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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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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;

f) state of the art in blood-glucose monitoring;

g) contamination by bloodborne pathogens.

NOTE This International Standard does not specify criteria for acceptable risks.

4.4 Ergonomics and human factors

The requirements specified in IEC 62366 pertaining to human factors apply.

The design of the blood-glucose monitoring system shall take into consideration ergonomic and human factors requirements for the following:

a) ease of operation;

b) ease of maintenance;

c) ease of cleaning and disinfection;

d) protection from "wear and tear" that might typically be encountered in the use environment, including impact of cleaning and disinfection on the equipment;

e) readability of the measured values;

f) unambiguous messages to the user, e.g. "low battery" or "low result", rather than simply "low".

NOTE 1 Blood-glucose monitoring systems intended for self-testing are used by lay persons with different physical and mental abilities.

NOTE 2 These systems are often transported by the users, who need to conduct measurements in a variety of settings.

4.5 User verification requirements

The design of the blood-glucose monitoring system shall allow the user to check:

a) correct functioning of the blood-glucose monitoring system, (i.e. system control); and

b) correct execution of the test including the sequence of the procedural steps.

User verification should be performed at the time of use.

NOTE "At the time of use" means before, during, or immediately after the execution of the test.

User verification should be integrated into the test if reasonably practicable.

User verification shall give unambiguous information.

5 Safety and reliability testing

5.1 General requirements

5.1.1 Test protocol

Test design, data analysis procedure and acceptance criteria shall be described in a protocol.

NOTE 1 The tests in Clause 5 are design verification activities, which are intended to provide assurance that the product has the capability to consistently meet the safety and reliability specifications set for it.

NOTE 2 This International Standard is not intended to specify all design verification activities that may be required to demonstrate that the design outputs meet the design input requirements for safety and reliability.

NOTE 3 The tests described in 5.2 to 5.8 are type tests.

NOTE 4 The tests described in 5.10 to 5.12 are performance tests.

The protocol shall specify the number of meters, reagent units, and replicate measurements per meter.

For performance tests, the protocol shall include statistical rationale.

Specified testing requirements are minimum requirements.

5.1.2 Meters and reagent systems

Meters and reagent systems shall be representative of routine production units.

For type tests, at least three meters should be used in each test.

For performance tests, at least 10 meters shall be used in each test.

5.1.3 Acceptance criteria

Pass/fail criteria for the type tests in 5.2 to 5.8 are specified in the applicable standards.

Pass/fail criteria for the performance test in 5.9 shall be based on acceptability of the effect of the challenge on bias and repeatability of the glucose measurements. The criteria should be related to the system accuracy performance criteria in 6.3.3.

The rationale for the acceptance criteria shall be documented in the protocol.

The blood-glucose monitoring system shall pass the acceptance criteria in each test protocol. Alternatively, the system shall be rendered non-functional and shall not display a numerical glucose result.

Failures to meet acceptance criteria shall be investigated.

5.2 Protection against electric shock

The requirements specified in IEC 61010-1 pertaining to protection from electric shock apply.

5.3 Protection against mechanical hazards

The requirements specified in IEC 61010-1 pertaining to protection against mechanical hazards apply.

5.4 Electromagnetic compatibility

The requirements specified in IEC 61326-1 and IEC 61326-2-6 pertaining to electromagnetic compatibility (EMC) apply.

If the meter can be connected to other equipment such as a computer or cell phone, then EMC testing shall also be performed on the meter when so connected unless the meter is incapable of performing a glucose test when connected to other equipment.

If risk assessment indicates that exposure to higher levels of radiation or electrostatic discharge presents an unacceptable residual risk to the lay person, then the device shall be tested at higher levels.

5.5 Resistance to heat

The requirements specified in IEC 61010-1 pertaining to heat resistance apply.

5.6 Resistance to moisture and liquids

The requirements specified in IEC 61010-1 pertaining to resistance to moisture and liquids apply.

5.7 Protection against liberated gases, explosion and implosion

The requirements specified in IEC 61010-1 pertaining to protection against liberated gases, explosion, and implosion apply.

5.8 Meter components

The requirements specified in IEC 61010-1 pertaining to meter components apply.

5.9 Performance test

A performance test shall be performed before and after each determination of mechanical resistance to vibration and drop testing (see 5.10) and protection against exposure to temperature and humidity levels (see 5.11 and 5.12).

Prior to each performance test the blood-glucose meter shall be equilibrated to 23 °C ± 2 °C.

A suitable control material should be used for the performance tests. The manufacturer's recommended control material may be used.

Analytical variability due to the sample, reagent system components and meter components shall be taken into consideration when designing the test and developing acceptance criteria.

A check strip, which simulates a reagent strip after reaction with glucose, or similar alternative to analysing the manufacturer's recommended control material, may be used to demonstrate the impact on measurement system performance.

Test samples shall be measured in the order specified in the protocol.

Average glucose concentration and repeatability shall be calculated before and after each challenge, and the difference shall be compared to the acceptance criteria.

— Acceptance test for bias: the difference between the average glucose concentration after the challenge and the average glucose concentration before the challenge shall be calculated and compared to the acceptance criteria for bias.

— Acceptance test for repeatability: the square root of the difference between the repeatability variance after the challenge and the repeatability variance before the challenge shall be calculated and compared to the acceptance criteria for repeatability. Alternatively, an F-test for equivalence of the variances may be performed.

5.10 Mechanical resistance to vibration and shock

5.10.1 Vibration test

a) To demonstrate resistance to vibration, the following steps shall be performed in sequence.

b) Perform the performance test described in 5.9.

c) Perform the vibration test as specified in IEC 60068-2-64.

d) After vibration testing is complete, repeat the performance test.

e) The requirements specified in IEC 60068-2-64 pertaining to the vibration test apply.

5.10.2 Drop test

a) To demonstrate drop durability, the following steps shall be performed in sequence.

b) Perform the performance test described in 5.9.

c) Perform the drop test as specified in IEC 61010-1.

d) After drop testing is complete, repeat the performance test.

5.11 Equipment temperature exposure limits for storage

5.11.1 High temperature test

a) To demonstrate acceptable performance after storage at high temperature, the following steps shall be performed in sequence.

b) Perform the performance test as described in 5.9.

c) Place each meter in an environmental chamber that shall be monitored for internal temperature.

d) Increase the temperature to 50 °C ± 2 °C and leave at this temperature for 8 h in the chamber.

e) Allow the meter to cool to a temperature of 23 °C ± 2 °C and repeat the performance test.

f) For those systems in which the reagent system is an integral component of the meter and cannot be separated from the device, the high temperature exposure conditions shall be limited to the use conditions specified by the manufacturer.

5.11.2 Low temperature test

a) To demonstrate acceptable performance after storage at low temperature, the following steps shall be performed in sequence.

b) Perform the performance test as described in 5.9.

c) Place the meter in an environmental chamber that shall be monitored for internal temperature.

d) Decrease the temperature to –20 °C ± 2 °C and leave at this temperature for 8 h in the chamber.

e) Allow the meter to warm to a temperature of 23 °C ± 2 °C and repeat the performance test.

f) For those systems in which the reagent system is an integral component of the meter and cannot be separated from the device, the low temperature exposure conditions shall be limited to the use conditions specified by the manufacturer.

5.12 Equipment humidity exposure limits for storage

a) To demonstrate acceptable performance after storage at high humidity, the following steps shall be performed in sequence.

b) Perform the performance test described in 5.9.

c) Place the meter in a humidity chamber.

d) Stabilize the relative humidity, non-condensing to 93 % ± 3 % and a temperature of 32 °C ± 2 °C.

e) Leave the meter in the humidity chamber for 48 h.

f) Remove the meter, equilibrate it until it reaches a temperature of 23 °C ± 2 °C and a relative humidity of < 60 % for 15 min and repeat the performance test.

6 Analytical performance evaluation

6.1 General requirements

6.1.1 Evaluation protocol

Evaluation of analytical performance characteristics shall be conducted as part of the manufacturer's design and development process. The requirements specified in ISO 13485 for design verification apply.

NOTE 1 The evaluations in Clause 6 are design verification activities, which are intended to provide assurance that the device has the capability to consistently meet the performance specifications set for it.

NOTE 2 This International Standard is not intended to specify all design verification activities that may be required to demonstrate that the design outputs meet the design input requirements for analytical performance.

The performance verification studies shall be performed according to a written protocol. The protocol shall specify the acceptance criteria, the statistical design, including the number and type of samples and the numbers of meters, reagent units and replication measurements, experimental conditions and other relevant details, and the data analysis procedures including the treatment of outliers.

Where a specified experimental requirement is not practicable, an alternative statistically valid study design shall be described and justified in the protocol.

The performance criteria for system accuracy in 6.3.3 shall not be directly applied to verification of other performance characteristics, such as precision, bias or influence quantities. Acceptability criteria for these components of system accuracy shall be determined by the manufacturer, taking into account their contribution to system accuracy performance.

All components of the blood-glucose monitoring system, including meters, reagent system and accessories, shall be representative of routine production units. Any differences shall be described and justified.

The blood-glucose monitoring system shall be adjusted according to the manufacturer's instructions (e.g. via coding, chips), if adjustment is required. No adjustments shall be made between replicate measurements unless the manufacturer's instructions specify an adjustment is required before each measurement.

The manufacturer's specified setup and control procedures shall be performed prior to each evaluation.

6.1.2 Samples

Samples shall meet the requirements of the instructions for use and be appropriate for the performance characteristic being evaluated. Additional requirements for samples may be specified in 6.2 to 6.5.

If higher glucose concentrations are needed, blood samples may be collected with an appropriate anticoagulant and then supplemented with a saline solution of 0,9 % mass concentration containing a high concentration of glucose. The dilution should be as minimal as possible and shall not significantly alter the sample matrix. Supplemented samples shall be allowed to stand for at least 15 min before use to allow the added glucose to equilibrate between the plasma and red blood cells.

If lower glucose concentrations are needed, blood samples may be collected with an appropriate anticoagulant and incubated to allow glycolysis to occur. The anticoagulated blood samples may be allowed to age until glucose is depleted to the desired levels. Incubation conditions (e.g. temperature, mixing) that produce samples compatible with the blood-glucose monitoring system being evaluated (e.g. without haemolysis) shall be determined by the manufacturer. The maximum temperature for aging shall be 37°C.

Commutability of modified samples shall be verified with the blood-glucose monitoring system being evaluated.

NOTE Reference[20] provides guidelines for demonstrating commutability of a reference material.

Unexpected results when using modified samples shall be investigated by comparison to fresh, unaltered blood samples.

6.1.3 Data exclusion criteria

If a measurement result is generated during a performance evaluation, it may be excluded from the data only in the following circumstances:

— the blood-glucose monitoring system user recognizes that an error was made and documents the details;

— the meter system error or failure requires the user to retest; if displayed, the meter error (e.g. error number or failure type) shall be documented;

— the meter QC results are out of tolerance or not obtained;

— the sample was tested when QC results from the reference measurement procedure were out of acceptable limits or were not obtained;

— the blood sample was outside the manufacturer's specifications for an influence quantity, such as packed cell volume;

— the change between first and last reference values indicate glucose instability in the sample based on predetermined criteria;

EXAMPLE Reference values differ by > 4 % at glucose ≥ 5,55 mmol/l(≥100 mg/dl) or > 0,22 mmol/l (>4 mg/dl) at glucose < 5,55 mmol/l (<100 mg/dl)

— information required to determine that the sample met the inclusion criteria is missing (e.g. no value for packed cell volume).

6.1.4 Data analysis and presentation of results

Data analysis shall be based on the statistical methods specified in the protocol.

Where data have been excluded, the reason for each exclusion shall be documented in the study report.

In addition to the specific requirements of 6.2 to 6.5, the following information shall be included in the study report:

a) a summary of the study design and reference to the evaluation protocol;

b) a full description of the samples used, including details of any sample alteration procedures that were used and identification of the samples that were altered;

c) detailed description of the reference measurement procedure, including relevant analytical performance characteristics, calibration traceability and validation or verification of imprecision and bias;

d) results and conclusions of the evaluation, including calculated statistical parameters with confidence intervals where appropriate;

e) a summary of data analysis procedures and references to the statistical methods;

f) a summary of outliers identified and excluded from statistical analysis, including the method of identification and the results of the investigation;

NOTE ISO 5725-2 and Reference[7] provide guidelines for identifying outliers.

g) graphical presentation of the results, where appropriate.

6.2 Measurement precision

6.2.1 General requirements

Measurement repeatability and intermediate measurement precision shall be evaluated in simulated conditions of intended use.

NOTE 1 ISO 5725-1 and Reference[7] describe general principles regarding the evaluation of precision of a measurement method.

NOTE 2 The experiments can be designed to evaluate the effect of such factors as different lots, different sample materials, different users, or other variables (e.g. effect of temperature, humidity).

When multiple factors are evaluated, analysis of variance (ANOVA) is the preferred statistical method.

6.2.2 Acceptance criteria

Acceptance criteria shall be established in the study protocol.

Criteria for measurement repeatability and intermediate measurement precision should be related to the system accuracy performance criteria in 6.3.3.

NOTE 1 Measurement repeatability and intermediate measurement precision, along with measurement bias, are components of system accuracy.

NOTE 2 Separate criteria for minimum acceptable precision and bias are not specified in this International Standard. The system accuracy evaluation in 6.3 is designed to verify acceptability of the combined effects of random error (imprecision) and systematic error (bias) for the blood-glucose monitoring system under evaluation.

6.2.3 Measurement repeatability

6.2.3.1 Study design

Measurement repeatability shall be evaluated with a series of measurements within a short interval of time, by a single individual using the same meter and reagent lot.

NOTE ISO 5725-1 and Reference[7] provide guidelines for determining the repeatability of a measurement method.

The measurement repeatability evaluation shall be conducted with a minimum of 10 meters, 3 reagent lots, and 5 samples with glucose concentrations representing hyperglycaemic, euglycaemic and hypoglycaemic conditions. At least 10 measurements shall be performed with each combination of meter, reagent lot and sample.

Measurement repeatability data shall be collected over a span of time not to exceed one day per meter and reagent lot combination. The evaluation shall be designed to minimize the effect of glucose instability in the sample.

The evaluation may be performed by a single user. If multiple users are included in the evaluation, the study design shall allow for the estimation of measurement repeatability using an appropriate statistical method.

Alternatively, an overall evaluation of measurement precision may be designed to estimate measurement repeatability together with the other variance components that comprise intermediate precision instead of following the procedure in 6.2.3.3. Analysis of variance (ANOVA) or other valid statistical methods may be used.

6.2.3.2 Samples

The measurement repeatability evaluation shall be performed with human blood samples. The preferred sample is venous blood collected into tubes containing an anticoagulant specified by the manufacturer.

The packed cell volumes shall be within 0,35 l/l to 0,50 l/l (35 % to 50 %).

A sample from each glucose concentration interval specified in Table 1 shall be used. The glucose concentration values of the samples may be determined by the blood-glucose monitoring system.

A preservative that does not interfere with the glucose measurements (e.g. maleimide, fluoride, monoiodoacetate), and is in accordance with the manufacturer's recommendations, may be added to the sample in sufficient amount to minimize glycolysis.

NOTE Despite the presence of fluoride, glycolysis has been reported to occur for up to 4 h.[8]

Table 1 — Blood-glucose concentration intervals for measurement repeatability evaluation

Interval	Glucose concentration mmol/l (mg/dl)
1	1,7 to 2,8 (30 to 50)
2	2,9 to 6,1 (51 to 110)
3	6,2 to 8,3 (111 to 150)
4	8,4 to 13,9 (151 to 250)
5	14,0 to 22,2 (251 to 400)

6.2.3.3 Evaluation procedure

The samples shall be equilibrated to a temperature of 23 °C ± 5 °C and maintained within ± 2 °C of the starting temperature during the evaluation.

The samples shall be thoroughly but gently mixed by inversion before taking each portion for measurement.

The reagent system units for each meter shall be taken from the same vial/package.

The evaluation shall be performed in the following sequence.

a) Assign a vial/package of reagent system units to each meter.

b) Take one reagent system unit out of a vial/package and apply the sample. Record the result.

c) Repeat step b) nine more times using the same meter.

d) Using the same sample, repeat steps b) and c) with each of the nine remaining meters and vials or packages. This results in a total of 10 measured values per sample per meter.

e) Take the next sample and repeat steps a) to d).

To confirm that the glucose concentration in each sample is stable, aliquots shall be removed immediately before the first and immediately after the last measurement by the blood-glucose monitoring system and measured in duplicate by the manufacturer's reference measurement procedure.

If these results exceed predetermined stability criteria (see 6.1.3), then the measured values for that sample shall not be used and all measurements shall be repeated with a different sample.

6.2.3.4 Data analysis and presentation of results

The average, standard deviation and coefficient of variation (CV) shall be calculated for each combination of glucose concentration and reagent lot.

The grand average, pooled variance, pooled standard deviation (with 95 % confidence interval) and pooled CV for each glucose concentration shall be calculated using the measurement results from all three reagent lots.

In addition to the requirements of 6.1.4, the following information shall be reported:

a) average of the glucose measured values for each sample;

b) measurement repeatability standard deviation (with 95 % confidence interval) and coefficient of variation (CV) for each glucose concentration ≥ 5,55 mmol/l (≥100 mg/dl) and standard deviation (with 95 % confidence interval) for each glucose concentration < 5,55 mmol/l (<100 mg/dl).

6.2.4 Intermediate measurement precision

6.2.4.1 Study design

Intermediate measurement precision shall be evaluated in normal conditions of use, by an individual using the same meter and reagent system lot over multiple days. The study design shall include multiple users and reagent lots.

The evaluation shall be conducted with a minimum of one measurement of each sample per day and shall be conducted with a minimum of 10 meters, 3 reagent lots and 3 glucose concentrations representing hyperglycaemic, euglycaemic and hypoglycaemic conditions, over at least 10 days.

NOTE ISO 5725-3 and Reference[7] provide guidelines for determining the intermediate precision of a measurement method.

6.2.4.2 Samples

The intermediate measurement precision evaluation shall be performed with control materials. The preferred samples are the control materials provided by the manufacturer. Alternative control materials may be used if approved by the manufacturer of the blood-glucose monitoring system.

Samples shall be prepared according to the instructions for use for the control material. Sample stability over the evaluation period shall be validated.

Samples shall be prepared with glucose concentrations in the intervals specified in Table 2. The glucose concentration values may be determined by the blood-glucose monitoring system.

Table 2 — Blood-glucose concentration intervals for intermediate measurement precision evaluation

Interval	Glucose concentration mmol/l (mg/dl)
1	1,7 to 2,8 (30 to 50)
2	5,3 to 8,0 (96 to 144)
3	15,5 to 23,3 (280 to 420)

6.2.4.3 Evaluation procedure

The reagent system units for each sample shall be taken from the same vial/package.

The evaluation shall be performed in the following sequence.

a) Assign a vial/package of reagent system units to each meter.

b) Take one reagent system unit out of each vial/package and apply the sample. Record the result.

c) Repeat step b) for each sample.

d) Repeat steps b) and c) once each day with each of the nine remaining meters and vials or packages for a total of 10 days. The same vial/package is used for each meter throughout the evaluation period.

6.2.4.4 Data analysis and presentation of results

The average, standard deviation and CV shall be calculated for each glucose concentration and reagent lot.

The grand average, pooled standard deviation (with 95 % confidence interval) and pooled CV for each glucose concentration shall be calculated using the measured values from all three reagent lots.

NOTE The pooled standard deviation and pooled CV are measures of the intermediate measurement precision of a single system over multiple days.

Analysis of variance is the preferred method for calculating intermediate precision and components of variance.

In addition to the requirements of 6.1.4, the following information shall be reported:

a) average of the glucose measured values for each sample;

b) intermediate measurement standard deviation (with 95 % confidence interval) and coefficient of variation (CV) for each glucose concentration ≥ 5,55 mmol/l (≥100 mg/dl) and standard deviation (with 95 % confidence interval) for each glucose concentration < 5,55 mmol/l (<100 mg/dl).

6.3 System accuracy

6.3.1 General requirements

System accuracy capability shall be evaluated with fresh blood samples by comparing glucose measurements from the blood-glucose monitoring system to reference glucose values.

The evaluation shall be conducted in actual conditions of use, preferably in a diabetes mellitus outpatient clinic or hospital setting. Ambient temperature shall be maintained at 23 °C ± 5 °C.

NOTE The 10 °C temperature interval includes the temperatures that typically exist in a clinic or hospital setting.

6.3.2 Glucose reference values

A reference measurement procedure that conforms to the traceability requirements of ISO 17511 shall be used to assign the glucose reference values. Glucose reference values shall be the average of at least duplicate measurements. An IVD medical device (e.g. in a medical laboratory) shown to have adequate performance characteristics may be used to assign the reference values. Traceability and performance information obtained from the manufacturer may be used to make this determination.

If the glucose reference measurement procedure is not intended to measure blood samples and it does not specify a procedure to remove cells, the aliquots of the sample shall be centrifuged immediately after collection to obtain plasma.

Trueness and precision of the reference IVD medical device shall be verified during the performance evaluation. Reference materials used for verification shall be suitable for this purpose and be qualified for commutability and stability.

NOTE 1 The Joint Committee for Traceability in Laboratory Medicine (JCTLM) lists reference materials, reference measurement procedures, and reference measurement laboratories that are suitable for assigning glucose reference values.[9]

NOTE 2 Some manufacturers of IVD medical devices provide trueness control materials intended for performance verification.

EXAMPLE 1 Trueness is verified by comparing measurement bias using suitable glucose reference materials to predetermined acceptability criteria for bias.

EXAMPLE 2 Precision is verified by comparing the standard deviation of daily measurements of a suitable glucose quality control material to predetermined acceptability criteria for intermediate precision.

6.3.3 Minimum system accuracy performance criteria

The blood-glucose monitoring system shall meet both of the following minimum criteria for acceptable system accuracy. The system accuracy performance criteria shall apply to system accuracy studies performed by trained operators using blood-glucose monitoring devices that have been properly maintained, adjusted and controlled in accordance with the instructions for use.

a) 95 % of the measured glucose values shall fall within either ± 0,83 mmol/l (±15 mg/dl) of the average measured values of the reference measurement procedure at glucose concentrations < 5,55 mmol/l (<100 mg/dl) or within ± 15 % at glucose concentrations ≥ 5,55 mmol/l (≥100 mg/dl).

b) 99 % of individual glucose measured values shall fall within zones A and B of the Consensus Error Grid (CEG) for type 1 diabetes.[10]

Criterion A shall be applied to each reagent lot individually. The measured values from each lot shall be analysed and reported separately.

Criterion B shall be applied to the 3 reagent lots taken together. All measured values from the 3 lots shall be combined before analysis and reporting.

NOTE 1 The system accuracy performance criteria for design verification are minimum criteria that do not take into account the influence of user technique. The appropriate design verification criteria for system accuracy are determined by the manufacturer.

NOTE 2 The design validation study (Clause 8) includes the user-to-user variability expected from lay users.

6.3.4 Study design

The minimum evaluation shall be conducted with 100 different subjects taking duplicate measurements from each of 3 reagent lots. The glucose concentrations shall span the measuring interval.

NOTE 1 The minimum study design to evaluate system accuracy will result in 600 glucose measured values (200 from each of 3 reagent lots).

The study shall be designed so that contributors to systematic error (measurement bias) and random error (measurement imprecision) that would normally be experienced by intended users will be included.

For blood-glucose monitoring devices that combine the skin puncture and measurement steps, an alternative statistically valid study design may be used.

More than one meter per subject may be used to minimize the time between replicate measurements. If more than two meters are used, the protocol shall specify that equal numbers of samples shall be measured with each meter.

NOTE 2 The evaluation procedure in 6.3.6 assumes each subject will use two different meters.

A validated disinfection method shall be available if a meter is to be used by more than one subject. The meter shall be cleaned and disinfected after each user to avoid the transfer of blood-borne pathogens.

6.3.5 Samples

The evaluation of system accuracy shall be performed with fresh capillary blood samples, each with sufficient volume for the blood-glucose monitoring system measurements and reference measurements specified in the study protocol.

Capillary blood samples shall be collected, prepared and processed according to the instructions for use for the glucose monitoring system, including sample pre-treatment where required. Sample containers designed for the collection of capillary blood shall be used. Containers may contain an anticoagulant recommended for use with the system.

The glucose concentration of each sample shall be determined by the glucose reference measurement procedure. The glucose concentrations shall be distributed in the bins specified in Table 3. Once a concentration bin is filled with samples, no additional samples shall be added to that bin.

Exclusion criteria for samples, such as packed cell volume, shall be based on the instructions for use for the glucose monitoring system.

Table 3 — Blood-glucose concentrations of samples for system accuracy evaluation

Bin #	Percentage of samples %	Glucose concentration mmol/l (mg/dl)
1	5	≤ 2,77 (≤ 50)
2	15	> 2,77 – 4,44 (> 50 – 80)
3	20	> 4,44 – 6,66 (> 80 – 120)
4	30	> 6,66 – 11,10 (> 120 – 200)
5	15	> 11,10 – 16,65 (> 200 – 300)
6	10	> 16,65 – 22,20 (> 300 – 400)
7	5	> 22,20 (> 400)

If the study population does not provide a sufficient number of fresh capillary blood samples with very low and very high glucose concentrations, modified capillary blood samples in which the glucose concentration has been raised or lowered may be substituted to achieve the required distribution, subject to the following limitations. Methods for adjusting the glucose concentration are described in 6.1.2.

— Bin #2: at least 8 capillary blood samples shall be unaltered.

— Bins #3 to #5: all capillary blood samples shall be unaltered.

— Bin #6: at least 5 capillary blood samples shall be unaltered.

6.3.6 Evaluation procedure

All reagent system units for a sample shall be taken from the same vial/package.

The evaluation shall be performed in the following sequence.

a) Assign numbers to the vials or packages (e.g. 1 to 10 for each reagent lot).

b) Obtain a sample of fresh capillary blood by skin puncture (e.g. fingerstick).

c) Remove an aliquot of the sample immediately before the first measurement by the blood-glucose monitoring system and obtain glucose measurements by the reference measurement procedure.

d) If the reference measurement procedure is designed for plasma samples, perform the plasma preparation procedure.

e) Remove two reagent system units from a vial/package and measure the glucose concentration in the sample using two different meters. Record the measured values.

f) Samples shall be applied to the reagent system unit as described in the instructions for use for the glucose monitoring system (e.g. directly from the subject's skin puncture or by an alternate procedure previously demonstrated to provide equivalent results).

g) If samples were modified as described in 6.1.2, they shall be applied in a manner that simulates the procedure specified in the instructions for use, taking into account possible influences such as sample temperature.

h) Change vials or packages every 10 subjects and ensure that reagent system units from each vials are used in the evaluation.

i) Repeat step d) for the other 2 reagent lots.

j) Remove an aliquot of the sample immediately after the last measurement by the blood-glucose monitoring system and obtain glucose measurements by the reference measurement procedure.

k) Evaluate the first and last reference values to verify sample stability. If these results indicate an unacceptable change in glucose concentration based on predetermined criteria (see 6.1.3), then the results for that subject shall be excluded. The rejected sample shall be replaced with another sample in the same glucose concentration bin.

l) Repeat steps b) to g) with the next subject.

6.3.7 Data analysis and presentation of results

6.3.7.1 General requirements

The complete set of data shall be documented and the selection of data used in the calculations shall be described.

Outlier data may not be eliminated from the data used in determining acceptable system accuracy, but may be excluded from the calculation of parametric statistics to avoid distorting estimates of central tendency and dispersion.

NOTE ISO 5725-2 and Reference[11] provide guidelines for identifying statistical outliers.

In addition to the requirements of 6.1.4, the following information shall be included in the study report:

a) total number of samples analysed;

b) interval of measured glucose values;

c) scatter plot of the data.

6.3.7.2 Graphical analysis

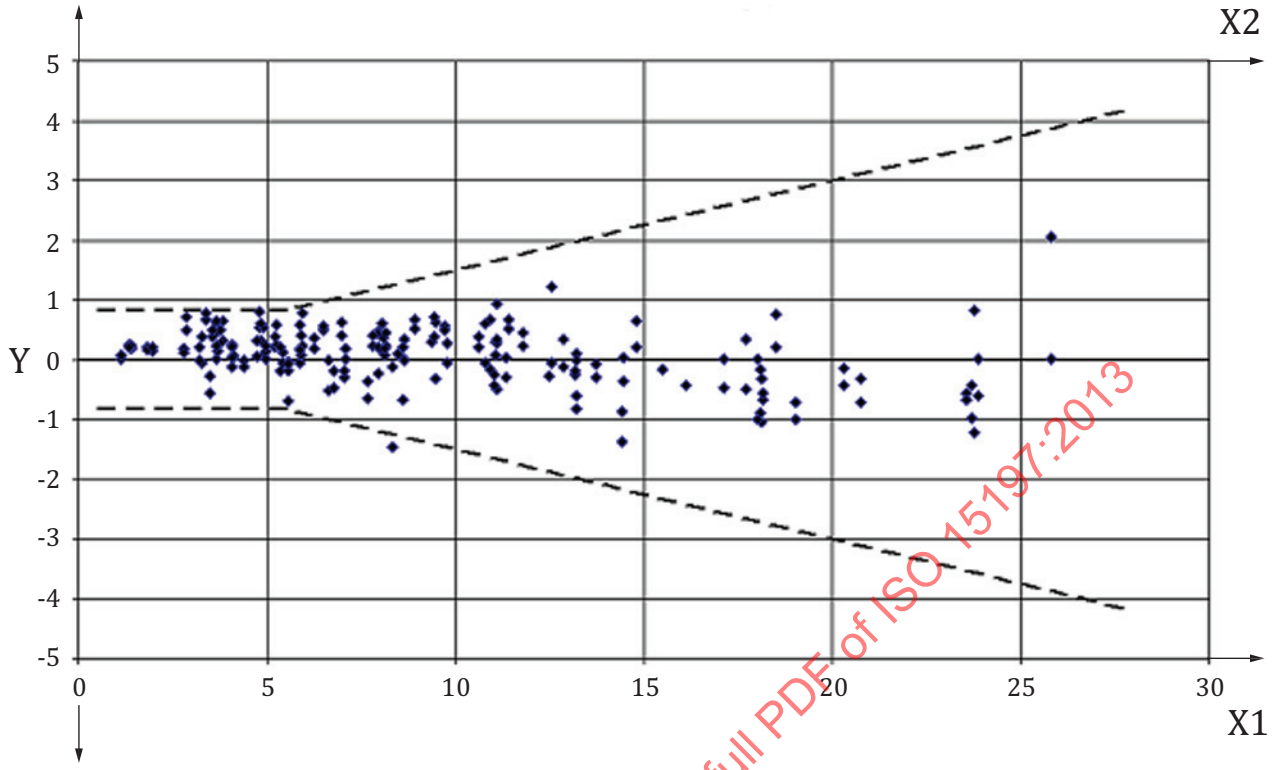
The average of the reference values shall be plotted as the independent variable. The difference between each individual measured value from the blood-glucose monitoring system and the average of the reference values shall be plotted as the dependent variable.

Outlier data should be represented by a different symbol.

NOTE 1 A difference plot is the recommended approach for determining system accuracy because statistical assumptions are minimal and the percentage of data points meeting the system accuracy performance criteria, as well as estimating bias, are easily calculated. References[11] and[12] provide guidelines for difference plots.

NOTE 2 Plotting percentage difference against concentration at low concentrations is generally not suitable for the graphical evaluation of system accuracy.

EXAMPLE A plot of measured values from an evaluation of a blood-glucose monitoring system is illustrated in Figure 1 (mmol/l) and Figure 2 (mg/dl). The two bold lines represent the system accuracy performance criteria from 6.3.3.



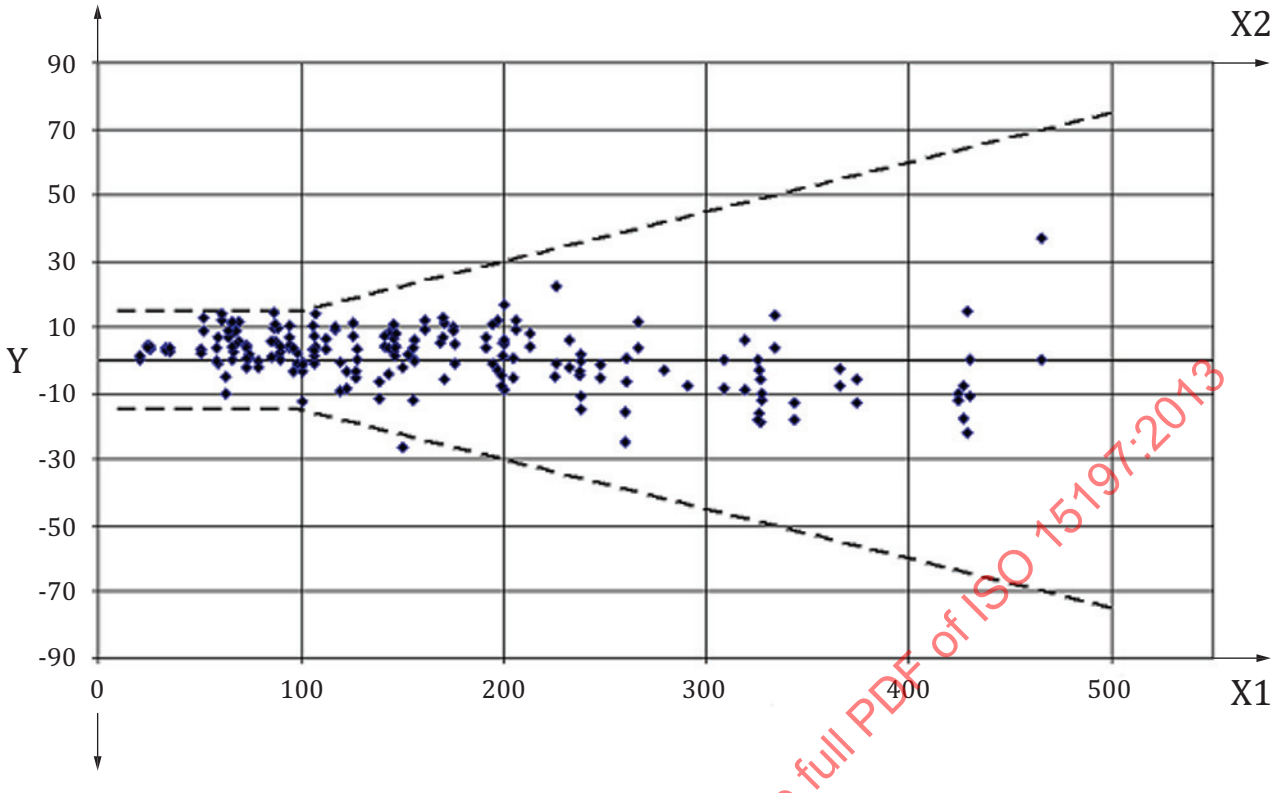
Key

X1 glucose concentration

X2 system accuracy plot — differences

Y difference

Figure 1 — System accuracy plot (mmol/l)



Key

X1 glucose concentration

X2 system accuracy plot — differences

Y difference

Figure 2 — System accuracy plot (mg/dl)

6.3.7.3 Determination of system accuracy acceptability

Acceptability of system accuracy performance shall be determined using all samples that met the inclusion criteria regardless of their glucose concentrations. All measured values from each reagent lot shall be included in the determination, including any measured values identified as statistical outliers, unless one of the specific data exclusion criteria in 6.1.3 were met.

The acceptability criteria specified in 6.3.3 shall be applied as follows.

Criterion A

For each lot individually, calculate the total number of acceptable values by adding the number of acceptable values at glucose concentrations < 5,55 mmol/l (<100 mg/dl) and the number of acceptable values at glucose concentrations ≥ 5,55 mmol/l (≥100 mg/dl). Calculate the percentage of acceptable values based on the total number of measured values. Each lot shall pass acceptability criterion A.

EXAMPLE 1 For the first lot, the total number of measured values is 200. For glucose concentration < 5,55 mmol/l (<100 mg/dl), 47 values with were within ± 0,83 mmol/l of the reference value. For glucose concentration ≥ 5,55 mmol/l (≥100 mg/dl), 146 values were within ± 15 % of the reference values. The total number of acceptable values is 47 + 146 = 193. Therefore 193 of 200 values (96,5 %) are within the system accuracy criteria defined in 6.3.3.

NOTE The number of samples in each concentration interval does not provide adequate statistical confidence to assess system accuracy separately within the concentration intervals.

Criterion B

For each lot, calculate the total number of values that fall in Zones A and B. Add the results from each of the 3 lots together. Calculate the percentage of Zone A and B values based on the total number of measured values across all 3 lots. The result shall pass acceptability criterion B.

EXAMPLE 2 The total number of measured values from all 3 lots is 600 (200 per lot). For lot 1, 198 values are in Zones A and B; for lot 2, all 200 values are in Zones A and B; for lot 3, 198 values are in Zones A and B. The total number of values in Zones A and B is 596. Therefore 596 of 600 values (99,3 %) are within Zones A and B.

6.3.7.4 Presentation of results for system accuracy

System accuracy results shall be presented in separate glucose concentration intervals in the instructions for use.

— For glucose concentrations < 5,55 mmol/l (<100 mg/dl), results shall be expressed as the percentage of values falling within the following intervals: ± 0,28 mmol/l (±5 mg/dl), ± 0,56 mmol/l (±10 mg/dl), and ± 0,83 mmol/l (±15 mg/dl).

— For glucose concentrations ≥ 5,55 mmol/l (≥100 mg/dl), results shall be expressed as the percentage of values falling within the following intervals: ± 5 %, ± 10 %, and ± 15 %.

The results shall be presented in a table for each concentration interval. The recommended formats are given in Tables 4 and 5. Percentage calculations shall be rounded to the nearest tenth of a percent.

The results across the entire measuring interval may be presented in a single table. The recommended format is given in Table 6. The interval spanning the highest and lowest reference concentration values shall be given.

EXAMPLE Tables 4, 5 and 6 illustrate the presentation of results from an evaluation study in which 100 subjects were enrolled. Three reagent lots were used, providing 600 measured values.

Table 4 — System accuracy results for glucose concentration < 5,55 mmol/l (<100 mg/dl)

Within ± 0,28 mmol/l (Within ± 5 mg/dl)	**Within ± 0,56 mmol/l** (Within ± 10 mg/dl)	**Within ± 0,83 mmol/l** (Within ± 15 mg/dl)
68/150 (45,3 %)	105/150 (70,0 %)	143/150 (95,3 %)

Table 5 — System accuracy results for glucose concentration ≥ 5,55 mmol/l (≥100 mg/dl)

Within ± 5 %	**Within ± 10 %**	**Within ± 15 %**
221/450 (49,1 %)	383/450 (85,1 %)	439/450 (97,6 %)

Table 6 — System accuracy results for glucose concentrations between X,XX mmol/l (XX mg/dl) and YY,Y mmol/l (YYY mg/dl)

Within ±0,83 mmol/l or ±15 % (Within ±15 mg/dl or ±15 %)
582/600 (97,0 %)

NOTE X,XX mmol/l (XX mg/dl) represents the lowest glucose reference value and YY,Y mmol/l (YYY mg/dl) represents the highest glucose reference value

6.4 Influence quantities

6.4.1 General requirements

The effect of influence quantities, such as packed cell volume and interfering substances in blood, shall be evaluated and addressed in the risk management process. Effects that exceed the acceptability criteria shall be disclosed in the instructions for use.

Three reagent lots shall be used for the evaluation of influence quantities.

Multiple meters may be used for the evaluation of influence quantities. The evaluation shall be designed to prevent meter-meter variation from confounding the observed effects.

6.4.2 Test sample requirements

The evaluation of influence quantities shall be performed with blood. The preferred sample is venous blood.

Samples may be collected from more than one donor.

Samples shall be equilibrated to a temperature of 23 °C ± 5 °C and maintained within ± 3 °C of the starting temperature during the evaluation procedure.

All measurements by the glucose monitoring system and the reference measurement procedures shall be completed within 36 h of sample collection. Further delay can lead to chemical or physical changes that could influence the glucose measurement results.

NOTE Fresh blood samples can experience changes in matrix upon aging and physical manipulation can affect the integrity of cell membranes. Such changes could affect the response of the blood-glucose monitoring system.

6.4.3 Packed cell volume evaluation

6.4.3.1 Study design

Evaluation of packed cell volume effects shall be conducted with a minimum of 5 packed cell volumes at each of 3 glucose concentrations. The glucose concentrations shall fall in the intervals specified in Table 2. The evaluation may be expanded to include additional glucose concentrations and packed cell volumes.

A multifactorial design (packed cell volume x glucose concentration) is preferred. Other experimental designs are acceptable with statistical justification.

Reference measurement procedures with suitable precision and trueness shall be used to assign the glucose and packed cell volume reference values.

6.4.3.2 Acceptance criteria

Acceptance criteria for packed cell volume effects shall be established in the study protocol.

The packed cell volume effects shall be described in the instructions for use if they meet either of the following performance criteria.

— For glucose concentrations < 5,55 mmol/l (<100 mg/dl), the difference between the average measured value at each packed cell volume level and the average measured value at the mid-level packed cell volume exceeds 0,55 mmol/l (10 mg/dl).

— For glucose concentrations ≥ 5,55 mmol/l (≥100 mg/dl), the difference between the average measured value at each packed cell volume level and the average measured value at the mid-level packed cell volume exceeds 10 %.

6.4.3.3 Sample preparation

The desired packed cell volumes may be prepared from blood by separating the plasma from the cells, then adding aliquots of plasma to packed cells in different proportions.

NOTE The integrity of blood samples can change upon aging and physical manipulation (e.g. pipetting can cause shearing of the cells and lead to haemolysis).

The highest and lowest packed cell volumes shall include the range of acceptable packed cell volume values specified in the labelling of the blood-glucose monitoring system. The mid-level sample shall be adjusted to 42 % ± 2 %.

The following procedure may be used to prepare 5 samples with desired packed cell volumes.

a) Divide the pooled blood into 5 equal portions.

b) Centrifuge each portion to separate the cells from the plasma.

c) Pool the resulting plasma.

d) Resuspend the packed cells in different volumes of plasma to create a series of samples that includes the highest and lowest acceptable packed cell volumes.

e) Assign a packed cell volume value to each sample using the reference measurement procedure.

The following procedure may be used to adjust the samples to the desired glucose concentrations.

— Divide the blood at each packed cell volume into 3 equal portions.

— Adjust the glucose concentrations to the desired values (see 6.1.2).

Other procedures that result in suitable samples for evaluating the effects of packed cell volume may be used.

6.4.3.4 Evaluation procedure

Each sample shall be gently but thoroughly mixed by inversion before taking an aliquot for measurement.

The packed cell volume evaluation shall be conducted in the following sequence. If multiple meters are used, meters shall be rotated to avoid introducing bias due to meter-meter differences.

a) Obtain duplicate glucose measurements by the reference measurement procedure.

b) Obtain at least 10 glucose measurements using test strips from the first reagent lot.

c) Obtain at least 10 glucose measurements using test strips from the second reagent lot.

d) Obtain at least 10 glucose measurements using test strips from the third reagent lot.

e) After meter testing is completed, obtain another set of duplicate glucose measurements by the glucose reference measurement procedure

f) Compare the reference glucose values from steps a) to e) to verify that the glucose concentration did not change during the evaluation.

g) If the results exceed predetermined stability criteria (see 6.1.3), then the measured values for that sample shall not be used and all measurements shall be repeated with a different sample.

6.4.3.5 Data analysis and presentation of results

For each glucose concentration and packed cell volume, data analysis shall be performed and presented separately for each reagent lot as follows.

a) The average and the standard deviation of the measured values from the blood-glucose monitoring system shall be calculated for each sample and reagent lot.

b) From the measured values from the blood-glucose monitoring system and the reference values, the glucose bias and % bias shall be calculated for each sample and reagent lot.

c) To determine the effect of packed cell volume on the measured values from the blood-glucose monitoring system, the difference between the average glucose bias and the average bias of the mid-level sample shall be calculated for each sample. The same calculation shall be performed for each sample using the % bias calculated in step b).

d) If the effects meet the acceptability criteria and the results across the 3 lots are statistically equivalent, all results at each glucose concentration may be averaged for presentation in the instructions for use.

In addition to the requirements of 6.1.4, the following information shall be included in the study report:

the results and conclusions of the study, including

— the packed cell volume for each sample,

— the glucose reference value for each sample;

a graphical presentation of the results, with packed cell volume plotted on the x-axis, the difference from the mid-level packed cell volume plotted on the y-axis, and the maximum allowable deviations (positive and negative limits) identified with a dashed line.

6.4.4 Interference testing

6.4.4.1 Study design

The evaluation shall be conducted at a minimum of 2 glucose concentrations, one within the interval of 2,8 mmol/l to 5,5 mmol/l (50 mg/dl to 100 mg/dl) and the other within the interval of 13,9 mmol/l to 19,4 mmol/l (250 mg/dl to 350 mg/dl).

Substances to evaluate for possible interference shall be identified by risk analysis. The requirements of ISO 14971 pertaining to hazard identification apply.

Annex A contains a list of substances that could be present in blood and have been found to interfere with a glucose measurement procedure. These substances shall be considered in the risk analysis. If a substance listed in Annex A is not evaluated experimentally, the decision shall be justified.

A paired-sample experimental design that compares measured glucose values from samples with an added substance to a control sample without the added substance is recommended. Other experimental designs (e.g. multifactorial) are acceptable with statistical justification.

NOTE Reference[13] provides guidelines for evaluating potentially interfering substances, including recommended test concentrations.

A reference measurement procedure with suitable precision and trueness shall be used to assign glucose reference values to the samples.

6.4.4.2 Acceptance criteria

Acceptance criteria for interference effects shall be established in the study protocol.

The interference effects shall be described in the instructions for use if they meet either of the following performance criteria.

— For glucose concentrations < 5,55 mmol/l (<100 mg/dl), the average difference between the test sample and the control sample exceeds 0,55 mmol/l (10 mg/dl).

— For glucose concentrations ≥ 5,55 mmol/l (≥100 mg/dl), the average difference between the test sample and the control sample exceeds 10 %.

6.4.4.3 Sample preparation

The following procedure may be used to prepare 4 samples with desired combinations of glucose and test substance concentration.

a) Obtain 2 pools of venous blood with glucose concentrations specified in 6.4.4.1.

b) Adjust the glucose concentrations, if necessary, using the methods described in 6.1.2.

c) Divide each pool into two portions: a test sample and a control sample.

d) Add a concentrated solution of test substance to the test sample to create the desired concentration.

e) Add an equal volume of the solvent used to dissolve the test substance to the control sample.

Other procedures that result in suitable samples for interference testing may be used.

6.4.4.4 Evaluation procedure

Each sample shall be gently but thoroughly mixed by inversion before taking an aliquot for measurement.

The interference testing shall be conducted in the following sequence:

a) Obtain duplicate glucose measurements by the reference measurement procedure.

b) Obtain at least 10 meters' measurements using test strips from the first reagent lot.

— A transfer pipette capable of delivering sample volumes within the manufacturer's recommended interval may be used to simulate routine sample application.

c) Obtain at least 10 meters' measurements using test strips from the second reagent lot.

d) Obtain at least 10 meters' measurements using test strips from the third reagent lot.

e) After meter testing is completed, obtain another set of duplicate glucose measurements by the reference measurement procedure.

f) Compare the reference glucose values from steps a) to e) to verify that the glucose concentration did not change during the evaluation.

— If the results exceed predetermined stability criteria (see 6.1.3), then the measured values for that sample shall not be used and all measurements shall be repeated with a different sample.

— If an interference effect exceeds the performance criteria in 6.4.4.2, perform a dose-response evaluation to determine the degree of interference as a function of test substance concentration.

g) Prepare a series of test samples (n=5) by mixing the sample containing the highest concentration of potentially interfering substance and the control sample in different proportions.

h) Obtain duplicate glucose measurements by the reference measurement procedure.

i) Obtain at least 10 meters' measurements from each sample using test strips from each of the 3 reagent lots.

j) After meter testing is completed, obtain another set of duplicate glucose measurements by the reference measurement procedure to verify that the glucose concentration has not changed.

k) Compare the reference glucose values from steps h) and j) to verify that the glucose concentration did not change during the evaluation.

If the results exceed predetermined stability criteria (see 6.1.3), then the measured values for that sample shall not be used and all measurements shall be repeated with a different sample.

6.4.4.5 Data analysis and presentation of results

For each substance being evaluated for possible interference, data analysis shall be performed and presented separately for each reagent lot as follows.

The average and the standard deviation of the measured values from the blood-glucose monitoring system shall be calculated for each sample.

The difference shall be calculated between the average of the test sample values and the average of the control sample values.

If the effects meet the acceptability criteria and the results across the 3 lots are statistically equivalent, all results at each glucose concentration may be averaged for presentation in the instructions for use.

If a dose-response evaluation was performed, the concentration of interfering substance that exceeds the performance criteria shall be determined.

The average and the standard deviation of the measured values from the blood-glucose monitoring system shall be calculated for each admixture, as well as the two samples used to make the admixtures.

If the effects meet the acceptability criteria and the results across the 3 lots are statistically equivalent, all results at each glucose concentration may be averaged for presentation in the instructions for use.

The interfering substance concentration that exceeds the acceptability criteria shall be calculated (e.g. using linear regression analysis if appropriate) for presentation in the instructions for use.

In addition to the requirements of 6.1.4, the following information shall be included in the study report.

a) A list of substances evaluated for possible interference, the test concentration, and the rationale for selection.

b) The rationale for not evaluating any of the substances listed in Annex A.

c) The results and conclusions of the study, including

   — the interferent test concentrations,

   — the glucose reference value for each sample,

   — graphical presentation of the results if a dose-response evaluation was performed, with the test substance concentration plotted on the x-axis, the difference between test and control results plotted on the y-axis, and the maximum allowable interference limit identified with a dashed line.

6.5 Stability of reagents and materials

6.5.1 General requirements

If the reagent system, control materials and other components may be subject to degradation over time, the conditions for storage and use shall be defined and validated.

6.5.2 Stability determination

The requirements specified in ISO 23640 that pertain to establishing stability performance and expiry dating apply.

7 Information supplied by the manufacturer

7.1 General requirements

The requirements of ISO 18113-1, ISO 18113-4 and ISO 18113-5 apply.

If a specific blood-glucose meter is required to be used with a specific reagent system, the label(s) [or outer container label(s)] and the instructions for use shall advise the lay person of this requirement.

The instructions for use shall describe the measurement units reported by the system, e.g. mmol/l or mg/dl.

The instructions for use shall describe whether the measured values from the blood-glucose meter are plasma-equivalent or blood-glucose concentrations.

7.2 Performance characteristics

The performance characteristics of the blood-glucose monitoring system shall be described in the instructions for use. In particular, the results of the repeatability evaluation (6.2.3.4), intermediate precision evaluation (6.2.4.4), the system accuracy evaluation (6.3.7), limitations due to packed cell volume (6.4.3.5) and interference effects (6.4.4.5), and the user performance evaluation (8.7) shall be summarized.

— The performance characteristics and other technical information shall be described in a format and language understandable by a lay person.

— Subclause 6.3.7.4 provides a recommended format (Table 4, Table 5 and Table 6) to summarize the results of the system accuracy evaluation.

— Subclause 8.7.2 provides a recommended format to summarize the results of the user performance evaluation.

If the blood-glucose monitoring system is affected by environmental factors, such as ambient temperature, humidity, pressure or oxygen (e.g. higher altitude), the conditions required to obtain accurate measured values shall be specified.

7.3 Options for supplying instructions for use

The procedural instructions required by a lay person to obtain an accurate examination result may be presented in a single instructions for use document, provided the meter and reagent strips are manufactured by the same manufacturer.

Other instructions required by ISO 18113-1, ISO 18113-4 and ISO 18113-5 or by this International Standard may be supplied on the labels or instructions for use of the individual system components.

8 User performance evaluation

8.1 General requirements

The user performance evaluation shall be performed prior to placing a new blood-glucose monitoring system into commercial distribution.

The requirements specified in EN 13612 apply.

NOTE 1 The evaluations in Clause 8 are design validation activities, which are intended to provide assurance that system performance will consistently meet the requirements of the intended use.

NOTE 2 This International Standard is not intended to specify all design validation activities that may be required to demonstrate that the blood-glucose monitoring system meets user needs and intended uses.

The user performance evaluation shall demonstrate that intended users are able to obtain accurate glucose measured values when operating the blood-glucose monitoring system, given only the instructions and training materials routinely provided with the system.

Accuracy of capillary blood-glucose values measured by lay persons shall be compared to capillary blood-glucose values measured by the reference measurement procedure.

Blood-glucose monitoring systems for self-testing shall be evaluated in a setting that allows lay persons to perform blood-glucose measurements without outside influence. Rationale for selection of the evaluation sites shall be documented in the study report.

The study shall be supervised by one or more healthcare providers trained in the use of the device under evaluation.

The evaluation may be conducted at multiple sites and may be performed using one lot of reagent.

The evaluation plan shall be documented in a detailed protocol, which shall be appended to the study report.

8.2 Acceptance criteria and evaluation of results

Acceptability of the blood-glucose measured values obtained by the study subjects shall be evaluated based on comparison to the reference glucose values.

95 % of the individual glucose measured values shall fall within ± 0,83 mmol/l (±15 mg/dl) of the measured values of the manufacturer's measurement procedure at glucose concentrations < 5,55 mmol/l (<100 mg/dl) and within ± 15 % at glucose concentrations ≥ 5,55 mmol/l (≥100 mg/dl).

Acceptability of the blood-glucose monitoring system shall be determined using the total number of measured values obtained by all of the subjects, including any measurement results identified as statistical outliers.

NOTE The total number of acceptable measured values consists of the number of acceptable glucose values at concentrations < 5,55 mmol/l (<100 mg/dl) added to the number of acceptable glucose values at concentrations ≥ 5,55 mmol/l (≥100 mg/dl).

Acceptability of system accuracy in concentration intervals above and below 5,55 mmol/l (100 mg/dl) shall not be determined separately.

8.3 Selection and preparation of subjects

At least 100 lay persons shall be recruited to participate in the study. The subjects shall be diabetic individuals representing different ages, genders and education levels.

Subjects shall be selected using the consecutive sampling method. All diabetic subjects who volunteer for the study and qualify in accordance with the study inclusion and exclusion criteria, the user requirements established by the manufacturer for the blood-glucose system (e.g. packed cell volume within the system's specified limits), and applicable regulatory requirements (e.g. written informed consent), shall be eligible to participate in the study.

Inclusion and exclusion criteria shall be consistent with limitations stated in the product labelling.

Subjects shall not have participated in a study or other activity involving the blood-glucose monitoring system being evaluated in this study.

Prior to performing self-testing, each study participant shall be given the product instructions for use and any training materials that are routinely provided with the blood-glucose monitoring system.

Participants shall review the materials and use the device in any manner described in the study protocol that represents how lay persons learn to use a new device.

No instructions, training, assistance, feedback or supplemental instructional materials other than those which will routinely accompany the device shall be provided to participants.

After reviewing the materials, study subjects may be allowed a reasonable opportunity to practice testing with the blood-glucose monitoring system. In such cases, the number of practice tests shall be limited and shall be defined in the study protocol.

8.4 Execution of study protocol

Each study subject shall collect their own blood sample by skin puncture (e.g. fingerstick) and perform one test using the blood-glucose monitoring system.

If the subject reports that a mistake has been made in performing self-testing, such as applying blood to the reagent incorrectly, or obtains a non-quantitative result, the subject shall be allowed to repeat self-testing and the study staff shall document the mistake in the study report.

The results of incorrectly performed tests shall be excluded from the determination of acceptability of the blood-glucose monitoring system. A maximum of three exclusions due to incorrectly performed self-testing shall be allowed per subject.

The number and specific nature of incorrectly performed tests shall be described in the study report.

8.5 Glucose reference values

Within 5 min after the user test, the supervising healthcare provider shall collect a capillary blood sample for measurement of the reference glucose value, for estimation of packed cell volume, and for determination of any other exclusion criterion specified in the study protocol.

The reference sample may be collected from the participant's skin puncture or from a second skin puncture performed by the supervising healthcare provider.

Collection of the reference sample from the study participant's skin puncture is preferred. If a second skin puncture is needed, it shall be documented in the study report.

The reference sample shall be measured by a glucose reference measurement procedure. The requirements of 6.3.2 apply to the assignment of glucose reference values.

8.6 Human factors

User techniques in operating the system, applying the sample and reading the result shall be observed by the healthcare providers supervising the study.

The human factors observations shall be documented in the study report.

8.7 Data analysis and presentation of results

8.7.1 General

Data shall be analysed by study site, if multiple sites are performing the study. Differences among the results from different sites shall be documented in the study report.

Data may be excluded from analysis if a documented error in performing the procedure occurs, as defined in the study protocol. The requirements described in 6.1.2 apply.

Outlier data shall not be eliminated from data analysis when determining acceptable system accuracy (8.2), but should be excluded from the calculation of parametric statistics to avoid distorting central tendency and dispersion estimates.

NOTE ISO 5725-2 and Reference[13] provide guidelines for identifying statistical outliers.

Where data have been excluded, the reason for the exclusion shall be documented in the study report.

The study results shall be presented as difference plots as described in 6.3.7.2.

Outlier data should be plotted with a different symbol.

Observations and results of the study shall be documented in a report. In addition, the following information shall be reported:

a) the total number of samples analysed;

b) the interval of glucose concentrations;

c) the glucose values measured with the device, the glucose reference values, and the packed cell volume values observed for each study participant.

d) a summary of the statistical analysis with confidence intervals;

e) a summary of any outliers excluded from statistical analysis, including the method of identification and the results of the investigation;

f) a scatter plot of the data;

g) a detailed description of the glucose reference measurement procedure, its calibration (including metrological traceability), and the validation or verification of its imprecision and bias;

h) references for the statistical analysis procedures.

8.7.2 The overall results shall be summarized for the instructions for use using the following format

A study evaluating glucose values from fingertip capillary blood samples obtained by ### lay persons showed the following results:

XX % within ±0,83 mmol/l (±15 mg/dl) of the medical laboratory values at glucose concentrations below 5,55 mmol/l (100 mg/dl), and YY % within ±15 % of the medical laboratory values at glucose concentrations at or above 5,55 mmol/l (100 mg/dl).

8.8 Evaluation of instructions for use

8.8.1 General

The instructions for use and messages displayed on the meter shall be evaluated for clarity and usefulness.

The evaluation shall be performed by the subjects participating in the user performance evaluation. Other lay persons may also participate in the evaluation.

8.8.2 Evaluation method

The evaluation method shall be conducted by a questionnaire designed to assess whether the users understood how to use the device correctly.

A typical questionnaire may consist of a series of statements, where evaluation participants are asked to indicate their degree of agreement with each statement on a scale of 1 to 5 (1 = strongly disagree; 3 = neutral; 5 = strongly agree).

EXAMPLE The questionnaire can include statements such as:

— The instructions were easy to follow.

— The test results displayed on the meter were easy to see.

— It was easy to understand the test results.

— The instructions clearly explain what to do if an error message is displayed on the glucose monitor.

Study participants shall also be given an opportunity to provide unrestricted comments on their experience when using the blood-glucose monitoring system and the instructions for use.

To avoid biasing the study results, the questionnaire shall be completed after the subject's self-testing has been completed.

8.8.3 Questionnaire results

The questionnaires shall be reviewed and evaluated to determine if the instructions for use and messages displayed on the meter are adequate.

Comments from the study participants and the results of the questionnaire, including recommended actions necessary to improve the clarity and usefulness of the instructions for use, shall be documented in the study report or in a separate report.

Annex A
(informative)

Possible interfering substances

A.1 Purpose

The purpose of this annex is to identify substances that could be present in the blood of intended users and that have been found to interfere with one or more glucose measurement procedures. This list is not intended to include all possible interfering substances and is not intended to require testing if there is no reason to suspect possible interference.

Manufacturers should consider whether these substances can potentially interfere with their system, as described in 4.3.2. Interference testing requirements are described in 6.4.4.

Decisions not to evaluate substances listed in this annex shall be justified in the risk analysis.

A.2 Possible interfering substances

a) Acetaminophen (paracetamol)

b) Ascorbate (ascorbic acid)

c) Bilirubin

d) Cholesterol

e) Creatinine

f) Dopamine

g) EDTA

h) Galactose

i) Gentisic acid

j) Glutathione

k) Haemoglobin

l) Heparin

m) Ibuprofen

n) Icodextrin

o) L-DOPA (L-3,4-dihydroxyphenylalanine)

p) Maltose

q) Methyl-DOPA

r) Pralidoxime Iodide (PAM)

s) Salicylate

t) Tolbutamide

u) Tolazamide

v) Triglycerides

w) Urate (uric acid)

x) Xylose

Annex B
(informative)

Traceability chain

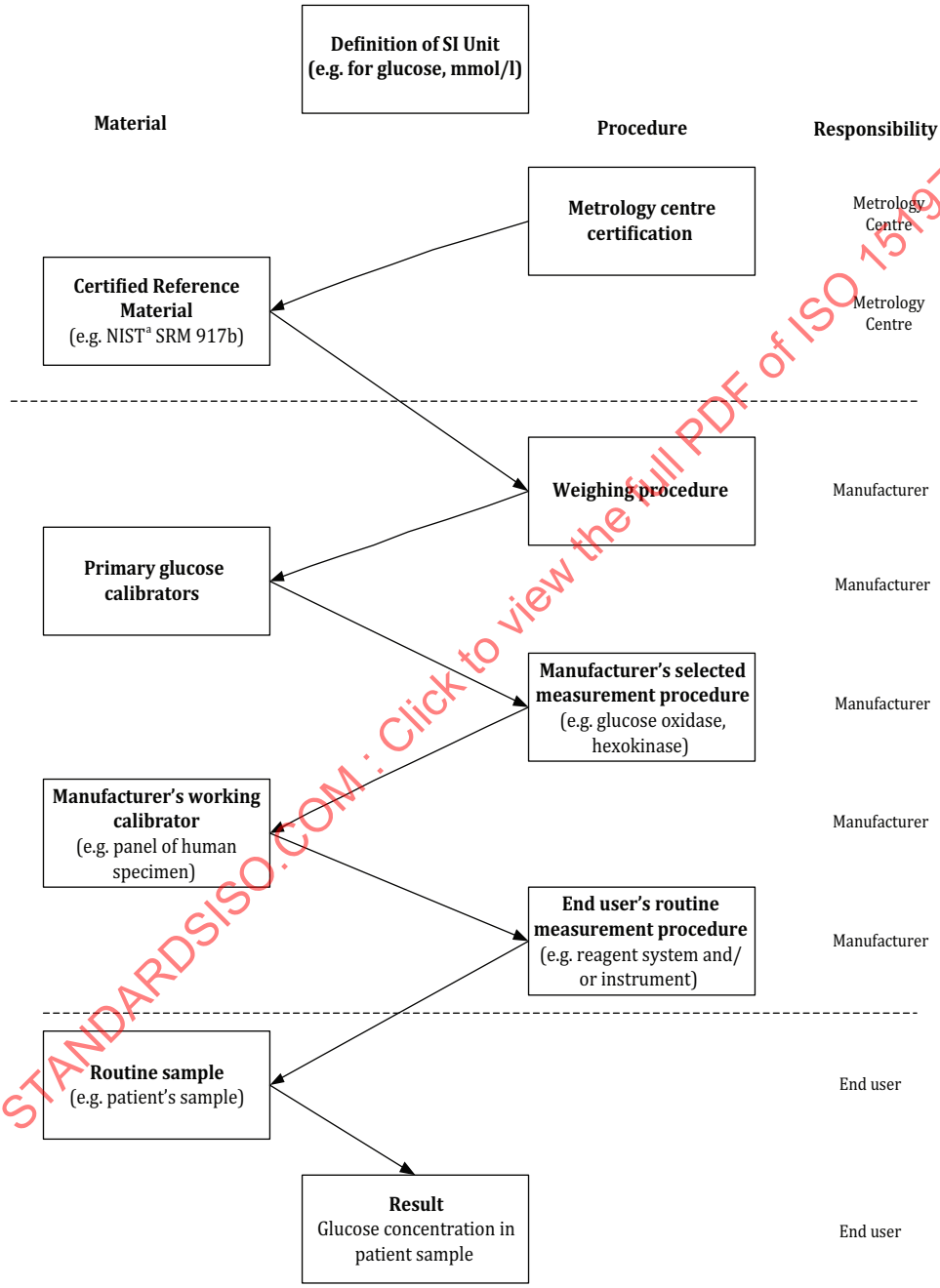


Figure B.1 — Example of a traceability chain for a factory–calibrated blood–glucose monitoring system

NOTE 1 The illustration given in Figure B.1 of a possible traceability chain is derived from ISO 17511:2003, 4.2.2 and Figure 1.

NOTE 2 This example is not intended to represent the only possible traceability chain for a blood-glucose monitoring system.

The *Joint Committee for Traceability in Laboratory Medicine* database[11] lists currently available higher-order reference materials and reference methods/procedures.