SLOVENSKI STANDARD
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Molekularne diagnostične preiskave in vitro - Specifikacije za predpreiskovalne procese metabolomike v urinu, serumu in plazmi venske krvi (ISO/DIS 23118:2020)

Molecular in vitro diagnostic examinations - Specifications for pre-examination processes in metabolomics in urine, venous blood serum and plasma (ISO/DIS 23118:2020)

Molekularanalytische in-vitro-diagnostische Verfahren - Spezifikationen für präanalytische Prozesse für Metabolomuntersuchungen in Urin, venösem Blutserum und –plasma (ISO/DIS 23118:2020)

Analyses 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) (ISO/DIS 23118:2020)

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Contents

Page

Foreword

ISO (the International Organization for Standardization) is a worldwide federation of national standards bodies (ISO member bodies). The work of preparing International Standards is normally carried out through ISO technical committees. Each member body interested in a subject for which a technical committee has been established has the right to be represented on that committee. International organizations, governmental and non-governmental, in liaison with ISO, also take part in the work. ISO collaborates closely with the International Electrotechnical Commission (IEC) on all matters of electrotechnical standardization.

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).

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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.

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

Metabolomics is the -omic science that deals with the characterization of the metabolome, in turn defined as the whole set of small molecules (molecular mass < 2000) in a certain biological system such as a cell, a tissue, an organ, or an entire organism [3]. The analyses are mainly performed via two major analytical techniques, namely mass spectrometry (MS) and nuclear magnetic resonance (NMR) [4-6]. The former has a sensitivity that can be as low as picomolar, requires sample separation and multiple experimental runs targeted to specific classes of compounds. The latter measures metabolites present at concentration above 1 µM and is mainly used for untargeted analyses, where all metabolites above the detection limit are observed simultaneously, independent of their chemical nature, without any separation procedure.

The metabolome is dynamic and quite sensitive to perturbations. The metabolome can change drastically during primary sample collection, transport, storage, and processing. As a result, the outcome from the diagnostic and research measurements may become an unreliable representation of the specific targeted physiological state or point in time, but instead describes an artificial profile generated during the pre-examination process. Pre-analytical variations have been identified to originate from two main sources: i) can result from enzymatic activity in the samples, mainly related to the presence of cells; ii)can result from chemical reactions (e.g. redox reactions) among metabolites or between metabolites and oxygen [7-13]. Moreover, the analyses can be influenced by the use of additives or by the introduction of contaminants, and therefore the selection of appropriate collection tubes and plasticware is also a critical aspect of the pre-examination phase.

Studies have been undertaken to establish the best pre-examination procedures in terms of maintenance of the original sample metabolome by identifying the critical steps and parameters affecting the metabolome composition. Additionally, standardization of the entire pre-examination workflow is needed to ensure comparability in multicenter studies. At the present state of the art, there are no defined pre-examination procedures for metabolomic samples. As a consequence, the procedures adopted by the various centers differentially influence the metabolome of the samples, making their comparison unreliable. The adoption of the present requirements for the pre-examination phase make it possible to compare and evaluate the results obtained from metabolic analysis.

This document draws upon such studies to codify and standardize the steps for urine, serum and plasma metabolomics analysis in what is referred to as the pre-analytical 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 in metabolomics in urine, venous blood serum and plasma

1 Scope

This document specifies requirements for the handling, documentation and processing of urine, venous blood plasma and serum intended for metabolomics analysis in the pre-examination processes. This document is applicable to metabolomics examinations and can be used by biomedical laboratories, customers of laboratories, in vitro diagnostics developers and manufacturers, institutions and companies performing biomedical research, biobanks, and regulatory authorities.

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
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)

3.2
examination
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.

Note 2 to entry: For metabolomic analysis, analyte isolation is not necessarily required.

[SOURCE: ISO 20166-1:2018, 3.10, modified — admitted term “analytical test” has been deleted and Note 2 entry has been added.]

3.3
fasting
abstinence from any solid or liquid food excluding water for at least 8 hours

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* (3.6) in biological systems that can be measured by 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 of the host organisms, of its microflora, deriving from food, drinks, drugs or pollutants.

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

3.7
metabolome
complete set of *metabolites* (3.6) to be found within an organism or a biological sample

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

3.8
metabolomics
comprehensive analysis of the *metabolome* (3.7) of a biological *specimen* (3.14) (e.g., organism, cell, tissue or *biofluids* (3.1))

3.9
MS-based metabolomics
use of *mass spectrometry* (3.4) to measure *metabolites* (3.6) in biological samples

3.10
nuclear magnetic resonance spectroscopy
NMR
method based on the selective absorption of high frequency radio waves by atomic nuclei subjected to a stationary magnetic field.

Note 1 to entry: NMR provides chemical and structural properties of molecules.

3.11
NMR-based metabolomics
use of NMR spectroscopy to measure *metabolites* (3.6) 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* (3.2) request, preparation and identification of the patient, collection of the primary sample(s), temporary storage, transportation to and within the analytical laboratory, aliquoting, retrieval

Note 1 to entry: The preanalytical phase can include preparative processes that can influence the outcome of the intended *examination* (3.2).

[SOURCE: 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* (3.2), 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.]

3.15
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* (3.6).

[SOURCE: ISO Guide 30:1992, 2.7]

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 15189or ISO/IEC 17020:2012, 8 and 7.2. The requirements on laboratory equipment, reagents, and consumables according to ISO 15189 shall be followed; ISO 15189, and ISO/IEC 17020:2012, 6.2 can also apply.

All steps of a diagnostic workflow can influence the final analytical test result and 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. It shall especially be investigated and ensured that the metabolites intended to be analysed are not compromised in a manner impacting the examination performance. This can be done, e.g. by applying the intended examination to specimens/samples which underwent time course studies reflecting the individual pre-examination process steps such as transport and storage and by implementing measures to prevent or reduce impacts by the identified pre-analytical variables.

In the absence of suitable specimen stabilization technologies, regarding the metabolome, the specimen collection shall 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) patient pretreatment (fasting, therapy, etc.);

b) the specimen collection from the patient;

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

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