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Molecular in vitro diagnostic examinations — Specifications for pre-examination processes for venous whole blood —

Part 1: Isolated cellular RNA

Analyses de diagnostic moléculaire in vitro — Spécifications relatives aux processus préanalytiques pour le sang total veineux —

Partie 1: ARN cellulaire extrait

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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).

Attention is drawn to the possibility that some of the elements of this document may be the subject of patent rights. ISO shall not be held responsible for identifying any or all such patent rights. Details of any patent rights identified during the development of the document will be in the Introduction and/or on the ISO list of patent declarations received (see www.iso.org/patents).

Any trade name used in this document is information given for the convenience of users and does not constitute an endorsement.

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.

A list of all parts in the ISO 20186 series can be found on the ISO website.

Introduction

Molecular in vitro diagnostics has enabled 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.

Blood cellular RNA profiles can change significantly after blood collection. Therefore, special measures need to be taken to secure good quality blood samples for cellular RNA examination and storage.

Standardization of the entire workflow from specimen collection to the cellular RNA examination is needed. Studies have been undertaken to determine the important influencing factors. This document draws upon such work to codify and standardize the steps for venous whole blood cellular RNA examination 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.

Molecular in vitro diagnostic examinations — Specifications for pre-examination processes for venous whole blood —

Part 1: Isolated cellular RNA

1 Scope

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

This document is applicable to any molecular in vitro diagnostic examination performed by medical laboratories. It is also intended to be used by laboratory customers, in vitro diagnostics developers and manufacturers, biobanks, institutions and commercial organizations performing biomedical research, and regulatory authorities.

Different dedicated measures are taken for stabilizing blood cell free circulating RNA and RNA in exosomes circulating in blood. These are not described in this document.

Different dedicated measures are taken for collecting, stabilizing, transporting and storing capillary blood as well as for collecting and storing blood by paper based technologies or other technologies generating dried blood. These are not described in this document.

This document does not cover the isolation of specific blood cells and subsequent isolation of cellular RNA therefrom.

RNA in pathogens present in blood is not covered by 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.

ISO 15189:2012, *Medical laboratories — Requirements for quality and competence*

3 Terms and definitions

For the purposes of this document, the following terms and definitions 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
ambient temperature
unregulated temperature of the surrounding air

3.2
analyte
component represented in the name of a measurable quantity

[SOURCE: ISO 17511:2003, 3.2]

3.3
backflow
flow of a liquid opposite to the usual or desired direction

3.4
blood cellular RNA
cellular RNA
RNA molecules present in blood cells

3.5
blood cellular RNA profile
amounts of different RNA molecules, that are present in blood cells and that can be measured in the absence of any losses, inhibition and interference

3.6
blood cellular RNA profile stabilizers
compounds, solutions or mixtures that are designed to minimize changes of the *blood cellular RNA profile* (3.5)

3.7
blood collection set
intravenous device specialized for venepuncture 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, such as a *blood collection tube* (3.8).

3.8
blood collection tube
tube used for blood collection, usually in a vacuum which forces blood from the vein through the needle into the tube

3.9
closed system
non-modifiable system provided by the vendor including all necessary components for the examination (i.e. hardware, software, procedures and reagents)

3.10
deoxyribonucleic acid
DNA
polymer of deoxyribonucleotides occurring in a double-stranded (dsDNA) or single-stranded (ssDNA) form

[SOURCE: ISO 22174:2005, 3.1.2]

3.11
deoxyribonuclease
DNase
enzyme that catalyzes the degradation of DNA into smaller components

3.12
examination
analytical test
set of operations having the object of determining the value or characteristics of a property

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

Note 1 to entry: Processes that start with the isolated *analyte* (3.2) and include all kinds of parameter testing or chemical manipulation for quantitative or qualitative examination.

3.13
examination performance
analytical test performance
analytical performance
ability of an examination procedure to measure or detect a particular *analyte* (3.2)

Note 1 to entry: Analytical performance is determined from analytical performance studies used to assess the ability of an in vitro diagnostic examination procedure to measure or detect a particular analyte.

Note 2 to entry: Analytical performance includes such characteristics as analytical sensitivity, detection limit, analytical specificity (interference and cross-reactivity), trueness, precision and linearity.

[SOURCE: ISO/TS 17822-1:2014, 3.2, modified — Two terms have been added.]

3.14
examination provider
analytical test provider
entity that provides the specific analytical test

3.15
interfering substance
endogenous or exogenous substances in clinical *specimens* (3.18)/*samples* (3.24) that can alter an *examination* (3.12) 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.

3.16
needle holder
barrel used in routine venepuncture procedures to hold the *blood collection tube* (3.8) in place and to protect the phlebotomist from direct contact with blood

3.17
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)* (3.18), transportation to and within the medical laboratory, 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.]

3.18
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 — Notes to entry have been omitted.]

3.19
primary sample collection device
apparatus specifically intended by an IVD manufacturer to obtain, contain and preserve a body fluid or tissue for in vitro diagnostic examination

Note 1 to entry: Includes devices intended to store a specimen prior to examination.

Note 2 to entry: Includes both vacuum and non-vacuum specimen collection devices.

[SOURCE: ISO 18113-1:2009, 3.55]

3.20
proficiency testing
evaluation of participant performance against pre-established criteria by means of interlaboratory comparisons

[SOURCE: ISO 17043:2010, 3.7, modified — Notes to entry have been omitted.]

3.21
ribonucleic acid
RNA
polymer of ribonucleotides occurring in a double-stranded or single-stranded form

[SOURCE: ISO 22174:2005, 3.1.3]

3.22
ribonuclease
RNase
enzyme that catalyses the degradation of RNA into smaller components

3.23
room temperature
temperature in the range of 18 °C to 25 °C

Note 1 to entry: The definition is given for the purposes of this document. Local or national regulations can have different definitions.

3.24
sample
one or more parts taken from a *primary sample* (3.18)

[SOURCE: ISO 15189:2012, 3.24, modified — The example has been omitted.]

3.25
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”.]

3.26
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.]

3.27
venous whole blood
blood collected after directly puncturing a vein, usually with a needle and syringe, or other collection device

3.28
verification
confirmation, through the provision of objective evidence, that specified requirements have been fulfilled

Note 1 to entry: The term "verified" is used to designate the corresponding status.

Note 2 to entry: Confirmation can comprise activities such as:

— performing alternative calculations;

— comparing a new design specification with a similar proven design specification;

— undertaking tests and demonstrations;

— reviewing documents prior to issue.

[SOURCE: ISO 9000:2015, 3.8.12, modified — Note 1 and Note 2 were not taken over.]

3.29
workflow
series of activities necessary to complete a task

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 15189:2012, 4.2, 5.4.4, 5.4.6 or ISO/IEC 17020:2012, 7.2 and Clause 8. The requirements on laboratory equipment, reagents, and consumables according to ISO 15189:2012, 5.3 shall be followed; ISO 15189:2012, 5.5.1.2 and 5.5.1.3 and ISO/IEC 17020:2012, 6.2 can also apply.

All steps of a diagnostic workflow can influence the final examination result. Thus, the entire workflow, including specimen/sample storage and transport conditions, and its impact on the stability of biomolecules intended to be examined shall be verified and validated. Workflow steps which cannot always be controlled shall be documented and their impact on the examination performance shall be investigated and mitigation measures shall be established to enable the required examination performance. In these cases, risk assessment is recommended.

Cellular RNA profiles can change significantly after blood collection, for example by gene induction, gene down regulation or RNA degradation[8][9][10][11]. These changes can vary individually in blood from different donors or patients[8][12][13][14][15], and can impact the validity and reliability of examination results.

Before or during the design of an examination, it should therefore be investigated and ensured that the specific blood cellular RNA profile(s) intended to be analysed is/are not compromised by the envisioned pre-examination process in a manner impacting the examination performance. This can, for example,