TECHNICAL SPECIFICATION

SPÉCIFICATION TECHNIQUE

TECHNISCHE SPEZIFIKATION

CEN/TS 16945

May 2016

ICS 11.100.10

English Version

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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Ref. No. CEN/TS 16945:2016 E

Contents

Page

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