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Clinical laboratory testing and in vitro medical devices — Requirements for in vitro monitoring systems for self-testing of oral anticoagulant therapy

Laboratoires d'analyses de biologie médicale et dispositifs médicaux de diagnostic in vitro — Exigences relatives aux systèmes d'autosurveillance des traitements par anti-coagulant oraux

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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.

The procedures used to develop this document and those intended for its further maintenance are described in the ISO/IEC Directives, Part 1. In particular, the different approval criteria needed for the different types of ISO documents should be noted. This document was drafted in accordance with the editorial rules of the ISO/IEC Directives, Part 2 (see www.iso.org/directives).

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

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

For an explanation of the voluntary nature of standards, the meaning of ISO specific terms and expressions related to conformity assessment, as well as information about ISO's adherence to the World Trade Organization (WTO) principles in the Technical Barriers to Trade (TBT), see www.iso.org/iso/foreword.html.

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

This second edition cancels and replaces the first edition (ISO 17593:2007), which has been technically revised.

The main changes are as follows:

— Updated with more current state of the art information that has evolved over several years.

— Subclause 8.4 Validation of measurement precision: added a more robust study design.

— Subclause 8.5.8.2 and 8.5.8.3: updated examples were added to reflect changes in criteria.

— Subclause 8.6 Minimum acceptable system accuracy : Updated requirements/performance criteria.

— Clause 9 Lay person performance evaluation: added clarity, revised performance criteria and increased sample size.

— Removed Annex F listing of publications.

Any feedback or questions on this document should be directed to the user's national standards body. A complete listing of these bodies can be found at www.iso.org/members.html.

Introduction

Oral-anticoagulation monitoring systems are in vitro diagnostic (IVD) medical devices that measure prothrombin time in fresh, untreated human blood specimens. Prothrombin time is an indicator of the ability of blood to clot. IVD medical devices for self-testing of oral-anticoagulation therapy are used predominantly by individuals who have heart valve replacements, or who are suffering from atrial fibrillation or deep vein thrombosis and are receiving oral anticoagulant therapy with vitamin K antagonist medicines (e.g. warfarin). Patients must maintain the level of anticoagulant in the blood high enough to reduce thrombin formation, yet low enough to avoid excessive bleeding. An oral-anticoagulation monitoring system allows the user to monitor anticoagulation therapy and take action to control the level of anticoagulant present in the blood. This document applies to oral-anticoagulation monitoring systems to be used by lay persons. The primary objectives are to establish requirements for oral-anticoagulation monitoring systems that will enable lay persons to achieve acceptable performance, and to specify procedures for manufacturers and other interested parties to demonstrate conformance of such systems to the requirements stated in this document.

Performance criteria for oral-anticoagulation monitoring systems were established, based on the state-of-the-art, which has been shown to offer significant benefit to patients [31]. The criteria are given in terms of "system accuracy", because metrological terms commonly used in International Standards (e.g. trueness and measurement uncertainty) would not be familiar to lay persons. System accuracy, which is affected by systematic bias and random effects (and is inversely related to measurement uncertainty), describes the degree to which the individual results produced by an oral-anticoagulation monitoring system agree with correct international normalized ratio (INR) values when the system is used as intended by lay persons. In setting the performance criteria, it is assumed that users will be properly selected and will receive the necessary training and that operating and control procedures will be followed in accordance with the manufacturer's instructions for use. It is also assumed that manufacturers will anticipate and mitigate the effects of reasonably foreseeable misuse, including reasonably foreseeable deviations from recommended operating and control procedures by the intended users.

Requirements that are unique to self-testing with oral anticoagulation monitoring systems, including specific content of information supplied by the manufacturer, are addressed in this document. General requirements that apply to all IVD medical devices and which are covered by other standards (e.g. IEC 61010-1, IEC 61010-2-101, ISO 13485, ISO 14971, ISO 23640 and ISO 18113-1, ISO 18113-4, ISO 18113-5) are incorporated by reference, when appropriate. While the goal is to standardize these requirements, it is also recognized that current national and regional usage by patients and regulatory authorities should be taken into consideration.

Clinical laboratory testing and in vitro medical devices — Requirements for in vitro monitoring systems for self-testing of oral anticoagulant therapy

1 Scope

This document specifies requirements for in vitro measuring systems for self-monitoring of vitamin-K antagonist oral anticoagulation therapy, including performance, quality assurance and user training and procedures for the validation of performance by the intended users under actual and simulated conditions of use.

This document applies solely to prothrombin time measuring systems used by lay persons for monitoring their own vitamin-K antagonist oral anticoagulation therapy, and which report results as international normalized ratios (INR).

This document 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 document is not applicable to:

— in vitro measuring systems for coagulation quantities assessing vitamin-K antagonist oral anticoagulation therapy used by physicians or healthcare providers;

— non-vitamin-K antagonist oral anticoagulation therapy (e.g. dabigatran);

— a comprehensive evaluation of all possible factors that can affect the performance of these systems;

— the medical aspects of oral-anticoagulation therapy.

2 Normative references

The following documents are referred to in the text in such a way that some or all of their content constitutes requirements of this document. For dated references, only the edition cited applies. For undated references, the latest edition of the referenced document (including any amendments) applies.

ISO 13485, *Medical devices — Quality management systems — Requirements for regulatory purposes*

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

ISO 15198, *Clinical laboratory medicine — In vitro diagnostic medical devices — Validation of user quality control procedures by the manufacturer*

ISO 17511, *In vitro diagnostic medical devices — Requirements for establishing metrological traceability of values assigned to calibrators, trueness control materials and human samples*

ISO 18113-1, *Clinical laboratory testing and in vitro diagnostic medical systems — Information supplied by the manufacturer (labelling) — Part 1: Terms, definitions and general requirements*

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

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

ISO 20916, *In vitro diagnostic medical devices — Clinical performance studies using specimens from human subjects — Good study practice*

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

IEC 60068-2-64:2008, *Environmental testing — Part 2: Test methods — Test Fh: Vibration, broad-band random (digital control) and guidance*

IEC 60601-1-2, *Medical electrical equipment - Part 1-2: General requirements for basic safety and essential performance - Collateral Standard: Electromagnetic disturbances - Requirements and tests*

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, radiofrequency, electromagnetic field immunity test*

IEC 61010-1:2010, *Safety requirements for electrical equipment for measurement, control and laboratory use — Part 1: General requirements*

IEC 61010-2-101:2015, *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*

EN 13532, *General requirements for in vitro diagnostic medical devices for self-testing*

WHO Technical Report Series, No. 889, 1999, Annex 3 — *Guidelines for thromboplastins and plasma used to control oral-anticoagulant therapy*

3 Terms and definitions

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

ISO and IEC maintain terminology databases for use in standardization at the following addresses:

— ISO Online browsing platform: available at https://www.iso.org/obp

— IEC Electropedia: available at https://www.electropedia.org/

3.1
accuracy
closeness of agreement between a measured quantity value and a true quantity value of a measurand

Note 1 to entry: For oral-anticoagulation monitoring systems, accuracy is measured by the extent to which measurements of *blood* (3.3) specimens from different patients agree with the *INR* (3.11) values traceable to a thromboplastin *international reference preparation (IRP)* (3.12).

[SOURCE: ISO/IEC Guide 99:2007, 2.13, modified — Notes 1, 2 and 3 to entry have been deleted, and a new Note 1 to entry has been added.]

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

[SOURCE: ISO 5725-1:1994, 3.8, modified — Note 1 to entry has been deleted.]

3.3
blood
circulating intravascular tissue of the body, consisting of suspended formed elements and fluid plasma

Note 1 to entry: In this document, the term "blood" refers to fresh, untreated blood.

3.4
capillary blood specimen
blood (3.3) collected after puncturing minute vessels that connect the arterioles and venules

Note 1 to entry: Often obtained by pricking a fingertip, capillary blood is usually collected without additives.

3.5
control interval
statistically justified values specified as acceptable measured values obtained using a given quality control

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

Note 1 to entry: Control materials for anticoagulation monitoring can be reactive or nonreactive. A reactive control material participates in a reaction with the *reagent* (3.28) components. A nonreactive control does not react with the *reagent* (3.28) components, but may provide control functionality through other means, e.g. a simulation of the reaction [see *physical control* (3.24)].

3.7
healthcare provider
individual authorized to deliver healthcare to a patient

Note 1 to entry: In this document, a healthcare provider is an individual, e.g. a doctor, nurse, technician, technical specialist, or appropriate assistant, that provides instruction to a self-testing patient.

3.8
integrated control
quality control that is inherent in a *reagent* (3.28) component of a measuring system, intended by the manufacturer to verify the performance of the measuring system

Note 1 to entry: The integrated functional control is run concurrently with a patient measurement, includes a reactive component, and provides a functional check of the measurement procedure. The integrated control results shall be within a predefined measurement interval for the measured value to be displayed.

3.9
intermediate precision condition
condition of measurement, out of a set of conditions that includes the same *measurement procedure* (3.19), same location, and replicate measurements on the same or similar objects over an extended period of time, but may include other conditions involving changes

[SOURCE: ISO/IEC Guide 99:2007, 2.22, modified — Notes 1, 2 and 3 to entryhave been deleted.]

3.10
intermediate precision
measurement precision under a set of *intermediate precision conditions* (3.9) of measurement

Note 1 to entry: The concept of intermediate levels of precision is described in ISO 5725-3:1994[6].

Note 2 to entry: Quantitative measures of intermediate precision depend on the stipulated conditions.

Note 3 to entry: Intermediate precision provides an indication of the variability that will be experienced by a user during typical use.

[SOURCE: ISO/IEC Guide 99:2007, 2.23, modified — Note 1 to entry has been deleted and new Note 1 to entry, Note 2 to entry, and Note 3 to entry have been added.]

3.11
international normalized ratio
INR
patient's *prothrombin time* (3.26) measurement result, which has been standardized for the potency of the thromboplastin used in the *measurement procedure* (3.19) and expressed relative to a normal population average

Note 1 to entry: For a discussion of the use of INR, see Poller, et al[35].

3.12
international reference preparation
IRP
reference calibrator maintained by the World Health Organization

Note 1 to entry: The IRP for thromboplastin is directly calibrated for potency against the original British comparative thromboplastin preparations used in the establishment of the *international normalized ratio (INR)* (3.11) system.

3.13
international sensitivity index
ISI
factor that allows the conversion of a patient's *prothrombin time* (3.26) measurement result to *international normalized ratio* (3.11) values

Note 1 to entry: For a discussion of the use of ISI and *INR* (3.11), see Poller, et al[35].

3.14
lay person
user of an oral-anticoagulation monitoring system who does not have specific formal medical, scientific, or technical knowledge related to oral-anticoagulation monitoring

Note 1 to entry: "Lay person" also includes, for example, a person's family member who performs the testing.

3.15
liquid quality control
liquid material that mimics patient specimens and monitors the testing process from specimen application to result interpretation

3.16
manufacturer's selected measurement procedure
measurement procedure (3.19) that is calibrated by one or more primary or secondary calibrators when available.

[SOURCE: ISO 17511:2020, 3.43, modified — Notes 1, 2 and 3 to entry have been deleted.]

3.17
manufacturer's standing measurement procedure
measurement procedure (3.19) used to assess (or assign values to) the end-user's calibrator

Note 1 to entry: A standing measurement procedure may be calibrated with a reference method or with the manufacturer's "working" or "master" calibrator.

3.18
manufacturer's working calibrator
working measurement standard
standard that is used routinely at the manufacturer's laboratory to calibrate or check material measures, measuring instruments or reference materials

Note 1 to entry: This standard is used routinely at the manufacturer's laboratory to calibrate or check material measures, measuring instruments or reference materials.

Note 2 to entry: This applies to a thromboplastin preparation used by the manufacturer during the preparation of a *prothrombin time (PT)* (3.26) reagent mixture.

Note 3 to entry: The assigned value of the manufacturer's working calibrator is metrologically traceable to that of the *international reference preparation (IRP)* (3.12).

3.19
measurement procedure
detailed description of a measurement according to one or more measurement principles and to a given measurement method, based on a measuring model and including any calculation to obtain a measurement result

[SOURCE: ISO/IEC Guide 99:2007, 2.6, modified — Notes 1, 2 and 3 to entry have been deleted.]

3.20
measurement reproducibility
reproducibilitymeasurement *precision* (3.25) under *reproducibility conditions* (3.31) of measurement

[SOURCE: ISO/IEC Guide 99:2007, 2.25, modified — Note 1 to entry has been deleted.]

3.21
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 measurement uncertainty, under defined conditions

Note 1 to entry: In some fields, the term is "measuring range" or "measurement range".

Note 2 to entry: This represents the interval of examination results over which the performance characteristics have been validated by the manufacturer.

[SOURCE: ISO/IEC Guide 99:2007, 4.7, modified — Note 2 to entry has been deleted and a new Note 2 to entry has been added.]

3.22
metrological 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

3.23
oral anticoagulant
vitamin K antagonists (e.g. warfarin) and non-vitamin K antagonist (e.g. direct oral anticoagulant) agents used for treating and preventing thromboembolic events

3.24
physical control
control device that does not include chemically reactive components and that is intended by the manufacturer to verify the performance of the instrument

Note 1 to entry: The physical control system may be in the form of an electronic device that provides a simulated reaction.

Note 2 to entry: The physical control result shall be within predefined limits, in order for the measuring system to be considered properly functional.

3.25
precision
closeness of agreement between 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 (CV) under the specified conditions of measurement.

Note 2 to entry: The 'specified conditions' can be, for example, *repeatability conditions* (3.29), *intermediate precision conditions* (3.9), or *reproducibility conditions* (3.31). See ISO 5725-1:1994.

Note 3 to entry: Measurement precision is used to define *repeatability* (3.30) of measurement, *intermediate precision* (3.10), and *measurement reproducibility* (3.20).

Note 4 to entry: Sometimes "measurement precision" is erroneously used to mean measurement accuracy.

[SOURCE: ISO/IEC Guide 99:2007, 2.15]

3.26
prothrombin time
PT
time required to clot a *blood* (3.3) specimen once exposed to a thromboplastin or tissue-factor derived *reagent* (3.28) material

3.27
prothrombin time measuring system
measuring system that records the time required for a specimen to clot after being exposed to a thromboplastin or tissue-factor derived *reagent* (3.28)

Note 1 to entry: The system includes the *reagent* (3.28) plus the instrument used to record the clotting time.

3.28
reagent
part of the in vitro diagnostic (IVD) medical device that produces a signal via a chemical or electrochemical reaction, which allows the quantity to be detected and its value measured in a specimen

3.29
repeatability condition
condition of measurement, out of a set of conditions 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: Repeatability condition is essentially unchanging conditions, intended to represent conditions resulting in minimum variability of measurement results.

Note 2 to entry: For the purposes of this document, "laboratories" should be interpreted as "locations".

[SOURCE: ISO/IEC Guide 99:2007, 2.20, modified — Notes 1 and 2 to entry have been deleted, and new Notes 1 and 2 to entry have been added.]

3.30
repeatability
measurement *precision* (3.25) under a set of *repeatability conditions* (3.29) of measurement

[SOURCE: ISO/IEC Guide 99:2007, 2.21]

3.31
reproducibility condition
condition of measurement, out of a set of conditions that includes different locations, operators, measuring systems, and replicate measurements on the same or similar objects

[SOURCE: ISO/IEC Guide 99:2007, 2.24, modified — Notes 1 and 2 to entry have been deleted.]

3.32
secondary reference measurement procedure
measurement procedure (3.19) that is calibrated by one or more primary calibrators

Note 1 to entry: The *measurement procedure* (3.19) for *prothrombin time* (3.26) measurements is sometimes referred to as a "secondary standard procedure".

3.33
system accuracy
closeness of agreement of a set of representative measurement results from a measuring system and their respective reference values

Note 1 to entry: The term *accuracy* (3.1) of measurement, when applied to a set of measurement results, involves a combination of random error components and a common systematic error or *bias* (3.2) component.

Note 2 to entry: Reference values are assigned by a *measurement procedure* (3.19) traceable to a reference measurement procedure of higher order.

Note 3 to entry: 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* (3.19) used to assign the reference values.

3.34
trueness
agreement between the average value obtained from a large series of measurement results and an accepted reference value

Note 1 to entry: A measure of trueness is usually expressed as *bias* (3.2).

3.35
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 to entry: Statistical sampling is not required for a type test.

[SOURCE: IEC 61326-1:2012, 3.1.13 , modified — Note 1 to entry added.]

3.36
user comformance
ability and willingness of the user of a measuring system to adhere to and operate within the defined specifications of a *measurement procedure* (3.19)

3.37
validation
confirmation, through the provision of objective evidence, that the requirements for a specific intended use or application have been fulfilled

Note 1 to entry: The word "validated" is used to designate the corresponding status.

Note 2 to entry: The use conditions for validation can be real or simulated.

Note 3 to entry: In design and development, validation concerns the process of examining an item to determine conformity with user needs.

Note 4 to entry: Validation is normally performed during the final stage of development, under defined operating conditions, although it may also be performed in earlier stages.

Note 5 to entry: Multiple validations may be carried out if there are different intended uses.

[SOURCE: ISO 9000:2015, 3.8.13, modified — Note 1 to entry was deleted and Notes 3, 4 and 5 to entry have been added.]

3.38
venous blood specimen
blood (3.3) collected after directly puncturing a vein, usually with a needle and syringe, or another collection device

Note 1 to entry: Venous blood may be collected without additives such as anticoagulants or preservatives, and if so, will be inherently unstable. Venous blood may also be collected in containers containing additives or preservatives with the intent to stabilize specific components.

3.39
verification
confirmation, through the provision of objective evidence, that specified requirements have been fulfilled

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

Note 2 to entry: Design verification is the application of tests and appraisals to assess conformity of a design to the specified requirement.

[SOURCE: ISO 9000:2015, 3.8.12, modified — Notes 1 and 2 to entry were deleted and new Note 2 to entry has been added.]

3.40
volume fraction of erythrocytes in blood
proportion of packed cells in a *blood* (3.3) specimen

Note 1 to entry: It is expressed as a fraction, but often given as a percentage (conventional) of the SI unit.

Note 2 to entry: It is sometimes referred to as "haematocrit", after the instrument originally used to estimate the volume fraction of erythrocytes in *blood* (3.3).

4 Design and development

4.1 General requirements

The requirements specified in ISO 13485 apply.

The requirements specified in EN 13532 apply to evaluation of the performance of the oral-anticoagulation monitoring system.

4.2 Measuring interval

The measuring interval of the system shall be at least 1,0 to 6,0 INR.

4.3 Safety

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

4.4 Risk management

4.4.1 Identification of hazards

The manufacturer shall decide upon the identification of potential hazards from knowledge of factors including, but not limited to, the following:

a) intended use of the product;

b) users' skills and limitations;

c) protection against unintentional change of settings (e.g. units reported);

d) likely deviations from recommended operating and control procedures;

e) influence of interfering substances.

NOTE Guidelines for evaluating potentially interfering substances are found in CLSI document EP07 [22].

4.4.2 Risk management

The requirements specified in ISO 14971 apply.

In performing risk assessment, the manufacturer shall consider:

a) severity of harm (e.g. potential harm to the patient),

b) probability of occurrence of harm (e.g. insufficient specimen volume or incorrect reagent unit placement), and

c) probability of the system failing to detect the mistake (e.g. deficient internal instrument sensors).

NOTE 1 This document does not specify levels of risk acceptability.

NOTE 2 Guidelines for identifying potential hazards from the use of "unit use devices" are found in CLSI document EP18-A2 [24].

NOTE 3 ISO TR 24971 provides guidance on the application of ISO 14971. Risk management includes risk analysis, risk evaluation, risk reduction and risk control.

4.5 Ergonomic and human factor aspects

The design of the oral-anticoagulation monitoring system shall take into consideration relevant ergonomic and human factors including, but not limited to, the following:

a) User aspects:
   1) selection;
   2) training;
   3) compliance.

b) User environment:
   1) temperature;
   2) humidity.

c) System properties:
   1) shock resistance;
   2) stability of reagents.

d) User interface:
   1) ease of operation;
   2) protection from typical "wear and tear" that can be encountered in the use environment;
   3) readability of reported results;
   4) fault conditions and error messages;
   5) unambiguous messages to the user (e.g. "low battery" or "low result") rather than only "low";