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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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ISO copyright office
Case postale 56 • CH-1211 Geneva 20
Tel. + 41 22 749 01 11
Fax + 41 22 749 09 47
E-mail copyright@iso.org
Web www.iso.org

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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 17593 was prepared by Technical Committee ISO/TC 212, *Clinical laboratory testing and* in vitro *diagnostic test systems*.

Introduction

Oral-anticoagulation monitoring systems are *in vitro* diagnostic medical devices that measure prothrombin time in fresh, unmodified human blood samples. Prothrombin time is an indicator of the ability of blood to clot. *In vitro* diagnostic 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. 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 International Standard 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 users to achieve acceptable performance, and to specify procedures for manufacturers and other interested parties to demonstrate conformance of such systems to this standard.

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 [68], [69]. 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 users. 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 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, that the device will be properly maintained, 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 maintenance, 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 International Standard. General requirements that apply to all *in vitro* diagnostic medical devices and are covered by other standards (e.g., IEC 61010, ISO 13485, ISO 14971 and ISO 18113) are incorporated by reference, where appropriate. In addition, national regulations may apply.

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

1 Scope

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

This International Standard pertains solely to prothrombin time measuring systems used by individuals for monitoring their own vitamin-K antagonist therapy, and which report results as international normalized ratios (INR).

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

— pertain to *in vitro* measuring systems for coagulation quantities assessing vitamin-K antagonist therapy used by physicians or healthcare providers,

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

— address the medical aspects of oral-anticoagulation therapy.

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 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 — Measurement of quantities in biological samples — Metrological traceability of values assigned to calibrators and control materials*

ISO 18113-1:—[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:—[1)], *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:—[1)], *Clinical laboratory testing and* in vitro *diagnostic medical systems — Information supplied by the manufacturer (labelling) — Part 5:* In vitro *diagnostic instruments for self-testing*

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*

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 13532:2002, *General requirements for* in vitro *diagnostic medical devices for self-testing*

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

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

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 in ISO 18113-1 and the following apply.

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

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

NOTE 2 For oral-anticoagulation monitoring systems, accuracy is measured by the extent to which measurements of blood samples from different patients agree with INR values traceable to a thromboplastin International Reference Preparation (IRP).

NOTE 3 Adapted from ISO 3534-1:2006, 3.11.

1) To be published.

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

[ISO 5725-1:1994, 3.8]

NOTE Bias is a measure of trueness. [VIM:1993]

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

NOTE In this International Standard, the term refers to fresh, nonanticoagulated blood.

3.4
capillary blood sample
blood collected after puncturing minute vessels that connect the arterioles and venules

NOTE Often obtained by pricking a fingertip; capillary blood is usually collected without additives, such as anticoagulants or preservatives. Therefore, it is inherently unstable.

3.5
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

NOTE 1 Adapted from EN 375:2001, 3.5.

NOTE 2 Control materials for anticoagulation monitoring may be reactive or nonreactive. A reactive control material participates in a reaction with the reagent components. A nonreactive control does not react with the reagent components, but may provide control functionality through other means, e.g., a simulation of the reaction (see physical control).

3.6
control interval
statistically justified values specified as acceptable measured values obtained using a given control material

3.7
healthcare provider
individual authorized to deliver health care to a patient

NOTE In this International Standard, a healthcare provider is an individual, such as a doctor, nurse, technician, technical specialist or appropriate assistant, that provides instruction to a self-testing patient.

3.8
integrated functional control
control material that is inherent in a reagent component of a measuring system, intended by the manufacturer to verify the performance of the measuring system

NOTE 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 must be within a predefined measurement interval for the measured value to be displayed.

3.9
international normalized ratio
INR
patient's prothrombin time measurement result, which has been standardized for the potency of the thromboplastin used in the measurement procedure and expressed relative to a normal population average

NOTE For a discussion of the use of INR, see Poller, et al. [30].

3.10
international reference preparation
IRP
reference calibrator maintained by the World Health Organization

NOTE The IRP for thromboplastin is directly calibrated for potency against the original British comparative thromboplastin preparations used in the establishment of the INR system.

3.11
intermediate precision of measurement
measurement precision under conditions intermediate between reproducibility conditions and repeatability conditions

NOTE 1 The concept of intermediate levels of precision is described in ISO 5725-3:1994[5].

NOTE 2 Quantitative measures of intermediate precision depend on the stipulated conditions.

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

3.12
intermediate precision conditions
conditions where independent measurement results are obtained with the same measurement method on identical samples in the same location, but where other variables, such as operators, equipment, calibration, environmental conditions and/or time intervals, differ

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

NOTE For a discussion of the use of ISI and INR, see Poller, et al. [30].

3.14
lay person
individual without formal training in a relevant 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 lay person is a user of an oral-anticoagulation monitoring device who does not have specific medical, scientific or technical knowledge related to oral-anticoagulation monitoring.

3.15
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 Adapted from ISO 17511:2003.

NOTE 2 This applies to a thromboplastin preparation used by the manufacturer during the preparation of a PT reagent mixture.

NOTE 3 The assigned value of the manufacturer's working calibrator is metrologically traceable to that of the IRP.

3.16
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 17511:2003, 4.2.2 f), shows the manufacturer's selected measurement procedure in the traceability chain.

3.17
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 17511:2003, 4.2.2 h) shows the manufacturer's standing measurement procedure in the traceability chain.

3.18
measurement procedure
set of operations, described specifically, used in the performance of particular measurements according to a given method

[VIM:1993, 2.5]

3.19
measuring interval
set of values of measurands for which the bias and imprecision are intended to lie within specified limits

NOTE 1 This represents the interval of examination results over which the performance characteristics have been validated by the manufacturer.

NOTE 2 Adapted from VIM:1993, 5.4.

3.20
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

[VIM:1993, 6.10]

3.21
physical control system
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 The physical control system may be in the form of an electronic device that provides a simulated reaction.

NOTE 2 The physical control result must be within predefined limits, in order for the measuring system to be considered properly functional.

3.22
precision of measurement
closeness of agreement between independent measurement results obtained under stipulated conditions

NOTE 1 Adapted from ISO 3534-2:2006.

NOTE 2 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 3 Precision of a given measurement procedure is subdivided according to the specified precision conditions. Particular sets of extreme conditions are termed "repeatability" (3.26) and "reproducibility" (3.28).

3.23
prothrombin time
PT
time required to clot a blood sample once exposed to a thromboplastin reagent material

3.24
prothrombin time measuring system
measuring system that records the time required for a sample to clot after being exposed to a thromboplastin or tissue-factor derived reagent

NOTE The system includes the reagent plus the instrument used to record the clotting time.

3.25
reagent
part of the *in vitro* diagnostic 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 sample

3.26
repeatability of measurement
precision of measurement under repeatability conditions

NOTE Adapted from ISO 3534-2:2006.

3.27
repeatability conditions
conditions where independent measurement results are obtained with the same method of measurement on identical samples in the same laboratory by the same operator using the same equipment within short intervals of time

NOTE 1 Adapted from ISO 3534-2:2006.

NOTE 2 Essentially unchanging conditions, intended to represent conditions resulting in minimum variability of measurement results.

NOTE 3 For the purposes of this International Standard, “laboratories” should be interpreted as “locations”.

3.28
reproducibility of measurement
precision of measurement under reproducibility conditions

NOTE Adapted from ISO 3534-2:2006.

3.29
reproducibility conditions
conditions where measurement results are obtained with the same method of measurement on identical samples in different laboratories with different operators using different equipment

NOTE 1 Completely changed conditions are 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”.

NOTE 3 Adapted from ISO 3534-2:2006.

3.30
secondary reference measurement procedure
measurement procedure that is calibrated by one or more primary calibrators

NOTE The measurement procedure for prothrombin time measurements is sometimes referred to as a “secondary standard procedure”.

3.31
system accuracy
closeness of agreement of a set of representative measurement results from a measuring system and their respective reference values

NOTE 1 The term accuracy of measurement, when applied to a set of measurement results, involves a combination of random error components and a common systematic error or bias component.

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.

NOTE 4 Adapted from ISO 15197:2003, 3.24.

3.32
trueness of measurement
closeness of agreement between the average value obtained from a large series of measurement results and an accepted reference value

NOTE 1 A measure of trueness is bias (3.2).

NOTE 2 Adapted from ISO 3534-2:2006.

3.33
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 a type test.

NOTE 2 Adapted from IEC 61326:2002.

3.34
user compliance
ability and willingness of the user of a measuring system to adhere to and operate within the defined specifications of a measurement procedure

3.35
venous blood sample
blood collected after directly puncturing a vein, usually with a needle and syringe, or another collection device

NOTE 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.

3.36
volume fraction of erythrocytes in blood
proportion of packed cells in a blood sample

NOTE 1 Expressed either as a fraction, often given as a percentage (conventional) of the SI unit.

NOTE 2 Sometimes referred to as “haematocrit”, after the instrument originally used to estimate the volume fraction of erythrocytes in blood.

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.

NOTE Clauses 6 and 8 describe design verification activities, which are intended to provide assurance that the product has the capability of meeting precision, trueness, safety and reliability specifications. Clause 9 describes design validation activities, which are intended to provide assurance that the device meets the user requirements.

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 Acceptability of risks

The manufacturer shall decide upon the acceptability of potential risks 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 maintenance, operating and control procedures;

e) influence of interfering substances.

NOTE Guidelines for evaluating potentially interfering substances are found in CLSI document EP7[25].

4.4.2 Risk assessment

The requirements specified in ISO 14971 apply.

In performing risk assessment, the manufacturer shall consider

a) severity of the consequences of an undetected failure (e.g., potential harm to the patient),

b) probability of occurrence of a mistake (e.g., insufficient sample 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 International Standard 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 [27].

NOTE 3 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:

- selection;
- training;
- compliance.

b) Use environment:

- temperature;
- humidity.

c) System properties:

- shock resistance;
- stability of reagents.

d) User interface:

- ease of operation;
- ease of maintenance;
- protection from typical “wear and tear” that might be encountered in the use environment;
- readability of reported results;
- fault conditions and error messages;
- unambiguous messages to the user (e.g., “low battery” or “low result”) rather than only “low”;
- user verification of proper system function.

4.6 Quality assurance and risk controls

4.6.1 General

Quality assurance of oral anticoagulation monitoring systems consists of multiple elements. See Annex E for descriptions of the various elements of quality assurance that may apply.

The manufacturer shall provide device-specific risk control measures, as required by the risk management plan. The requirements specified in ISO 14971 apply.

The risk control measures, including any limitations, shall be described in the instructions for use and the training program as appropriate.

Risk control measures shall address the education and training of users and healthcare providers (see Clause 7), as well as the following elements.