SLOVENSKI STANDARD
SIST-TS CEN/TS 16945:2016

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Molekularne diagnostične preiskave in vitro - Specifikacije za predpreiskovalne procese metabolomike v urinu, serumu in plazmi venske krvi

Molecular in vitro diagnostic examinations - Specifications for pre-examination processes for metabolomics in urine, venous blood serum and plasma

Molekularanalytische in-vitro-diagnostische Verfahren - Spezifikationen für präanalytische Prozesse für Metabolomuntersuchungen in Urin, venösem Blutserum und -plasma

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Molecular in vitro diagnostic examinations - Specifications for pre-examination processes for metabolomics in urine, venous blood serum and plasma

Tests de diagnostic moléculaire in vitro - Spécifications relatives aux processus préanalytiques pour l'analyse du métabolome dans l'urine et le sang veineux (sérum et plasma)

Molekularanalytische in-vitro-diagnostische Verfahren - Spezifikationen für präanalytische Prozesse für Metabolomuntersuchungen in Urin, venöses Blutserum und -plasma

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EUROPEAN COMMITTEE FOR STANDARDIZATION
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European foreword

This document (CEN/TS 16945:2016) has been prepared by Technical Committee CEN/TC 140 “In vitro diagnostic and medical devices”, the secretariat of which is held by DIN.

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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 of these molecules can change drastically during primary sample collection, transport, storage, and processing thus introducing biases and 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 standardization of the entire process from sample collection to metabolomics 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 urine, serum and plasma metabolomics analysis in what is referred to as the preanalytical phase.

Metabolomics, the global profiling of metabolites (namely molecules with a molecular weight MW ≤ 2 000 Da [3]) in biological samples, is the determination of the dynamic multi-parametric metabolic response of living systems to pathophysiological stimuli and/or genetic modification. Metabolomics studies, which can be semiquantitative or quantitative, help in identifying metabolic profiles that are characteristic for given pathological conditions, for disease prognosis, for the evaluation of the individual response to medical intervention and pharmaceutical treatments. Metabolites are physically and chemically different, and include e.g. sugars, acids, bases, and lipids [3]. This diversity of metabolites and the dynamic range of their concentration in biological samples complicate the separation and detection methods and make it impossible to identify all the metabolites in a single experiment. However, new high-throughput technologies based on NMR (nuclear magnetic resonance) spectroscopy and MS (mass spectrometry) hold great potential due to their ability to look at large parts of the whole metabolome, although with different sensitivity. These two main analytical platforms are now well standardized. Equally well established are the statistical approaches needed to extract information from the huge amount of data resulting from metabolomic analysis.

The metabolic profiles are very sensitive to preanalytical variations that can result from enzymatic activity in the samples and chemical reactions (e.g. oxidation, [4], [5]). This Technical Specification series provides guidelines arising from systematic studies conducted on the most commonly employed biofluids: urine and blood derivatives, serum and plasma.

1 Scope

This Technical Specification covers the preanalytical phase and recommends the handling, documentation and processing of urine, venous blood plasma and serum intended for metabolomics analysis. This Technical Specification is applicable to metabolomics examinations and is of importance to biomedical laboratories, customers of laboratories, *in vitro* diagnostics developers and manufacturers, institutions and companies performing biomedical research, biobanks, and regulatory authorities.

The adoption of the described procedures for the preanalytical phase make it possible to compare and evaluate the results obtained from metabolic profiling analysis.

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 apply.

3.1
analytical phase
processes that start with the isolated analyte and include all kind of parameter testing or chemical manipulation for quantitative or qualitative analysis

Note 1 to entry: For metabolomic analysis, analyte isolation is not necessarily required.

3.2
biofluid
biological fluid which can be excreted (such as urine or sweat), secreted (such as breast milk, saliva or bile), obtained with a needle (such as blood or cerebrospinal fluid), or produced as a result of a pathological process (such as blister or cyst fluid)

3.3
fasting
abstinence from any solid or liquid food excluding water

3.4
mass spectrometry
MS
method used to analyse chemical compounds on the basis of their mass to charge ratio

3.5
metabolic profiling
use of analytical platforms to simultaneously measure the ensemble of metabolites that are accessible to the employed (or selected) technique

EXAMPLE Examples for such techniques are NMR and MS.

3.6
metabolites
small molecules (≤ 2000 Da) that are intermediates and/or products of metabolism

Note 1 to entry: For further information see [3].

3.7
metabolome
complete set of metabolites to be found within an organism or a biological sample

Note 1 to entry: For further information see [3].

3.8
metabolomics
scientific study of the whole metabolome present within a biological sample (e.g., organism, cell, tissue or biofluids) under a given set of conditions

3.9
MS-based metabolomics
use of mass spectrometry to measure metabolites in biological samples

3.10
Nuclear magnetic resonance spectroscopy
NMR
method where the resonance magnetic properties of atomic nuclei are used to determine physical and chemical properties of atoms and molecules

[SOURCE: ISO/TS 80004-6:2013, 4.26]

3.11
NMR-based metabolomics
use of NMR spectroscopy to measure metabolites in biological samples

3.12
plasma
liquid part of unclotted blood

Note 1 to entry: Plasma samples can contain anti-coagulants.

3.13
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, 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

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

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

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

3.16
serum
liquid that can be separated from clotted blood

3.17
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 analytes for the purpose of this document are metabolites.

[SOURCE: ISO Guide 30:1992, 2.7]

4 General Considerations

For general statements on specimen collection and handling (including avoidance of cross contaminations) see EN ISO 15189:2012, 5.2.6, 5.4.4. 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 specimen stability and storage conditions, and analytical steps should be verified and validated (see EN ISO 15189).

In the absence of suitable specimen stabilization technologies, regarding the metabolome, the specimen collection should be carried out in hospital premises or institutions where there are immediate suitable biofluid processing procedures available.

Specifically for specimens intended to be analysed by metabolomics, the following steps shall be considered:

a) the specimen collection from the patient;

b) the selection of collection containers and packages (e.g. cooling box, box for storing and transportation);

c) the selection of stabilization procedures (e.g. any compounds added for stabilizing the specimen);

d) the recording of any additions or modifications to the specimen;

e) the recording of types and quantity and description of specimens.

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

5 Urine

5.1 Outside the laboratory

5.1.1 Urine collection manual

5.1.1.1 Information on the primary specimen donor

The documentation should include, but is not limited to:

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

b) the health status and relevant lifestyle factors of the urine donor (e.g. healthy, disease type, diet, gender, age);

c) the information about medical treatment and special treatment prior to urine collection (e.g. anaesthetics, medications);

d) the collection time, including information about fasting, previous activities.

See also EN ISO 15189:2012, 5.4.4.

5.1.1.2 Selection and labelling of collection containers

The laboratory shall define the container intended for urine collection.

Additives are usually not used, because they can interfere with the analytical method. If they are required, their impact on the analytical performance and outcome shall be analysed. Additives can be harmful (e.g. toxic or corrosive).

A sufficient minimum volume of urine should be collected according to the requirements of the preanalytical preparation steps and the analytical test. For the labelling (specimen identification) of the urine collection tube a routine procedure (EN ISO 15189:2012, 5.4.4.3, e)) or a procedure with additional information (e.g. 2D-barcode) shall be used.

5.1.1.3 Urine collection and reception from the specimen donor

Instruction for the urine collection shall be given to the donor, including any safety measures concerning additives in the collection container.

The first midstream urine of the morning should be collected after a minimum of 8 h fasting. Drinking can influence urine metabolite concentrations. This requires a normalization. Specify, if collected at different times, or for 24-h collection. Any variations to standard instructions shall be validated.

NOTE This enables to perform the metabolomics analysis of urine where donors are synchronized having similar metabolic conditions. Research or dedicated analytical tests can require different patient conditions.

Any clinical procedure affecting the specimen collection shall be documented. The total volume to be collected shall be documented

The identity of the person receiving the specimen from the patient and the time of urine collection according to EN ISO 15189, 5.4.4.3, f) shall be documented.

5.1.1.4 Information on the urine specimen and storage requirements at the urine collection site

As metabolic profiles can change after urine collection and can thereby affect the validity and reliability of the analytical test result, the documentation on the primary urine specimen shall include the time and date of urine collection.

The whole urine specimen should be kept refrigerated at 2 °C to 8 °C for a maximum of 2 h and shall not be frozen prior to centrifugation and/or filtration to avoid cell disruption upon ice crystal formation, unless specified differently by the analytical test.

The allowed urine specimen total storage duration includes the time for storage at the point of urine collection, transportation to the testing laboratory and further storage at the testing laboratory or other institutions.

5.1.2 Transport requirements

During transport, the specimen should be kept cool (temperature range 2 °C to 8 °C).

Appropriate measures shall be taken to secure temperature specifications and to reduce time for the delivery, which should be completed within 2 h from collection.

The use of a pneumatic tube transport system should be validated, as it can impact specimen quality due to high acceleration/deceleration forces [12].

5.2 Inside the laboratory

5.2.1 Specimen reception

The urine specimen reception time and conditions (e.g. labelling, transport conditions, volume, leaking and precipitation) of the received specimens shall be documented. Nonconformities of labelling, transport conditions and urine volume differences to specifications described for the urine collection or specimen preparation requirements shall be documented.

Where there are nonconformities in transport conditions, overall storage and transport time or urine volume that could affect the validity and reliability of the analytical test result [6], [7], a new specimen should be obtained.

If required for the analytical test, specimen properties should be assessed (e.g. pH-value, creatinine concentration, blood and/or bacterial contaminations).

5.2.2 Storage requirements

The storage temperature and time interval between specimen receipt and sample processing for urine shall be documented.

The storage temperature should be according to 5.1.1.4.