3.)

4. the labelling of the transport container (e.g., registration-number, barcode (1D or 2D), primary sample type, quantity, and organ tissue of origin) and additional documentation (information as specified in 5.1.1, 5.1.2, and 5.1.3, 1. to 3.). If a single sample container contains several aliquots of the same specimen, and the aliquots represent different features (e.g., tissue type, disease status, location) this shall be documented.

Specimens should be transferred without delay into the transport container after the removal from the body. The container should then be kept on wet-ice or at 2 °C to 8 °C in order to minimize RNA profile changes.

The temperatures of the transport container's surroundings during cold ischemia time (e.g., temperatures in different rooms, transport) should be documented. If the temperature cannot be measured, the temperature range should be estimated by classification as ambient temperature, room temperature, or at 2 °C to 8 °C.

5.2 Transport requirements

The laboratory in partnership with the clinical or surgery department shall establish a protocol for the transport procedure of the specimen.

If the primary tissue sample is not already frozen, it should be transported on wet-ice or at 2 °C to 8 °C without delay in order minimize changes to the RNA profile.

NOTE There is evidence that RNA in tissues can be stabilised in plastic bags under vacuum when kept at 0 °C to 4 C° during transport [1] before the samples are archived for biobanks or used for histopathological evaluation.

The compliance with the protocol for the transport procedure shall be documented. Any deviations from the protocol shall be described and documented.

6 Inside the laboratory

6.1 Information on the primary tissue sample receipt

The name of the person receiving the primary tissue sample shall be documented. The tissue sample arrival time and conditions (e.g., labelling, transport conditions including temperature, tissue type and quantity of the primary sample, leaking/breaking of the container) of the received samples shall be documented. Any deviations from the established protocol for the transport procedure (see 5.2) shall be documented.

NOTE Temperature conditions during transport can influence the quantitative RNA profile and RNA quality.