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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*.

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 relative or absolute deficiency in insulin secretion or by insulin resistance leading to abnormal 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 laypersons. The primary objectives are to establish requirements that result in acceptable performance and to specify procedures for demonstrating conformance to this International Standard.

Performance criteria for blood-glucose monitoring systems were established from the accuracy (precision and trueness) required for individual glucose results. System accuracy criteria, also known in the *in vitro* diagnostics (IVD) industry as total error criteria (see NCCLS EP21-P[35]), are used in this International Standard because some of the metrological terms commonly used in International Standards (e.g. uncertainty) would not be familiar to lay users. *System accuracy*, which is affected by systematic bias and measurement uncertainty, describes the degree to which the individual results produced by a glucose monitoring system agree with the true glucose values when the system is used as intended by laypersons.

The criteria for system accuracy are based on three considerations (see References [2] to [21] in the Bibliography):

a) the effectiveness of current technology for monitoring patients with diabetes mellitus, as demonstrated in clinical outcome studies using state-of-the-art monitoring devices;

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

c) the state-of-the-art of currently available technology, as evidenced by the performance of existing commercial products.

In arriving at the performance criteria, desirable goals had to be weighed against the capabilities of existing devices (the current state-of-the-art) and their effectiveness in clinical outcome studies. It was decided that overly demanding performance requirements would cause manufacturers to focus design improvements on analytical performance at the expense of other important attributes. For example, frequency of testing by diabetic patients can be as important as the accuracy of an individual result, and greater convenience of glucose self-testing improves patient compliance. The system accuracy criteria define the minimum acceptable performance of a blood-glucose measuring device intended for self-monitoring.

Future advances in technology are expected, which should result in improved performance of glucose monitoring devices. Such performance improvements will be driven by the competitive marketplace, particularly through reduction of dependence on user technique.

Requirements that are unique to self-monitoring devices for blood-glucose, including the content of information supplied by the manufacturer, are addressed in this International Standard. General requirements that apply to all *in vitro* diagnostic medical devices and are covered by other standards [e.g. ISO 13485 and ISO 14971] are incorporated by reference where appropriate.

Although this International Standard does not apply to measurement procedures with results on an ordinal scale (e.g. visual, semiquantitative measurement procedures), 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 and procedures for the verification and the validation of performance by the intended users. These systems are intended for self-testing by laypersons 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, or

— apply to measurement procedures with results on an ordinal scale (e.g. visual, semiquantitative test methods).

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:—[1)], In vitro *diagnostic medical devices — Measurement of quantities in biological samples — Metrological traceability of values assigned to calibrators and control materials*

IEC 60068-2-64:1993, *Environmental testing — Part 2: Test methods — Test Fh: Vibration, broad-band random (digital control) and guidance*

IEC 61010-1:2001, *Safety requirements for electrical equipment for measurement, control, and laboratory use — Part 1: General requirements*

IEC 61010-2-101:2002, *Safety requirements for electrical equipment for measurement, control and laboratory use — Part 2-101: Particular requirements for* in vitro *diagnostic (IVD) medical equipment*

1) To be published.

IEC 61000-4-2, *Electromagnetic compatibility (EMC) — Part 4-2: Testing and measurement techniques — Electrostatic discharge immunity test*

IEC 61000-4-3, *Electromagnetic compatibility (EMC) — Part 4-3: Testing and measurement techniques — Radiated, radio-frequency, electromagnetic field immunity test*

IEC 61326, *Electrical equipment for measurement, control and laboratory use — EMC requirements*

EN 376, *Information supplied by the manufacturer with* in vitro *diagnostic reagents for self-testing*

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

EN 13640, *Stability testing of* in vitro *diagnostic reagents*

3 Terms and definitions

For the purposes of this document, the following terms and definitions apply.

3.1
accuracy
closeness of agreement between a test result and the accepted reference value

[ISO 3534-1:1993]

NOTE 1 The term "accuracy", when applied to a set of test results, involves a combination of random error components and a common systematic error or bias component. [VIM:1993]

NOTE 2 For a measure of the accuracy of results of a blood-glucose monitoring system, see 3.24.

3.2
bias
difference between the expectation of the test results and an accepted reference value

[ISO 5725-1:1994]

3.3
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 Blood-glucose monitoring systems measure glucose in capillary blood samples, but may express results as either the glucose concentration in blood or the equivalent glucose concentration in plasma. Concentrations in this International Standard refer to the type of results reported by the system.

3.4
blood-glucose meter
component of a blood-glucose monitoring system that converts the result of a chemical reaction into the glucose concentration of the sample

3.5
commutability of a material
ability of a material to yield the same numerical relationships between results of measurements by a given set of measurement procedures, purporting to measure the same quantity, as those between the expectations of the relationships obtained when the same procedures are applied to other relevant types of material

[ISO 15194:2002]

NOTE For reference materials used to calibrate measurement procedures intended for biological samples, "other relevant types of material" include a large number of samples from healthy and relevantly diseased individuals.

3.6
control material
substance, material, or article intended by the manufacturer to be used to verify the performance characteristics of an *in vitro* diagnostic medical device

[EN 375:2001]

3.7
information supplied by the manufacturer with the medical device
all written, printed, or graphic matter on a medical device or any of its containers or wrappers, or accompanying a medical device, relating to the identification, technical description and use of the medical device, but excluding shipping documentation and promotional material

NOTE 1 Adapted from EN 1041:1998.

NOTE 2 In some countries, information supplied by the manufacturer is called “labelling”.

3.8
instructions for use
information supplied by the manufacturer with an *in vitro* diagnostic medical device concerning the safe and proper use of the reagent or the safe and correct operation, maintenance, and basic troubleshooting of the instrument

NOTE 1 Adapted from EN 375:2001 and EN 591:2001.

NOTE 2 Instructions for use for *in vitro* diagnostic reagents for self-testing is described in EN 376.

NOTE 3 Instructions for use for *in vitro* diagnostic instruments for self-testing is described in EN 592.

NOTE 4 Instructions for use may take the form of package insert sheets and/or user manuals.

3.9
intermediate precision
precision under conditions intermediate between reproducibility conditions and repeatability conditions

NOTE The concept of intermediate levels of precision is described in ISO 5725-3:1994.

3.10
intermediate precision conditions
conditions where independent test results are obtained with the same method on identical test items in the same location, but where other variables such as operators, equipment, calibration, environmental conditions and/or time intervals differ

NOTE Intended to measure precision in conditions leading to variability representative of actual use. Quantitative measures of intermediate precision depend on the stipulated conditions.

3.11
label
printed, written, or graphic information placed on a device or container

NOTE Adapted from EN 375:2001.

3.12
layperson
individual who does not have formal training in a specific field or discipline

NOTE 1 Adapted from the definition of “lay user” in EN 376:2002.

NOTE 2 For the purposes of this International Standard, a user of a blood-glucose monitoring device who does not have specific medical, scientific or technical knowledge related to blood-glucose monitoring.

3.13
lot
batch
one or more components or finished devices that consist of a single type, model, class, size, composition, or software version that are manufactured under essentially the same conditions and that are intended to have uniform characteristics and quality within specified limits

NOTE In Directive 98/79/EC[37] and in European Standards the term “batch” is preferred.

3.14
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 ISO 17511:—, 4.2.2 f), shows the manufacturer's selected measurement procedure in the traceability chain.

3.15
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 ISO 17511:—, 4.2.2 h) shows the manufacturer's standing measurement procedure in the traceability chain.

3.16
package insert
instructions for use and other information for the reagent system or control material that is supplied within the package, but not attached to any part of the package

3.17
packed cell volume
volume fraction of the erythrocytes in blood

NOTE 1 Expressed either as a decimal fraction (SI) or as a percentage (conventional). SI units (L/L) are implied.

NOTE 2 Sometimes referred to as “haematocrit” after the instrument originally used to estimate packed cell volume.

3.18
precision of measurement
closeness of agreement between independent test results obtained under stipulated conditions

[ISO 3534-1:1993]

NOTE 1 The degree of precision is expressed numerically by the statistical measures of imprecision of measurements, such as standard deviation and coefficient of variation, that are inversely related to precision. Quantitative measures of precision depend on the stipulated conditions.

NOTE 2 Precision of a given measurement procedure is subdivided according to the specified precision conditions. Particular sets of extreme conditions are termed “repeatability” (3.20) and “reproducibility” (3.22).

3.19
reagent system
part of the *in vitro* diagnostic medical device that produces a signal via a chemical or electrochemical reaction, which allows the analyte (e.g. glucose) in a sample to be detected and its concentration measured

3.20
repeatability
precision under repeatability conditions

[ISO 3534-1:1993]

3.21
repeatability conditions
conditions where independent test results are obtained with the same method on identical test items in the same laboratory by the same operator using the same equipment within short intervals of time

[ISO 3534-1:1993]

NOTE 1 Essentially unchanged conditions, intended to represent conditions resulting in minimum variability of test results.

NOTE 2 For the purposes of this International Standard, “laboratories” should be interpreted as “locations.”

3.22
reproducibility
precision under reproducibility conditions

[ISO 3534-1:1993]

3.23
reproducibility conditions
conditions where test results are obtained with the same method on identical test items in different laboratories with different operators using different equipment

[ISO 3534-1:1993]

NOTE 1 Completely changed conditions, intended to represent conditions resulting in maximum variability of test results.

NOTE 2 For the purposes of this International Standard, “laboratories” should be interpreted as “locations”.

3.24
system accuracy

closeness of agreement of a set of representative test results from a measuring system and their respective reference values

NOTE 1 The term accuracy, when applied to a set of test results, involves a combination of random error components and a common systematic error or bias component. [VIM:1993]

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

NOTE 3 System accuracy may be expressed as the interval that encompasses 95 % of the differences observed between the results of the system being evaluated and their reference values. This interval also includes measurement uncertainty from the measurement procedure used to assign the reference values.

3.25
traceability
property of the result of a measurement or the value of a standard whereby it can be related to stated references, usually national or international standards, through an unbroken chain of comparisons all having stated uncertainties

[VIM:1993, 6.10]

3.26
trueness
closeness of agreement between the average value obtained from a large series of test results and an accepted reference value

[ISO 3534-1:1993]

NOTE The measure of trueness is usually expressed in terms of bias (3.2).

3.27
type test
test of one or more samples of equipment (or parts of equipment) made to a particular design, to show that the design and construction meet one or more requirements of the applicable standard

NOTE 1 Statistical sampling is not required for blood-glucose monitoring equipment.

NOTE 2 Adapted from IEC 61326.

3.28
user adjustment of 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

4 Design and development

4.1 General requirements

The requirements specified in ISO 13485 apply.

NOTE Clause 6, 7.2 and 7.3 describe design verification activities, which are intended to provide assurance that the system has the capability of meeting its precision, trueness, safety, and reliability specifications. Clause 8 describes design validation activities, which are intended to provide assurance that system accuracy meets user requirements.

4.2 Safety

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

4.3 Traceability

The requirements specified in ISO 17511 apply to the manufacturer's calibration process.

NOTE 1 The manufacturer's selected or standing measurement procedure may measure glucose in either blood or plasma samples. If plasma samples are used, the blood-glucose monitoring system may report results as plasma glucose equivalents, even though the samples measured by the blood-glucose monitoring system are blood.

NOTE 2 The traceability chain should include as few steps as practical to minimize combined uncertainty.

NOTE 3 A traceability chain for a typical factory-calibrated blood-glucose monitoring system is shown in Annex B. This example is not intended to represent the only possibility of a suitable traceability chain.

4.4 Ergonomic/human factor aspects

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

a) ease of operation;

b) ease of maintenance;

c) protection from "wear and tear" that might typically be encountered in the use environment;

d) readability of the measured results;

e) 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-measurement may be used by laypersons with different physical and mental abilities.

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

NOTE 3 It is not expected that a single blood-glucose monitoring system will meet the needs of all possible users or settings.

4.5 Risk analysis

The requirements specified in ISO 14971 apply.

The manufacturer shall decide the acceptability of potential risks from knowledge of factors including but not limited to

a) intended use of the product,

b) users' skills and limitations,

c) protection against unintentional change of essential parameters (e.g. units reported), or

d) influence of interfering substances.

NOTE Guidelines for evaluating potentially interfering substances are found in NCCLS EP7-A[31].

In performing risk analysis, the manufacturer shall evaluate the

e) probability of occurrence of a failure (e.g. insufficient sample volume or incorrect test strip placement),

f) probability of the system not detecting a failure, and

g) consequences of an undetected failure.

NOTE This International Standard does not specify levels of risk and acceptability.

4.6 User verification

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.

NOTE User verification should be done at the time of use. "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 possible.

User verification shall give unambiguous information.

5 Information supplied by the manufacturer

5.1 Labels for the blood-glucose meter

The blood-glucose meter shall be identified by labels including, at a minimum, the following information:

a) name or trade name of the manufacturer and address of the manufacturer;

b) product name or designation (this information shall directly appear on a label affixed to the device);

c) intended purpose (a statement that the device is an *in vitro* diagnostic medical device for self-testing shall be included, as well as information regarding the reagent system to be used with the device);