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In vitro diagnostic test systems — Requirements for blood-glucose monitoring systems for self-testing in managing diabetes mellitus

Systèmes d'essais de diagnostic in vitro — Exigences relatives aux systèmes d'autosurveillance de la glycémie destinés à la prise en charge du diabète sucré

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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.

International Standards are drafted in accordance with the rules given in the ISO/IEC Directives, Part 2.

The main task of technical committees is to prepare International Standards. Draft International Standards adopted by the technical committees are circulated to the member bodies for voting. Publication as an International Standard requires approval by at least 75 % of the member bodies casting a vote.

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.

ISO 15197 was prepared by Technical Committee ISO/TC 212, *Clinical laboratory testing and in vitro diagnostic test systems.*

This second edition cancels and replaces the first edition (ISO 15197:2003), the clauses, subclauses and annexes of which have been technically revised.

Introduction

Blood-glucose monitoring systems are *in vitro* diagnostic medical devices used predominantly by individuals affected by diabetes mellitus. Diabetes mellitus is caused by a deficiency in insulin secretion or by insulin resistance leading to abnormally high concentrations of glucose in the blood, which may result in acute and chronic health complications. When used properly, a glucose monitoring system allows the user to monitor and take action to control the concentration of glucose present in the blood.

This International Standard is intended for blood-glucose monitoring systems used by lay persons. The primary objectives are to establish requirements that result in acceptable performance and to specify procedures for demonstrating conformance to this International Standard.

Minimum performance criteria for blood-glucose monitoring systems were established from the analytical requirements (precision and trueness) for individual glucose measurement results. "System accuracy" is the term used in this International Standard to communicate the analytical capability of a blood-glucose monitoring system to the intended users (i.e. lay persons), who would not be familiar with metrological terms commonly used in laboratory medicine. System accuracy describes the ability of a glucose monitoring system to produce measurement results that agree with true glucose values when the system is used as intended. The concept of "system accuracy" includes measurement bias and measurement precision.

The requirements for system accuracy are based on three considerations:

— the effectiveness of current technology for monitoring patients with diabetes mellitus;

— recommendations of diabetes researchers as well as existing product standards and regulatory guidelines; and

— the state-of-the-art of blood-glucose monitoring technology.

In arriving at the performance requirements specified in the second edition of this International Standard, desirable goals had to be weighed against the capabilities of existing blood-glucose monitoring technology. The revised performance criteria in this edition are the result of improvements in technology since publication of the first edition. The considerations that formed the basis for the minimum acceptable analytical performance of a blood-glucose measuring device intended for self-monitoring are described in Annex C.

Requirements that are unique to self-monitoring devices for blood-glucose are addressed in this International Standard. Requirements that apply in general to all *in vitro* diagnostic medical devices are incorporated by reference to other standards where appropriate.

Although this International Standard does not apply to glucose monitoring systems that provide measured values on an ordinal scale (e.g. visual, semiquantitative measurement procedures) or medical devices that measure blood-glucose continuously for self-monitoring, it may be useful as a guide for developing procedures to evaluate the performance of such systems.

In vitro diagnostic test systems — Requirements for blood-glucose monitoring systems for self-testing in managing diabetes mellitus

1 Scope

This International Standard specifies requirements for *in vitro* glucose monitoring systems that measure glucose concentrations in capillary blood samples, for specific design verification procedures and for the validation of performance by the intended users. These systems are intended for self-measurement by lay persons for management of diabetes mellitus.

This International Standard is applicable to manufacturers of such systems and those other organizations (e.g. regulatory authorities and conformity assessment bodies) having the responsibility for assessing the performance of these systems.

This International Standard does not:

— provide a comprehensive evaluation of all possible factors that could affect the performance of these systems,

— pertain to glucose concentration measurement for the purpose of diagnosing diabetes mellitus,

— address the medical aspects of diabetes mellitus management,

— apply to measurement procedures with measured values on an ordinal scale (e.g. visual, semiquantitative measurement procedures), or to continuous glucose monitoring systems,

— apply to glucose meters intended for use in medical applications other than self-testing for the management of diabetes mellitus

2 Normative references

The following referenced documents are indispensable for the application 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 13485, *Medical devices — Quality management systems — Requirements for regulatory purposes*

ISO 14971, *Medical devices — Application of risk management to medical devices*

ISO 17511, *In vitro diagnostic medical devices — Measurement of quantities in biological samples — Metrological traceability of values assigned to calibrators and control materials*

ISO 18113-1, *In vitro diagnostic medical devices — Information supplied by the manufacturer (labelling) — Part 1: Terms, definitions and general requirements*

ISO 18113-4, *In vitro diagnostic medical devices — Information supplied by the manufacturer (labelling) — Part 4: In vitro diagnostic reagents for self-testing*

ISO 18113-5, *In vitro diagnostic medical devices — Information supplied by the manufacturer (labelling) — Part 5: In vitro diagnostic instruments for self-testing*

ISO 23640, *In vitro diagnostic medical devices — Evaluation of stability of in vitro diagnostic reagents*

IEC 60068-2-64, *Environmental testing — Part 2-64: Tests — Test Fh: Vibration, broadband random and guidance*

IEC 61010-1, *Safety requirements for electrical equipment for measurement, control, and laboratory use — Part 1: General requirements*

IEC 61010-2-101, *Safety requirements for electrical equipment for measurement, control and laboratory use — Part 2-101: Particular requirements for in vitro diagnostic (IVD) medical equipment*

IEC 61326-1, *Electrical equipment for measurement, control and laboratory use — EMC requirements — Part 1: General requirements*

IEC 61326-2-6, *Electrical equipment for measurement, control and laboratory use — EMC requirements — Part 2-6: Particular requirements — In vitro diagnostic (IVD) medical equipment*

IEC 62366, *Medical devices — Application of usability engineering to medical devices*

EN 13612, *Performance evaluation of in vitro diagnostic medical devices*

3 Terms and definitions

For the purposes of this document, the terms and definitions given in ISO 18113-1 and the following apply.

3.1
blood-glucose monitoring system
measuring system consisting of a portable instrument and reagents used for the *in vitro* monitoring of glucose concentrations in blood

Note 1 to entry: Blood-glucose monitoring systems measure glucose in capillary blood samples, but can express measured values as either the glucose concentration in capillary blood or the equivalent glucose concentration in capillary plasma. Concentrations in this International Standard refer to the type of measured values reported by the system.

3.2
blood-glucose meter
component of a blood-glucose monitoring system that converts the product of a chemical reaction into the glucose concentration of the sample

3.3
capillary blood-sample
blood sample collected by skin puncture

Note 1 to entry: A finger punctured by a lancet is commonly called a “fingerstick”.

3.4
commutability of a reference material
property of a reference material, demonstrated by the closeness of agreement between the relation among the measurement results for a stated quantity in this material, obtained according to two given measurement procedures, and the relation obtained among the measurement results for other specified materials

Note 1 to entry: The reference material in question is usually a calibrator and the other specified materials are usually routine samples.

Note 2 to entry: The measurement procedures referred to in the definition are the one preceding and the one following the reference material (calibrator) in question in a calibration hierarchy. See ISO 17511 for further information.

Note 3 to entry: The stability of commutable reference materials is monitored regularly.

[ISO/IEC Guide 99:2007, definition 5.15]

Note 4 to entry: Although blood would be the ideal matrix for reference materials for blood-glucose monitoring devices, such materials are not available at this time.

3.5
consecutive selection method
sampling method for a research study in which all subjects that meet the enrolment criteria are accepted in the order they volunteer for the study

Note 1 to entry: This method will provide unbiased samples as long as no confounding variables are introduced during the trial period. For example, if a study lasts one morning, study subjects might not be representative of the target population, since subjects who visit the clinic in the morning might not be representative of all subjects who visit the clinic.

Note 2 to entry: Adapted from Reference.[5]

3.6
disinfection
process of destroying pathogenic organisms or rendering them inert

Note 1 to entry: Adapted from Reference.[6]

3.7
influence quantity
quantity that, in a direct measurement, does not affect the quantity that is actually measured, but affects the relation between the measurement indication and the measurement result

EXAMPLE 1 Frequency in the direct measurement with an ammeter of the constant amplitude of an alternating current.

EXAMPLE 2 Amount-of-substance concentration of bilirubin in a direct measurement of haemoglobin amount-of-substance concentration in human blood plasma.

EXAMPLE 3 Temperature of a micrometer used for measuring the length of a rod, but not the temperature of the rod itself which can enter into the definition of the measurand.

EXAMPLE 4 Background pressure in the ion source of a mass spectrometer during a measurement of amount-of-substance fraction.

Note 1 to entry: An indirect measurement involves a combination of direct measurements, each of which may be affected by influence quantities.

Note 2 to entry: Adapted from ISO/IEC Guide 99:2007, definition 2.52.

3.8
intermediate measurement precision
intermediate precision
measurement precision under a set of conditions of measurement that includes the same measurement procedure, same location and replicate measurements on the same or similar objects over an extended period of time, and can include other conditions involving changes

Note 1 to entry: Interpretation of intermediate measurement precision requires that the changed and unchanged conditions be specified, particularly variables such as calibrations, reagent lots, measuring systems, operators and environmental conditions.

Note 2 to entry: In evaluating IVD medical devices, the intermediate precision conditions are generally selected to represent the actual use conditions of the IVD medical device over an extended period of time.

Note 3 to entry: Relevant statistical concepts are given in ISO 5725-3.

Note 4 to entry: Intermediate precision can be expressed quantitatively in terms of the dispersion characteristics of the measured values, such as standard deviation, variance, and coefficient of variation.

Note 5 to entry: Adapted from ISO/IEC Guide 99:2007, definitions 2.22 and 2.23.

3.9
lay person
individual without formal training in a relevant field or discipline

Note 1 to entry: For the purposes of this International Standard, a lay person is a user of a blood-glucose monitoring device who does not have specific medical, scientific or technical knowledge related to blood-glucose monitoring.

Note 2 to entry: Adapted from ISO 18113-1, definition 3.34.

3.10
manufacturer's selected measurement procedure
measurement procedure that is calibrated by one or more primary or secondary calibrators and validated for its intended use

Note 1 to entry: ISO 17511:2003, Figure 1 shows the manufacturer's selected measurement procedure in the traceability chain.

Note 2 to entry: See ISO 17511:2003, 4.2.2 f).

3.11
manufacturer's standing measurement procedure
measurement procedure that is calibrated by one or more of the manufacturer's working calibrators or higher types of calibrator and validated for its intended use

Note 1 to entry: ISO 17511:2003, Figure 1 shows the manufacturer's standing measurement procedure in the traceability chain.

Note 2 to entry: See ISO 17511:2003, 4.2.2 h).

3.12
measurement accuracy
accuracy
closeness of agreement between a measured quantity value and a true quantity value of the measurand

Note 1 to entry: The concept "measurement accuracy" is not a quantity and is not given a numerical quantity value. A measurement is said to be more accurate when it offers a smaller measurement error.

Note 2 to entry: The term "measurement accuracy" is not used for measurement trueness and the term "measurement precision" is not used for measurement accuracy, which, however, is related to both these concepts.

Note 3 to entry: "Measurement accuracy" is sometimes understood as closeness of agreement between measured quantity values that are being attributed to a measurand.

[ISO/IEC Guide 99:2007, definition 2.13]

3.13
measurement bias
bias
estimate of a systematic measurement error

Note 1 to entry: Bias is inversely related to trueness.

Note 2 to entry: An estimation of bias is the average value of a series of measurements minus a reference quantity value.

Note 3 to entry: Adapted from ISO/IEC Guide 99:2007, definition 2.18.

3.14
measurement precision
precision
closeness of agreement between measurement indications or measured quantity values obtained by replicate measurements on the same or similar objects under specified conditions

Note 1 to entry: Measurement precision is usually expressed numerically by measures of imprecision, such as standard deviation, variance or coefficient of variation under the specified conditions of measurement.

Note 2 to entry: The "specified conditions" can be, for example, repeatability conditions of measurement, intermediate precision conditions of measurement, or reproducibility conditions of measurement (see ISO 5725-3).

Note 3 to entry: Measurement precision is used to define measurement repeatability, intermediate measurement precision, and measurement reproducibility.

Note 4 to entry: Replicate measurements means measurements that are obtained in a manner not influenced by a previous measurement on the same or similar sample.

Note 5 to entry: Adapted from ISO/IEC Guide 99:2007, definition 2.15.

3.15
measurement repeatability
repeatability
measurement precision under a set of conditions of measurement that includes the same measurement procedure, same operators, same measuring system, same operating conditions and same location, and replicate measurements on the same or similar objects over a short period of time

Note 1 to entry: In clinical chemistry, the term within-run precision or intra-series precision is sometimes used to designate this concept.

Note 2 to entry: In evaluating an IVD medical device, repeatability conditions are generally selected to represent essentially unchanged conditions (called repeatability conditions) resulting in the minimum variability of measured values. Repeatability information can be useful for troubleshooting purposes.

Note 3 to entry: Repeatability can be expressed quantitatively in terms of the dispersion characteristics of the measured values, such as repeatability standard deviation, repeatability variance and repeatability coefficient of variation. Relevant statistical terms are given in ISO 5725-2.

Note 4 to entry: Adapted from ISO/IEC Guide 99:2007, definitions 2.20 and 2.21.

3.16
measurement reproducibility
reproducibility
measurement precision under conditions of measurement that includes different locations, operators, measuring systems, and replicate measurements on the same or similar objects

Note 1 to entry: In clinical chemistry, the term laboratory-to-laboratory precision is sometimes used to designate this concept.

Note 2 to entry: In evaluating an IVD medical device, reproducibility conditions are generally selected to represent maximally changed conditions (called reproducibility conditions) resulting in the variability of measured values that would be encountered when comparing measurement results among independent laboratories, such as would occur in inter-laboratory comparison programmes (e.g. proficiency testing, external quality assurance or laboratory standardization trials).

Note 3 to entry: Reproducibility can be expressed quantitatively in terms of the dispersion characteristics of the measured values, such as reproducibility standard deviation, reproducibility variance and reproducibility coefficient of variation. Relevant statistical terms are given in ISO 5725-2.

Note 4 to entry: The different measuring systems can use different measurement procedures.

Note 5 to entry: A specification should give the conditions changed and unchanged, to the extent practical.

Note 6 to entry: Adapted from ISO/IEC Guide 99:2007, definitions 2.24 and 2.25.

3.17
measurement trueness
trueness
closeness of agreement between the average of an infinite number of replicate measured quantity values and a reference quantity value

Note 1 to entry: Measurement trueness is not a quantity and thus cannot be expressed numerically, but measures for closeness of agreement are given in ISO 5725-1.

Note 2 to entry: Measurement trueness is inversely related to **systematic measurement error**, but is not related to **random measurement error**.

Note 3 to entry: **Measurement accuracy** should not be used for "measurement trueness" and vice versa.

[ISO/IEC Guide 99:2007, definition 2.14]

3.18
measuring interval
set of values of quantities of the same kind that can be measured by a given measuring instrument or measuring system with specified instrumental uncertainty, under defined conditions

Note 1 to entry: The measuring interval over which the performance characteristics of an IVD medical device have been validated has been called the reportable range.

Note 2 to entry: The lower limit of a measuring interval is not necessarily the same as the detection limit. See ISO 18113-1:2009, A.2.8, for further information.

Note 3 to entry: For a discussion of the difference between interval and range, see ISO 18113-1:2009, A.2.11.

Note 4 to entry: Adapted from ISO/IEC Guide 99:2007, definition 4.7.

3.19

metrological traceability
property of a measurement result whereby the result can be related to a reference through a documented unbroken chain of calibrations, each contributing to the measurement uncertainty

Note 1 to entry: For this definition, a reference can be a definition of a measurement unit through its practical realization, or a measurement procedure including the measurement unit for a nonordinal quantity, or a measurement standard.

Note 2 to entry: Metrological traceability requires an established calibration hierarchy. The sequence of measurement standards and calibrations that is used to relate a measurement result to a reference is called a traceability chain. A metrological traceability chain is used to establish metrological traceability of a measurement result, including calibrator values. See ISO 17511 for examples of traceability chains pertaining to IVD medical devices.

Note 3 to entry: Specification of the stated reference must include the time at which this reference was used in establishing the calibration hierarchy, along with any other relevant metrological information about the reference, such as when the first calibration in the calibration hierarchy was performed.

Note 4 to entry: For measurements with more than one input quantity in the measurement model, each of the quantity values should itself be metrologically traceable and the calibration hierarchy involved can form a branched structure or a network. The effort involved in establishing metrological traceability for each input quantity should be commensurate with its relative contribution to the measurement result.

Note 5 to entry: A comparison between two measurement standards can be viewed as a calibration if the comparison is used to check and, if necessary, correct the quantity value and measurement uncertainty attributed to one of the measurement standards.

Note 6 to entry: The abbreviated term traceability is sometimes used to mean metrological traceability as well as other concepts, such as sample traceability or document traceability or instrument traceability or material traceability, where the history (trace) of an item is meant. Therefore, the full term of metrological traceability is preferred if there is any chance of confusion.

Note 7 to entry: Adapted from ISO/IEC Guide 99:2007, definition 2.41.

3.20
metrological traceability chain
traceability chain
sequence of measurement standards and calibrations that is used to relate a measurement result to a reference

Note 1 to entry: A metrological traceability chain is defined through a calibration hierarchy.

Note 2 to entry: A metrological traceability chain is used to establish metrological traceability of a measurement result.

Note 3 to entry: A comparison between two measurement standards may be viewed as a calibration if the comparison is used to check and, if necessary, correct the quantity value and measurement uncertainty attributed to one of the measurement standards.

[ISO/IEC Guide 99:2007, definition 2.42]

3.21
packed cell volume
volume fraction of the erythrocytes in blood

Note 1 to entry: Expressed either as a decimal fraction (SI) or as a percentage (conventional). SI units (L/L) are implied.

Note 2 to entry: Sometimes referred to as "haematocrit" after the instrument originally used to estimate packed cell volume.

3.22
reagent system
in vitro diagnostic medical device that produces a signal, in response to a measurable quantity

EXAMPLE For glucose monitoring devices, the signal can be a chemical or electrochemical response to glucose in a blood sample

3.23
reference measurement procedure
measurement procedure accepted as providing measurement results fit for their intended use in assessing measurement trueness of measured quantity values obtained from other measurement procedures for quantities of the same kind, in calibration, or in characterizing reference materials

[ISO/IEC Guide 99:2007, definition 2.7]

3.24
reference quantity value
reference value
quantity value used as a basis for comparison with values of quantities of the same kind

Note 1 to entry: A reference quantity value can be a true quantity value of a measurand, in which case it is unknown, or a conventional quantity value, in which case it is known.

Note 2 to entry: A reference quantity value with associated measurement uncertainty is usually provided with reference to

— a material, e.g. a certified reference material,

— a device, e.g. a stabilized laser,

— a reference measurement procedure,

— a comparison of measurement standards.

[ISO/IEC Guide 99:2007, definition 5.18]

3.25
system accuracy
closeness of agreement between a set of representative results from a measuring system and their respective reference values

Note 1 to entry: The term accuracy, when applied to a set of measured values, involves a combination of random error components and a common systematic error or bias component.

Note 2 to entry: Reference values are assigned by a measurement procedure traceable to a reference measurement procedure of higher order.

Note 3 to entry: In this International Standard, system accuracy is expressed as the interval that encompasses the measurement results from 95 % of the samples being evaluated.

Note 4 to entry: See ISO 18113-1, A.2.4 for further discussion of "system accuracy".

3.26
type testing
conformity testing on the basis of one or more specimens of a product representative of the production

Note 1 to entry: A one-time test intended to verify adequacy of the design of a product to meet a safety standard.

3.27
user adjustment of a blood-glucose monitoring system
procedure described in the instructions for use in which the user enters a number, inserts a code strip or chip, etc., so that the system achieves acceptable performance characteristics

Note 1 to entry: Based on the concept of "adjustment of a measuring system" given in ISO/IEC Guide 99:2007, definition 3.11.

3.28
user verification of a blood-glucose monitoring system
design feature that allows the user to confirm the correct functioning of the blood-glucose monitoring system and the correct execution of the measurement procedure

4 Design and development

4.1 General requirements

The requirements specified in ISO 13485 pertaining to design and development apply.

4.2 Metrological traceability

The requirements specified in ISO 17511 pertaining to calibration and metrological traceability apply.

The manufacturer's selected or standing measurement procedure in the calibration hierarchy may measure glucose in either capillary blood or capillary plasma samples.

If capillary plasma samples are used with the manufacturer's selected measurement procedure, then the blood-glucose monitoring system may report glucose measurement results as plasma glucose equivalents, even though the samples being measured by the blood-glucose monitoring system are capillary blood.

NOTE 1 Plasma-equivalent results are preferred.

If measured values of the blood-glucose monitoring system are reported in units of a different sample matrix (e.g. plasma instead of blood), the manufacturer shall provide details of the conversion and supporting validation data to users upon request

The traceability chain should include as few steps as practical to minimize the combined measurement uncertainty.

NOTE 2 A traceability chain for a typical factory-calibrated capillary blood-glucose monitoring system is shown in Annex B. This example is not intended to represent the only possibility of a suitable calibration hierarchy.

4.3 Safety and risk management

4.3.1 General requirements

The requirements specified in IEC 61010-1 and IEC 61010-2-101 pertaining to safety apply.

The requirements specified in ISO 14971 pertaining to risk assessment and risk control apply.

NOTE ISO 14971, Annex H, contains guidance for risk management of *in vitro* diagnostic medical devices.

4.3.2 Risk assessment and control

Risks shall be assessed at a minimum from the following possible causes of hazardous situations:

a) interference by endogenous and exogenous blood components, other than the measurand, including where appropriate those listed in Annex A;

b) influence of packed cell volume on the measured values;

c) failure to adjust the meter properly, e.g. coding;

d) use of expired reagents;

e) improper test strip insertion;

f) insufficient sample volume;

g) result beyond the measuring interval displayed, e.g. higher or lower;

h) font style and size of display for visually impaired users;

i) misread of the measured value if the display has a missing segment;

j) impact of battery removal on stored data or values;

k) effect of moving the device or touching buttons during measurement;

l) hazards associated with transmitting data, e.g. by cable, wireless;

m) risk control measures shall be implemented where necessary to reduce or control the risks to an acceptable level.

4.3.3 Risk acceptability criteria

The risk acceptability criteria shall, at a minimum, take into account the following factors when evaluating risks to users:

a) intended use of the blood-glucose monitoring system;

b) established performance criteria;

c) intended user population, e.g. users' skills and limitations;

d) system's ability to detect a failure;

e) consequences of an undetected failure;