INTERNATIONAL STANDARD

**ISO 17593**

First edition
2007-04-15

# 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*



Reference number
ISO 17593:2007(E)



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Published in Switzerland

# Contents

Page

# Foreword

ISO (the International Organization for Standardization) is a worldwide federation of national standards bodies (ISO member bodies). The work of preparing International Standards is normally carried out through ISO technical committees. Each member body interested in a subject for which a technical committee has been established has the right to be represented on that committee. International organizations, governmental and non-governmental, in liaison with ISO, also take part in the work. ISO collaborates closely with the International Electrotechnical Commission (IEC) on all matters of electrotechnical standardization.

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

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

Attention is drawn to the possibility that some of the elements of this document may be the subject of patent rights. ISO shall not be held responsible for identifying any or all such patent rights.

ISO 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.

#### 4.6.2 Measurement verification

Each measurement reported by the oral-anticoagulation monitoring system shall be verified internally by the measuring system.

The nature and extent of internal verification to be performed by the measuring system shall be determined by the results of the risk analysis.

NOTE It is desirable that the use of out-of-date reagents be prevented.

#### 4.6.3 Control of system performance

The manufacturer shall provide a control procedure and instructions for the use of control materials.

The control procedure shall be validated. The requirements specified in ISO 15198 apply.

Control material may consist of a liquid control, an integrated control or a combination of both.

If a physical control is used (e.g., a check strip), the manufacturer shall provide instructions for when a physical control shall be run on the instrument.

Before each measurement of a blood sample, a measurement verification shall be made by a monitor self-check, using an internal or external physical control system.

Control measurements using liquid control materials shall be performed each time a new package of reagents is used, when an unexpected result occurs, and as required by local regulations. Alternatively, liquid controls may be replaced by an integrated functional control.

Actions to be taken when controls are out-of-range shall be given in the instructions for use.

#### 4.6.4 Verification of self-testing performance

The manufacturer shall recommend a procedure for users to verify the acceptability of self-testing results.

Verification may be based on a comparison between results obtained by the user and a healthcare provider at specified intervals. An interval of six months or less is recommended. With new self-testers, more frequent intervals may be necessary to verify the technique, e.g. monthly.

#### 4.6.5 Evaluation of user compliance in following the manufacturer's and the physician's instructions

The manufacturer shall recommend, in the instructions for use for the healthcare professional, suitable procedures for monitoring and evaluating user compliance with the manufacturer's and the physician's instructions.

### 4.7 Metrological traceability

The requirements specified in ISO 17511 shall apply to the manufacturer's process for calibrating the oral-anticoagulation monitoring devices.

The measurement results of the manufacturer's selected and/or standing measurement procedure shall be traceable to those of the WHO manual tilt-tube measurement procedure using an International Reference Preparation (IRP) of thromboplastin ([44] in the Bibliography).

NOTE 1 The WHO tilt-tube measurement procedure uses fresh, citrated plasma, whereas devices for self-testing use fresh, untreated blood. Calibration of the devices involves parallel measurement of fresh plasma and blood from the same patients. In this case, the blood samples are the calibrator.

If the manufacturer's standing measurement procedure uses blood, then calibration of the procedure against the WHO IRP and tilt-tube method shall occur through parallel measurement of blood and plasma. Calibration of the end-user's routine measurement procedure shall use blood.

If the manufacturer's standing measurement procedure uses plasma, then plasma shall be used to calibrate the procedure against the WHO IRP and tilt-tube method. Parallel measurement of plasma and blood shall occur during calibration of the end-user's routine measurement procedure (e.g., using the same lot of reagents).

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

NOTE 2 An example of a traceability chain for a typical factory-calibrated oral-anticoagulation monitoring system is shown in Annex B, Figure B.1. The illustration of a full traceability chain is taken from ISO 17511:2003, Figure 5. This example is not intended to represent the only possibility of a suitable traceability chain.

Control measures shall be implemented within each step of the calibration process, in order to monitor, assess and control drift and variability.

NOTE 3 The process capability index (Cpk) can be used to define and detect unacceptable drift. See bibliographic reference [40].

Calibration of the manufacturer's standing measurement procedure shall be verified at predefined intervals against the manufacturer's selected measurement procedures. ISO 15193 and ISO 15194 may be used as guides.

The manufacturer's working calibrator may be a representative panel of fresh capillary or venous blood samples, that span the measuring interval to ensure commutability of the calibrator between reference measurement procedures. Manufacturers should define the procedure and the time period during which the fresh samples may be used.



## 5 Information supplied by the manufacturer

### 5.1 General requirements

The information supplied to users by the manufacturer shall be clear and concise, using plain terms that are readily understood by a lay person.

The information shall be well organized and easy to read.

Symbols and illustrations should be used where appropriate. Symbols shall conform to International Standards. If symbols are used for which no standard exists, the symbols shall be described within the text.

The language(s) of the country in which the oral-anticoagulation monitoring system is distributed shall be used. Additional languages are optional.

The content of instructions for use shall be understandable by persons without a scientific or technical background.

Instructions for use shall include a revision number, or the year and month of issue.

### 5.2 Labels for the oral-anticoagulation monitoring instrument

The oral-anticoagulation monitoring instrument shall be identified by labels including, as 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 use, including a statement that the device is an *in vitro* diagnostic medical device for self-measurement, as well as information regarding the reagents to be used with the device;

d) lot or serial number appearing directly on a label affixed to the device;

e) conditions for storage and handling, if appropriate;

f) a reference to the user manual or instructions for use.

Where appropriate and allowed by regulations, information on the label should take the form of symbols. Symbols shall conform to applicable regulations and International Standards. All symbols shall be described in the information supplied with the oral-anticoagulation monitoring instrument.

### 5.3 Instructions for use of the oral-anticoagulation monitoring system

The requirements specified in ISO 18113-5 apply.

The system shall be accompanied by instructions for use, which shall include the following information:

a) name or trade name and address of the manufacturer, the name and address of the distributor, if applicable, and how to access help;

NOTE For *in vitro* diagnostic medical devices marketed in the European Union, Directive 98/79/EC [34] requires the name and address of an "authorized representative" if the manufacturer is not located in the European Union.

b) product name or designation;

c) intended use of the device;

d) the principle of the measurement procedure;

e) manufacturer's standing measurement procedure and/or reference material designated by the manufacturer to evaluate performance characteristics;

f) type of samples used by the manufacturer for calibration (e.g., blood or plasma);

g) specific reagents to be used;

h) measurement procedure to be followed when using the device, including:

- the sequence of steps to prepare the instrument for the measurement, to execute the measurement (including the volume and recommended appearance of the sample) and to maintain the instrument;
- the sequence of adjustment (e.g., use of a number, code strip, code chip), measurement and verification, and the allowed time intervals between them;
- the measurement units reported by the device for the INR values (e.g., percent);
- advice on how to proceed when error messages, unexpected results or results outside the specified measuring interval are generated by the instrument.

i) environmental conditions (e.g., temperature and relative humidity) in which the system may be used;

j) detailed procedure to be followed by the user in adjusting the device, if applicable;

k) detailed user control procedures, including identification of the control material to be used to assure that the oral-anticoagulation monitoring system is operating properly, the importance of performing the control procedures, and advice on how to proceed if control results are not acceptable;

l) type of sample to be used, as well as any special conditions of collection and pretreatment;

m) precautions to be taken to reduce the risk of infection (e.g., from prior use of the instrument or improper disposal of biohazardous materials);

n) precautions to be taken to prevent system damage (e.g., from electrostatic discharge, magnetic fields, and heat, humidity, shock and other external influences or other environmental conditions, as applicable (see Clause 5 in IEC 61010-2-101:2002);

o) description and explanation of any symbols used on labels and in the instructions for use;

p) guidance on action to be taken by the user as a consequence of the result, including:

— a reference to the instructions given by a healthcare provider, and a warning not to deviate from these instructions on the basis of the result without consulting the healthcare provider;

— advice on how to proceed if the result is questionable to the user;

— indication of how the monitoring system alerts the user when the result is outside the specified measuring interval (e.g., error messages, fault notifications);

q) information on the safe disposal of the system and its components, where appropriate.

The instructions for use shall state what actions to take if the verification indicates an invalid result.

## 5.4 Labels for the reagents and control material

The reagents and control material shall be identified by a label or labels.

The requirements specified in ISO 18113-4 apply.

In addition, the following information shall be included on the label(s):

a) indication of the period of time during which the reagent shall be used after the first opening of the immediate reagent container, expressed as months and/or days;

b) a reference to the instructions for use;

c) the instrument specified to be used with the reagents.

Warning statements should be included on the label concerning:

d) use of the reagents with the specified oral-anticoagulation monitoring instrument to promote reliable measurement results;

e) safe disposal of the reagents after use.

The language(s) of the country in which the reagents and control materials are distributed shall be used; additional languages are optional.

## 5.5 Instructions for use for reagents and control material

Reagents and control materials provided for use with an oral-anticoagulation monitoring system shall be accompanied by instructions for use.

The requirements specified in ISO 18113-4 apply.

In addition, the following information shall be included in the instructions for use:

a) an indication of how to access help from the manufacturer and/or distributor;

b) the instrument specified to be used with the reagents and control material;

c) the ISI of the reagent;

d) the storage conditions (e.g., temperature, humidity, exposure to light);

e) a warning statement (for reagents) concerning the need to tightly seal the cap of the immediate container to protect reagent strips or sensors from exposure to air;

f) the measuring interval, indicating the upper and lower limits within which INR results are reported;

g) the performance characteristics stated in language that is understandable by the intended user; the percent agreement of the reported INR values with the reference measurement procedure shall be based on the studies in Clauses 8 and 9,

h) any interfering substances, sample conditions (e.g., haemolysis, icterus, lipemia) or physiological conditions (e.g., changes in peripheral circulation) known to affect the accuracy of results;

i) the measurement procedure used to evaluate the performance characteristics of the system, and a statement describing the metrological traceability of measurement results to a reference measurement procedure or reference material of higher order;

j) the measurement procedure to be followed including:

   — the sequence of steps to prepare the reagents and execute the measurement;

   — the timing between the individual steps, if applicable;

k) a detailed control procedure and control materials to be used to verify that the oral-anticoagulation monitoring system is operating within its performance specifications.

Required information regarding reagents and/or control materials may be included in the instructions for use of the instrument or system if the manufacturer of the instrument or system is the same as the manufacturer of the reagents. If there is a change in this information, the changed information shall be placed in the instructions for use for the reagents.



# 6 Safety and reliability testing

## 6.1 General requirements

### 6.1.1 Protocol

Safety and reliability testing shall be performed by the manufacturer according to a written protocol. The protocol shall, as a minimum, specify the test designs, including the number of instruments, reagent units and replicate measurements per instrument, and the data analysis procedures and acceptance criteria. The results of the safety and reliability testing shall be documented in a report.

Specified testing requirements are minimum requirements.

For performance tests, the protocol shall include a statistical rationale for the test design.

NOTE 1 The tests described in 6.2 to 6.8 are type tests.

NOTE 2 The tests described in 6.9 to 6.12 are performance tests.

#### 6.1.2 Instruments and reagents

Instruments and reagents selected for testing shall be representative of routine production units.

For type tests, at least three instruments shall be used in each test.

For performance tests, at least ten instruments shall be used in each test.

#### 6.1.3 Acceptance criteria

Acceptance criteria for bias and repeatability for the performance tests in 6.10 to 6.13 should be derived from the system accuracy criteria in 8.6.1. The rationale for the acceptance criteria shall be documented in the protocol.

The oral-anticoagulation monitoring system shall either pass the acceptance criteria in each test protocol or the system shall be rendered nonfunctional and shall not display a numerical INR result.

Failures to meet acceptance criteria shall be investigated.

### 6.2 Protection against electric shock

The requirements specified in IEC 61010-1:2001, Clause 6, apply.

### 6.3 Protection against mechanical hazards

The requirements specified in IEC 61010-1:2001, Clause 7, apply.

### 6.4 Electromagnetic compatibility

The requirements specified in IEC 61326 apply.

In addition, the requirements specified in Annex A apply.

### 6.5 Resistance to heat

The requirements specified in IEC 61010-1:2001, Clause 10, apply.

### 6.6 Resistance to moisture and liquids

The requirements specified in 11.1, 11.2 and 11.3 of IEC 61010-1:2001 apply.

### 6.7 Protection against liberated gases, explosion and implosion

The requirements specified in 13.1 and 13.2.2 of IEC 61010-1:2001 apply.

### 6.8 Instrument components

The requirements specified in 14.1, 14.4, 14.5 and 14.6 of IEC 61010-1:2001 apply.

### 6.9 Performance test

The performance test shall be performed before and after each determination of mechanical resistance to shock, vibration and impact (see 6.10) and protection against exposure to temperature and humidity levels (see 6.11 and 6.12). Pass/fail criteria shall be based on the effect of the challenge on system bias and repeatability.

Prior to each performance test, the oral-anticoagulation monitoring instrument shall be equilibrated to 23 °C ± 2 °C. The manufacturer's recommended control material or a suitable alternative should be used for the performance tests.

It may be difficult to separate the variability due to sample and reagent components from the variability due to instrument components. This should be taken into consideration when designing the test and developing acceptance criteria.

A check strip, which simulates a reagent strip after reaction, or other suitable control material, may be used to verify that system performance has not been affected.

NOTE Electronic control systems may report results in units (e.g. mV) different from those reported for blood samples. In this case, the average and repeatability of the values reported by the device may be used.

The order of measurement of test samples shall be specified in the protocol.

The average INR value and repeatability SD shall be calculated before and after each challenge, and the difference compared to the acceptance criteria.

a) Bias: the difference between the average INR value after the challenge and the average INR value before the challenge shall be calculated and compared to the acceptance criteria for bias.

b) 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.

## 6.10 Mechanical resistance to shock, vibration and impact

### 6.10.1 Vibration test protocol

Perform the performance test described in 6.9.

Perform the vibration test as specified in 8.3 of IEC 60068-2-64:1993.

After vibration testing is complete, repeat the performance test.

The requirements specified in 8.3 of IEC 60068-2-64:1993 apply.

### 6.10.2 Drop test protocol

To verify resistance to damage from dropping, perform the baseline performance test as specified in 6.9.

Perform the drop test as specified in 8.2 of IEC 61010-1:2001.

After drop testing is complete, repeat the performance test.

The requirements specified in 8.2 of IEC 61010-1:2001 apply.

## 6.11 Temperature exposure limits

### 6.11.1 High-temperature test protocol

Perform the performance test as specified in 6.9.

Place the instrument in an environmental chamber that can be monitored for internal temperature.

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

Remove the instrument from the environmental chamber, and allow it to cool to a temperature of 23 °C ± 2 °C and repeat the performance test.

For those systems in which the reagents are an integral component of the instrument and cannot be separated from the device, the high-temperature exposure conditions shall be limited to the use conditions specified by the manufacturer.

#### 6.11.2 Low-temperature test protocol

Perform the performance test as specified in 6.9.

Place the instrument in an environmental chamber that can be monitored for internal temperature.

Decrease the temperature to − 20 °C ± 2 °C and leave the instrument at this temperature for 8 h in the chamber.

Allow the instrument to reach a temperature of 23 °C ± 2 °C in the environmental chamber to avoid condensation from the moist outside air contacting the cold instrument. Remove the instrument from the chamber and repeat the performance test.

For those systems in which the reagents are an integral component of the instrument and cannot be separated from the device, the low-temperature exposure conditions shall be limited to the use conditions specified by the manufacturer.

### 6.12 Humidity-exposure test protocol

Perform the baseline performance test as specified in 6.9.

Place the instruments in a temperature- and humidity-controlled chamber.

Stabilize the relative humidity (RH), noncondensing to 90 % ± 3 %, and the temperature to 32 °C ± 2 °C.

Leave the instruments in the chamber for 48 h at the specified temperature and humidity.

Transfer the instruments from the chamber to ambient conditions of relative humidity < 60 % and a temperature of 23 °C ± 2 °C, and wait 15 min.

Assessment of the degree and effects of moisture absorption is the purpose of this test. Any moisture absorbed by the device during the time in the chamber is intentionally retained. The temperature should approach ambient during the 15 min delay, but complete equilibration is not required.

Repeat the performance test.

### 6.13 Reagent storage and use testing

Conditions for the storage, use and transport of reagents and control materials shall be defined and verified.

Stability of reagents and control materials through the expiration dates shall be demonstrated. The requirements specified in EN 13640 apply.

## 7 Training and education programs

### 7.1 Training of healthcare providers

The manufacturer shall design and validate a training program for healthcare providers. The training program shall educate healthcare providers in the proper use of the system, patient selection and patient education.

The training program for healthcare providers shall include recommended patient selection criteria and a description of user characteristics likely to predict success in using the system.

The predictive user characteristics should include

— ability to understand the concept of oral-anticoagulant therapy and its risks,

— willingness to perform oral-anticoagulation self-testing and participate actively with a healthcare provider in documentation and information exchange for therapy adjustment,

— sufficient manual dexterity and visual acuity, and

— demonstrated patient compliance.

In cases where the patient does not meet the criteria, the training program should advise that measurements may be carried out by trained relatives or other third parties who meet the selection criteria.

## 7.2 Education of patients and other users

The manufacturer shall establish and provide an education program for patients and other users of the device. The program shall include the following elements:

— basic information about blood clotting and anticoagulation therapy;

— explanation of “prothrombin time” and INR results;

— explanation of the patient-specific individual therapeutic interval;

— training in skin puncture and prothrombin time self-testing;

— tasks of users and healthcare providers in oral-anticoagulation self-testing;

— recordkeeping by the patient and healthcare provider;

— description of control procedures and system self-checks;

— emphasis on the proper interpretation of control results;

— actions necessary when control results are not within the target limits;

— protocol for communication between patients and healthcare providers;

— actions necessary when results are not within the individual therapeutic interval;

— action necessary in the event of additional diseases, emergencies or accidents.

The education program shall provide sufficient technical knowledge regarding the general concept of oral-anticoagulant therapy and shall teach practical skills to perform prothrombin time self-testing and control procedures.

An evaluation of the user’s ability to perform self-testing properly shall be made on completion of the education program.

The evaluation should include a practical test of technical proficiency and/or a written test of comprehension.

NOTE 1 Periodic re-evaluation of users to assess compliance and verify continuing competence may be advisable.

The manufacturer shall provide a method for documentation of successful completion of the education program by the user.

NOTE 2 The training may be documented by the manufacturer or the healthcare professional.

# 8 System performance verification

## 8.1 General

System performance verification studies shall be conducted as part of the manufacturer's design control system to demonstrate that the oral-anticoagulation monitoring system meets specifications for trueness, precision and system accuracy.

The requirements specified in ISO 13485 apply.

## 8.2 Contributors to measurement uncertainty

Factors that affect the accuracy (precision and trueness) of INR results and contribute to measurement uncertainty shall be identified and taken into consideration when designing the verification protocol(s).

These factors include intra-individual biological variability, measurement uncertainty of the assigned value of the calibrator (lack of a higher-order reference material and limitations of the WHO reference measurement procedure), factor sensitivity differences, reagent lot-to-lot differences, reagent instability and measurement imprecision.

NOTE 1 Specificity with respect to interfering substances and effects of isolated coagulation factor deficiencies are not addressed in the system performance verification studies.

NOTE 2 The designated reference measurement procedure, the WHO tilt-tube method, is difficult to perform, highly dependent on user technique and valid only for INR values between 1,0 and 4,5. Attempts to develop a true calibrator have not been successful. The reference measurement procedure and calibrator can contribute significantly to increased measurement uncertainty of prothrombin time measurements.

## 8.3 System performance verification study

The system performance verification study shall be performed according to a written protocol. The protocol shall, as a minimum, specify the experimental details, data analysis procedures and acceptance criteria. Statistical designs, including the numbers of instruments, reagent units, sample replication and acceptance criteria, shall be justified in the protocol. The results of the performance verification study shall be documented in a report.

All components of the system selected for evaluation, including instruments, reagents and accessories, shall be representative of the product intended for sale.

The oral-anticoagulation monitoring system shall be adjusted prior to the verification study, according to the manufacturer's instructions (e.g., via coding, chips). No adjustments shall be made between replicate measurements, unless the manufacturer's instructions specify an adjustment before each measurement.

The manufacturer's recommended control procedures shall be performed prior to each verification study.

The unique nature of prothrombin time measurements, the characteristics of the specific self-testing system and the instability of the samples shall be taken into account when designing experimental protocols for verifying system performance.

The appropriate sample for each verification study is specified in 8.4 and 8.5. An alternative sample may be used to evaluate specific variables (e.g., instrument-to-instrument precision) if equivalence to fresh capillary blood is demonstrated.

NOTE 1 Although individuals taking vitamin K antagonist are the intended users of the device, the protocol requires that samples from a group of individuals not taking vitamin K antagonist be included in the study for the purpose of verifying acceptable accuracy (precision and trueness) throughout the measuring interval, including below the therapeutic interval.

NOTE 2 Trained operators may perform the system performance verification studies. Lay persons perform the system performance studies described in Clause 9.

## 8.4 Verification of measurement precision

### 8.4.1 General

The measurement precision of the anticoagulation monitoring system used in self-testing shall be verified in actual or simulated conditions of use.

The repeatability and intermediate precision of measurement shall be verified against performance criteria derived from the system accuracy criteria in 8.5. The acceptance criteria shall be documented in the protocol.

Analysis of variance is the preferred statistical method to use when multiple factors are evaluated. Choices of number of instruments, reagent lots and replicates for precision testing should be based on the sources of variability obtained from the results of the analysis of variance.

NOTE 1 Refer to ISO 5725-1 [3] for general principles regarding the evaluation of precision of a measurement method. The definitions and concepts of repeatability, reproducibility and intermediate levels of precision are described in ISO 5725-1, ISO 5725-2 and ISO 5725-3 [4], [5], [6].

Because precision verification requires departure from the routine measurement procedure, such as taking multiple measurements from one or more samples, the data should be checked against objective validity criteria to detect effects of sample instability.

NOTE 2 Only limited verification of the reproducibility of INR measurements can be made directly over time, across multiple lots, and across multiple analysts owing to the instability of blood samples. The accuracy verification (see 8.5) is designed to include the uncertainty due to these variables.

NOTE 3 Surrogate samples (e.g., control samples) and alternative evaluation approaches may be necessary to estimate the contribution of specific variables. Such evaluations are an essential part of design verification, but since study designs tend to be device-specific they are outside the scope of this International Standard.

### 8.4.2 Verification of measurement repeatability

#### 8.4.2.1 General

Measurement repeatability shall be evaluated from duplicate samples of capillary blood. To approximate repeatability conditions, both samples shall be taken and measurements made within a short period of time.

The rationale for the experimental design shall be documented in the protocol.

NOTE Refer to ISO 5725-2 [5] for guidelines for determining the repeatability of a measurement procedure.

#### 8.4.2.2 Samples

The repeatability verification study shall be performed with fresh capillary blood samples from at least 30 patients receiving vitamin K antagonist therapy, and at least 15 individuals not receiving therapy. The patients shall be selected so that INR values span the measuring interval of the system, with at least 15 patients in each of the intervals specified in Table 1.

Two samples shall be taken from each patient by skin puncture (e.g., two separate fingersticks).

The INR value of each sample shall be determined using the oral-anticoagulation monitoring system.

The volume fraction of erythrocytes in blood (haematocrit) shall be within 0,35 to 0,50 L/L (35 % to 50 %).

**Table 1 — INR intervals for verification of measurement repeatability**

| Interval | INR values |
|---|---|
| Nontherapeutic | Below 2,0 |
| Low therapeutic | 2,0 to 3,0 |
| High therapeutic | 3,1 to 4,5 |

NOTE Surrogate sample materials may be used in place of actual patient samples for testing the high therapeutic interval.

#### 8.4.2.3 Instruments and reagents

Measurement repeatability may be verified using one or more instruments and one or more reagent lots. If more than one instrument or reagent lot is used, the experimental design shall allow analysis of repeatability within a single instrument and/or within a single lot (e.g., analysis of variance procedure).

### 8.4.3 Verification of intermediate measurement precision

#### 8.4.3.1 General

The verification of intermediate measurement precision shall be conducted in normal conditions of use (i.e., by an individual user across multiple days with the same instrument).

Manufacturers shall utilize analysis of variance to determine the significant sources of measurement uncertainty to include in the intermediate precision testing. The rationale for the experimental design shall be documented in the protocol. As a minimum, manufacturers shall include the components of uncertainty due to lot-to-lot, instrument-to-instrument and day-to-day.

Intermediate measurement precision shall be verified across the measuring interval of the instrument.

NOTE Refer to ISO 5725-3 for guidelines on determining intermediate measurement precision.

##### 8.4.3.1.1 Samples

Intermediate precision shall be verified using control materials in the low therapeutic interval (INR 2,0 to 3,0) and the high therapeutic interval (INR 3,1 to 4,5).

Control materials shall be prepared according to the manufacturer's instructions for use. Stability of control samples over the evaluation period shall be validated.

##### 8.4.3.1.2 Instruments and reagents

At least ten instruments shall be selected to verify the intermediate measurement precision of the oral-anticoagulation monitoring system.

The verification study may be performed on a single lot of reagents if data are available that demonstrate that intermediate precision (including repeatability) is not significantly dependent on the reagent lot. Otherwise, multiple lots shall be used and the experiment shall be designed to include lot-to-lot variability. The number of lots used shall be justified (minimum = 3).

A lot or part of a lot shall be examined. If a complete lot is not available, the part and status of the material shall be recorded.

Reagent units shall be taken from at least ten vials or packages. The verification protocol shall ensure that data from the different variables (e.g., lot, instrument) are not confounded.

#### 8.4.3.2 Verification procedure

The minimum design to verify intermediate precision over multiple days requires one measurement per day of each sample for 10 days for each of ten instruments.

The procedure may be modified to accommodate multiple reagent lots. The reagent units shall be taken from the same vial/package for each sample.

### 8.4.4 Data analysis

#### 8.4.4.1 Data validity

Prior to analysis, data shall be evaluated to identify errors and evidence of sample instability. Obvious errors (e.g., transcription errors, insufficient sample volume) should be documented and corrected. No data may be eliminated without cause (i.e., for statistical reasons alone).

Sample instability, expressed as a drift in results, can be identified through statistical analysis of each sample's replicate results. The following guidelines apply.

— For the repeatability data, calculate the Duplicate Range Limit from all of the data. If precision is related to INR, then the Duplicate Range Limit will also depend on INR as larger differences between replicates may be expected at higher INR values. The rationale for this limit is based on the statistical distribution of the range and also depends on the precision of the system. The limit is calculated by following these steps:

1) Calculate the difference between the duplicate measurements for each sample.

2) Calculate the average result for each sample.

3) Obtain an estimate of within-sample precision from a different study or from the system specifications. As precision usually decreases with the INR, it should be expressed as a coefficient of variation (CV).

4) For each patient sample, multiply the average result by the CV and then by 4,2. This value is the Duplicate Range Limit for that patient.

5) For example, suppose that two results for a patient are 2,4 and 2,6. The average is 2,5. If a CV of 5 % is used as an estimate for within-patient precision, then the duplicate range limit is $2,5 \times 0,05 \times 4,2$, or 0,525. Since the actual difference is 0,2, it would be accepted. If the two replicates were 2,2 and 2,8, then the average would still be 2,5, but this difference would exceed the duplicate range limit.

NOTE 1 Duplicate differences exceeding the Duplicate Range Limit have a 99,7 % probability that they are invalid data, which may be due to sample instability or drift ([40] in the Bibliography).

— For intermediate precision, use all of the data to calculate the data exclusion limit. This limit is based on a run of 10 samples and is designed to detect either a high or low outlier. This value is calculated by following these steps:

1) For each sample, calculate the average and standard deviation (SD) from the run of 10.

2) Also determine the minimum and maximum value from the run of 10.

3) Calculate the following statistics: (Maximum – Average)/SD and (Average – Minimum)/SD.

4) Take the larger of the two numbers. This represents the possible suspect point.

5) If the result of step 4 is larger than 2,48, then the suspect exceeds the Data Exclusion Limit.

NOTE 2 Data values exceeding the Data Exclusion Limit have a 99 % probability that their extreme value is not due to the basic imprecision of the system. They should be considered as outliers. They represent cases of extreme performance that would not be expected in normal use ([41] in the Bibliography).

NOTE 3 Guidelines for identifying outliers are found in ISO 5725-2:1994 [5] and in CLSI document EP5 [24].

The following requirements apply to data exclusion.

— Data determined to be statistical outliers shall not be discarded. Data analysis shall be performed and results reported with and without the outliers included.

— For repeatability, exceeding the acceptable difference between duplicates indicates sample instability. Both measurements shall be considered invalid and shall not be used in repeatability calculations.

— For intermediate precision, a trend exceeding the acceptable limit indicates sample instability. All measurements using the sample shall be considered invalid and not be used in calculations.

— If a procedural mistake or instrument malfunction occurred during testing, an investigation shall be conducted to determine the cause. The investigation and its conclusions shall be documented in the report.

— If a cause is found, the outcome from the affected sample shall be considered invalid and shall not be used in calculations.

— Data rejected for cause (e.g., confirmed analyst error) may be replaced with new measurement results.

— If a cause cannot be determined, data analysis shall be performed, and the results reported with and without the data in question.

#### 8.4.4.2 Repeatability analysis

The average, standard deviation and coefficient of variation for repeatability shall be calculated using documented statistical procedures.

The following information shall be reported for each set of samples:

a) grand average of the observed INR values;

b) repeatability standard deviation with 95 % confidence interval and value interval (minimum and maximum values) and coefficient of variation (CV) for each set of INR values;

c) summary of any invalid data identified and excluded from statistical analysis, including the method of identification and the results of the investigation;

d) references to the statistical analysis procedures.

NOTE To compute the SD of the values of measurement or reference system (m/r), only ranges are needed.

$$SD_{t/r} = \sqrt{\frac{1}{2n}\sum_{i=1}^{n}\left(x_{1i} - x_{2i}\right)^2}$$

(Reference [36] in the Bibliography)

To obtain a confidence interval for $\sigma^2$ or $\sigma$, use is made of the fact that $nsd^2/\sigma^2$ is distributed as chi-square with $2n - n = n$ degrees of freedom.

Therefore, an upper $(1 - \alpha)$ confidence limit $(ul)$ is given by:

$$ul(\sigma^2_{t/r}) = \frac{n \cdot sd^2_{t/r}}{\chi^2_{n;\alpha}}$$

$$ul\left(\sigma_{t/r}\right) = \sqrt{ul(\sigma^2_{t/r})}$$

#### 8.4.4.3 Intermediate precision analysis

The average, standard deviation and coefficient of variation for intermediate precision shall be calculated for each sample using documented statistical procedures.

Analysis of Variance (ANOVA) is the preferred method for data analysis for intermediate precision.

The following information shall be reported for each sample:

a) grand average of the observed INR values for each sample;

b) intermediate precision standard deviation with 95 % confidence interval and coefficient of variation (CV) for INR values from each sample;

c) summary of any invalid data identified and excluded from statistical analysis, including the method of identification and the results of the investigation;

d) references to the statistical analysis procedures.

## 8.5 Verification of system accuracy

### 8.5.1 General requirements

System accuracy shall be verified in actual or simulated conditions of use.

The system accuracy verification study shall be designed to include systematic effects (bias) and random effects (imprecision) that would be experienced by an individual user in anticipated conditions of use.

NOTE The relationship of accuracy to trueness and precision is discussed in ISO 5725-1.

The measurement procedure used as a basis for system accuracy verification shall be of higher metrological order than that used for calibration of the end-users routine measurement procedure or if of the same order, shall be linked to the WHO tilt-tube method through a separate unbroken pathway.

The requirements specified in EN 13612 apply.

### 8.5.2 Study population

Subjects enrolled in the study shall meet the selection criteria required in 7.1.

One hundred and eighty (180) oral-anticoagulated patients shall be enrolled at a minimum of three sites. In addition, 20 normal subjects shall be enrolled across the sites.

Demographic data, targeted INR and the indication for oral-anticoagulation therapy shall be recorded for each patient, and demographic data for normal individuals.

INR values of the study subjects shall cover the measurement interval from 1,0 INR to 6,0 INR, as measured by the manufacturer's standing measurement procedure or the alternative measurement procedure. INR values above 6,0 should be excluded.

At least 5 % of the study subjects ($n = 10$) shall have an INR value between 4,6 and 6,0 (see Table 2 in 8.5.3). If the required number of patients with an INR above 4,5 cannot be obtained at the initial study sites, expansion of the study to additional sites may be necessary.

Each patient's individual therapeutic interval shall be recorded.

### 8.5.3 Samples

Either fresh capillary blood samples or fresh or stabilized venous blood samples shall be used for the verification of system accuracy.

For the manufacturer's selected measurement procedure, citrated plasma shall be used.

Fresh capillary blood samples shall be collected by skin puncture (e.g. fingerstick). Each sample shall be collected with a separate finger puncture. Sample containers designed for the collection of capillary blood should be used, if applicable.

Samples shall be prepared and processed according to the instructions for use, including sample pretreatment if required.

Each sample shall have sufficient volume to be measured by the oral-anticoagulation monitoring device and at least in duplicate by the manufacturer's measurement procedure.

Exclusion criteria, such as the volume fraction of erythrocytes (packed cell volume, haematocrit), shall be based on the manufacturer's instructions for use and specified in the protocol. However, samples with volume fractions of erythrocytes from 35 % to 50 % shall be included.

The INR values should be distributed as specified in Table 2. INR values shall be determined by the oral-anticoagulation monitoring system.

**Table 2 — INR values of samples for system accuracy verification**

| Number fraction of samples [a] % | INR values |
|---|---|
| 10 to 15 | Below 2,0 |
| 15 to 40 | 2,0 to 2,8 |
| 15 to 40 | 2,9 to 3,7 |
| 10 to 30 | 3,8 to 4,5 |
| 5 to 10 | 4,6 to 6,0 |

[a] Once a category is filled (i.e., the maximum allowed percentage has been reached), no more samples may be added to that category.



### 8.5.4 Instruments and reagents

The system accuracy verification study in 8.5.7 assumes that each subject will use one instrument. Using more than one instrument per subject may be necessary to minimize the time between duplicate measurements. If more than one instrument is used, the instruments shall be rotated through the protocol so that equal numbers of samples are measured with each instrument.

NOTE Using multiple instruments increases the intermediate measurement variance, because instrument-to-instrument variability would not be observed by a single patient performing testing on the same instrument. It also averages the specific influences of individual instruments (potentially increasing or decreasing measurement bias).

If different subjects use the same instrument, cleaning the instrument may be necessary to avoid the transfer of bloodborne pathogens. Manufacturers should validate a cleaning procedure and include cleaning information in the user's manual.

At least two reagent lots shall be included in the system accuracy verification study.

### 8.5.5 Manufacturer's selected measurement procedure

The manufacturer shall establish a selected and/or standing measurement procedure traceable to the manual tilt-tube reference measurement procedure using an International Reference Preparation (IRP) of thromboplastin.

The procedure shall specify the sample collection procedure regarding citrate concentration and brand mark of the collection device.

The requirements specified in ISO 17511 apply.

The requirements specified in Clauses 5 and 6 of WHO Technical Report Series, No. 889, 1999, apply.

NOTE 1 A routine coagulation measurement procedure (e.g., in a hospital or outpatient clinic laboratory) that is traceable to the manual tilt-tube reference measurement procedure using an International Reference Preparation (IRP) of thromboplastin and is validated for precision and trueness by comparison to the manufacturer's selected or standing measurement procedure may be used to assign the reference values.

A detailed description of the measurement procedure used to determine the reference values, including traceability to the manual tilt-tube reference measurement procedure using an International Reference Preparation (IRP) of thromboplastin, or equivalence to the manufacturer's selected or standing measurement procedure, shall be documented in the protocol.

NOTE 2 Examples of suitable traceability chains for the manufacturer's selected measurement procedure are shown in Annex B, Figures B.2 and B.3.

If the manufacturer contracts with a reference measurement laboratory, then appropriate measures shall be taken to verify that the laboratory is qualified to perform the measurement procedure.

NOTE 3 ISO 15195 may be used as a guide.

### 8.5.6 Study design

System accuracy may be verified using either a one- or two-step comparison.

In the one-step comparison, capillary blood is compared to venous blood without anticoagulant (if claimed as an acceptable sample type) and citrated plasma.

In the two-step comparison, capillary blood is compared to venous blood without anticoagulant, and venous blood without anticoagulant is compared to citrated plasma. This approach may be used if the relationship between venous and capillary blood is established.

NOTE Either procedure allows several replicates of each venous blood sample to be measured. Therefore, an assessment of the different sources of variability (e.g., reagent lots, instruments, volume fraction of erythrocytes) may be made with increased statistical power.

Individual measurements from the oral-anticoagulation monitoring system shall be compared to reference INR values determined by the manufacturer's measurement procedure (i.e., a selected or standing measurement procedure or by another validated measurement procedure that has been shown to produce equivalent results).

### 8.5.7 Procedure

#### 8.5.7.1 General

The manufacturer may choose to follow a one-step procedure or two-step procedure. The advantages and disadvantages of each procedure are described in 8.5.7.2 and 8.5.7.3.

The following experimental designs represent the minimum requirements to verify system accuracy. The procedures may be modified to accommodate multiple reagent lots or other factors.

#### 8.5.7.2 One-step procedure

Two capillary blood samples shall be collected from each subject, according to the manufacturer's instructions for use, for duplicate measurement on the oral-anticoagulation monitoring system.

Simultaneously, a citrated venous blood sample shall be collected from the subject by an experienced phlebotomist in accordance with the requirements of the reference measurement procedure (see 8.5.5). If the manufacturer intends the device to be used for venous, nonanticoagulated blood, this sample type shall be collected. Venous blood without anticoagulant may be used for plasma testing, after addition of citrate anticoagulant and separation of platelet-poor plasma.

The capillary samples and venous blood samples (if applicable) shall be measured on the device under evaluation, according to the manufacturer's instructions for use, and the result shall be recorded on the data collection sheet.

After measurement on the oral-anticoagulation monitoring system (if applicable), the venous blood sample shall be processed and analyzed by the manufacturer's standing measurement procedure or alternative measurement procedure (see 8.5.5) and the INR result shall be recorded on the data collection sheet.

The volume fraction of erythrocytes (haematocrit value) shall be measured on each sample to verify that the value is within the acceptable interval specified for the device. The results shall be recorded on the data collection sheet.

#### 8.5.7.3 Two-step procedure

In the two-step procedure,

a) during the first step, the equivalency of venous and capillary blood shall be shown, and

b) during the second step, venous blood without anticoagulant as a sample for the blood device, and venous citrated plasma for the respective comparison method from the same venous sample, shall be used.

In the first step, two capillary blood samples shall be collected from each subject according to the manufacturer's instructions for use, for duplicate measurement on the oral-anticoagulation monitoring system.

Simultaneously, a venous blood sample shall be collected from the subject by an experienced phlebotomist, in accordance with the requirements of the self-testing system.

The samples shall be measured on the device under evaluation, according to the manufacturer's instructions for use, and the result recorded on the data collection sheet.

Once capillary and venous blood without anticoagulant have been demonstrated to be equivalent, the second step comparison (i.e., between samples of venous blood without anticoagulant and citrated plasma) can be undertaken. This comparison may be conducted at sites which are distant in time and place from the original capillary/venous equivalency studies.

NOTE 1 For the purposes of this International Standard, "equivalent" means not significantly different (slope = 0,95 to 1,05, intercept = ± 0,1 INR), in an experiment with appropriate statistical power.

In the second step, a venous blood sample without anticoagulant shall be measured on the device under evaluation, according to the manufacturer's instructions for use, and the result recorded on the data collection sheet.

The venous blood sample shall be processed immediately and measured by the reference measurement procedure (see 8.5.5) and the INR result shall be recorded on the data collection sheet.

The volume fraction of erythrocytes (haematocrit value) shall be measured on each sample to verify that the value is within the acceptable interval specified for the device. The results shall be recorded on the data collection sheet.

The two-step procedure is recommended for sites when fingersticks are not feasible (see Reference [35] in the Bibliography).

NOTE 2 Fingersticks may not be feasible because the inconvenience added for the patient due to two parallel punctures, one capillary and one venous, may be

— not accepted by the patients, they will not give informed consent, and/or

— not accepted by the investigator, because difficulties in procedural timings are experienced.

### 8.5.8 Data analysis

#### 8.5.8.1 General

Prior to analysis, the data sheets shall be evaluated to identify obvious errors (e.g., transcription errors, insufficient volume of blood sample). Corrections should be made as appropriate.

No data accepted by the user as valid may be excluded from the assessment of system accuracy. The following guidelines apply to the verification of system accuracy:

a) All procedural errors, instrument malfunctions and control failures shall be investigated to determine the cause. The investigation and its conclusions shall be documented in the report.

b) If a result was accepted by the user as valid, even though an error message was given, if a control limit was exceeded or if a procedural error occurred, such a result shall not be rejected. The reason that the user ignored the error message, control failure or procedural error shall be investigated.

c) The data shall be examined for statistical outliers by a procedure defined in the protocol. Regression and correlation analyses shall be performed and reported with and without the outlier data. Outlier data points shall be included in the plots using a different symbol. Guidelines for identifying outliers are found in ISO 5725-2:1994 [5] and in CLSI document EP9 [26].

Results shall be plotted and analysed and the following information shall be reported:

— total number of samples analysed;

— interval of INR values, as measured by the reference measurement procedure;

— graphical plots of the data with appropriate statistics (see examples in 8.5.8.2 and 8.5.8.3);

— results of the system accuracy assessment (see 8.6.2 and 8.6.3);

— summary of outliers identified and excluded from statistical analysis, including the procedure for identifying the outliers and the outcome of the investigation into their cause; and

— literature references for the statistical analysis procedures.

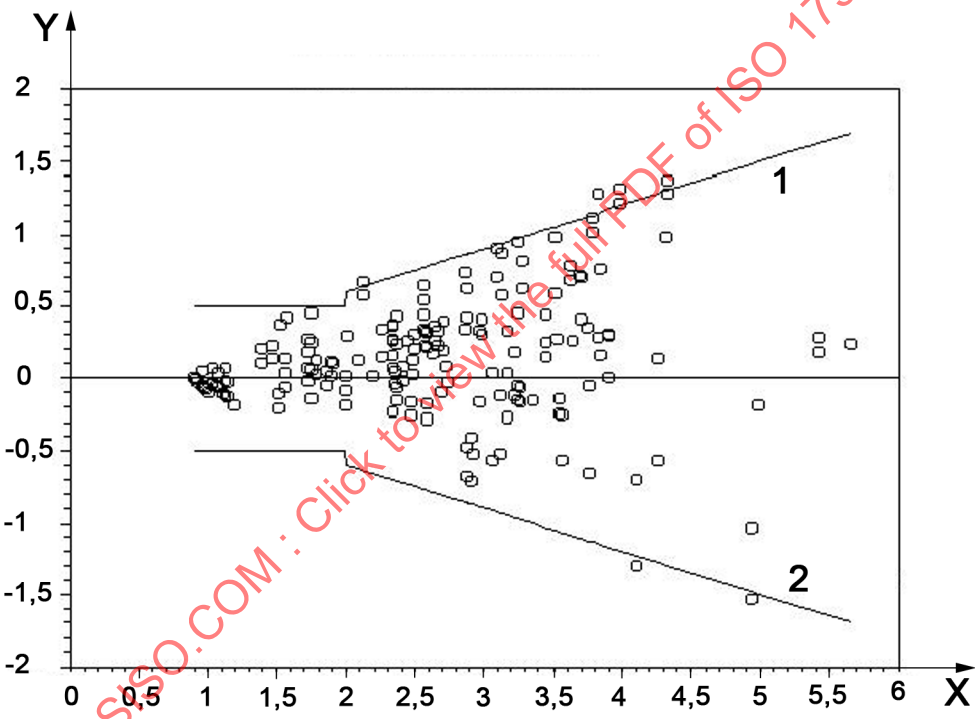
#### 8.5.8.2 Difference plots

The difference between individual results from the oral-anticoagulation monitoring system and the reference values shall be plotted as the dependent variable. The reference values shall be plotted as the independent variable. Reference values may be averages of replicate measurements.

Difference plots are the recommended approach for depicting system accuracy because statistical assumptions are minimal and the percentage of data points meeting the system accuracy criteria, as well as estimating bias, are easily calculated. See CLSI document EP9 [26] or Bland and Altman [32].

Plotting percentage difference against INR values at low INR values is generally not suitable for the graphical evaluation of system accuracy. Actual INR differences should be used. A recommended cutoff value is 2,0 INR.

EXAMPLE A plot of results from a verification study of an oral-anticoagulation monitoring system is illustrated in Figure 1. The upper and lower lines represent the acceptance criteria from 8.6.1.






**Key**

X reference INR values
Y difference (observed INR value-reference)
1 upper limit of acceptability
2 lower limit of acceptability

**Figure 1 — IRN difference plot**

Assessment of system accuracy shall be based on all data accepted by the user. The following statistics shall be reported for each INR interval in Table 3:

a) Bias (calculated as the average of the differences between the oral-anticoagulation monitoring system results and the reference values) as well as the standard deviation of the differences and the standard error of the average difference.

b) Percent of results within the acceptability criteria for system accuracy described in 8.6.1. See 8.6.2.

c) Interval that encompasses 95 % of the differences.

#### 8.5.8.3 Regression analysis

Individual results of the oral-anticoagulation monitoring system shall be plotted as the dependent variable and the reference values as the independent variable. Reference values may be averages of replicate measurements. Identical scales and intervals shall be used for the *x*- and *y*-axes.

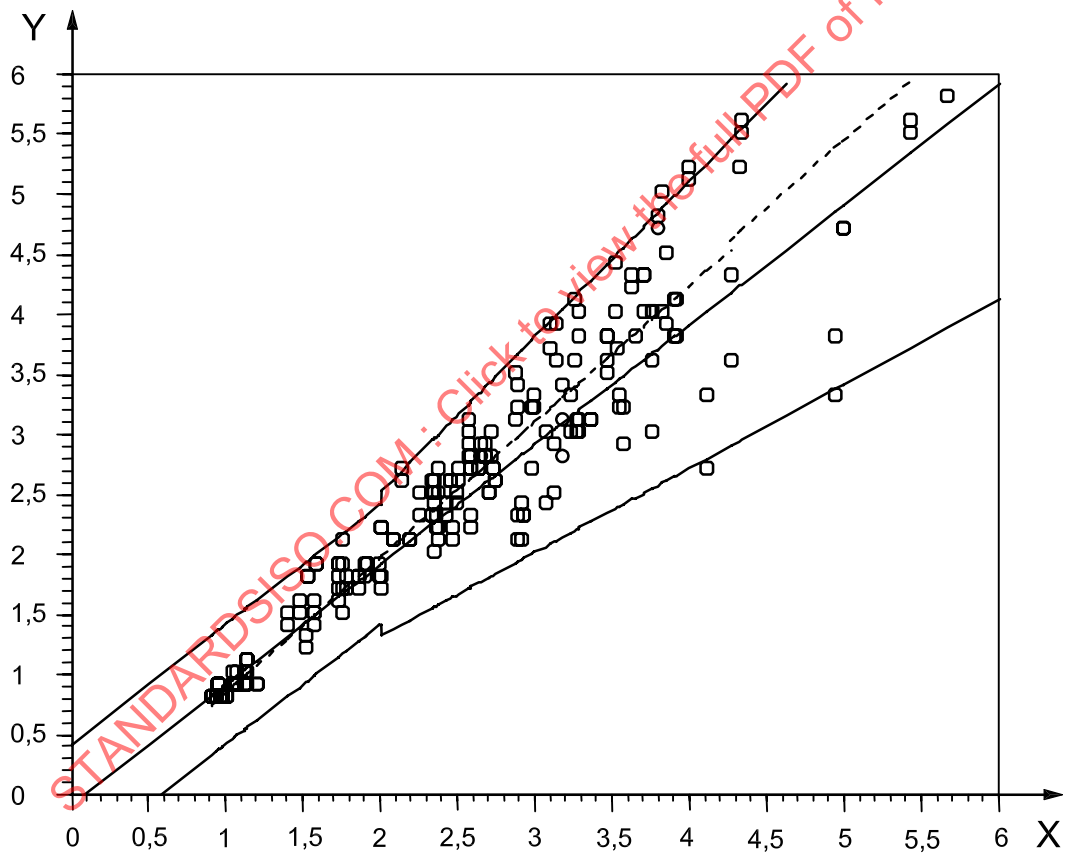
The slope and *y*-intercept shall be calculated by a suitable regression analysis procedure. The method used shall be specified in the protocol.

NOTE 1 Examples include least-squares linear regression, Deming regression, orthogonal regression (a special case of the Deming regression), or Passing/Bablock regression. Appropriate regression analysis depends on the data meeting certain statistical assumptions. For an evaluation of regression procedures for method comparison studies and guidance in selecting an appropriate regression analysis procedure, see Linnet [23] or Stöckl [33].

NOTE 2 Bias can be calculated from the regression equation at selected INR values (e.g., at medical decision concentrations). See CLSI document EP9 [26].

EXAMPLE A regression plot from a verification study of an oral-anticoagulation monitoring system is illustrated in Figure 2. The two outer lines represent the acceptance criteria from 8.6.1. The regression slope is 1,132 ± 0,054; the y-intercept is −0,2 ± 0,1; the correlation coefficient is 0,943.






**Key**

X reference INR values
Y observed INR values
1 upper limit of acceptability
2 regression line
3 line of identity
4 lower limit of acceptability

**Figure 2 — Regression plot**

The following shall be reported for each evaluation site:

— a scatter plot of the data with the estimated regression line and the $y = x$ line;

— the slope and intercept of the linear regression line with confidence intervals;

— the Pearson's correlation coefficient $r$.

Outlier data may have an undue influence on estimates of central tendency and dispersion. Statistical parameters should be calculated with and without outlier data, and all data shall be shown in the regression plot, with outlier data points indicated by a different symbol.

## 8.6 Minimum acceptable system accuracy

### 8.6.1 System accuracy requirement

The minimum acceptable accuracy for results produced by an oral-anticoagulation monitoring system for self-testing shall be as follows:

— ninety percent (90 %) of the differences between results from the oral anticoagulation monitoring system and results from the reference measurement procedure, in the combined INR ranges below 2,0 and 2,0 to 4,5, shall be within the limits in Table 3;

— the bias (average difference) between the oral-anticoagulation monitoring system and the reference measurement procedure in the therapeutic interval (INR 2,0 to 4,5) shall be less than or equal to ± 0,3 INR;

— bias results for the supratherapeutic interval (INR 4,6 to 6,0) shall be reported.

**Table 3 — Performance criteria**

| **INR interval** | **Allowable difference** (90 % of results) | **Allowable bias** (average difference) |
|---|---|---|
| Below 2,0 | ± 0,5 | NA |
| 2,0 to 4,5 | ± 30 % | ± 0,3 |
| 4,6 to 6,0 | NA | NA |
| NA = not applicable. | | |

NOTE 1 The minimum acceptable accuracy criteria are based on the performance of currently marketed anticoagulation monitoring systems, which represent the state-of-the-art. These systems have been shown to offer significant benefits to patients. See [67], [68] in the Bibliography. See Annex F for more information.

Although no performance criteria are listed for INR values in the interval of 4,6 to 6,0, the difference and bias should be calculated and reported.

NOTE 2 The criteria apply to system accuracy verification studies in which professional system operators have received proper training, the device has been properly maintained, and required adjustment and control procedures have been followed, in accordance with the manufacturer's instructions for use.

### 8.6.2 System accuracy assessment

Acceptability of the oral-anticoagulation monitoring system shall be determined using all of the 400 results obtained from the 200 subjects. The total number of acceptable results in each INR interval shall be added to determine the number of acceptable results. The percentage of acceptable results is calculated as the number of acceptable results times 100, divided by the total number of results.

### 8.6.3 Data presentation

Results in the INR intervals in Table 3 shall be presented separately because different performance criteria apply to each interval; see 8.6.1.

The results shall be presented in a table for each INR interval.

Recommended formats for healthcare professionals and lay users are shown in Tables 4 and 5. The data are from the example in 8.6.2. The interval represents the INR values evaluated in 8.6. The upper limit of the measuring interval may be higher; see 4,2.

**Table 4 — Example of presentation of system accuracy results for professional labelling**

| INR interval | Within 0,3 INR | Within 0,5 INR | Average INR difference |
|---|---|---|---|
| Below 2,0 | 100 % | 100 % | 0,1 |

| INR interval | Within 10 % | Within 20 % | Within 30 % | Average INR difference |
|---|---|---|---|---|
| 2,0 to 4,5 | 75 % | 90 % | 100 % | 0,3 |
| 4,6 to 6,0 | 65 % | 90 % | 100 % | 0,3 |

**Table 5 — Example of presentation of system accuracy results for lay user labelling**

| INR interval[a] | % acceptable results |
|---|---|
| 1,2 to 4,5 | 97 % |
| [a] System accuracy was evaluated over this interval of INR results. | |

## 9 User performance evaluation

### 9.1 General

A user performance evaluation shall be performed by the manufacturer prior to placing a new oral-anticoagulation monitoring system into commercial distribution. The requirements specified in EN 13612 apply.

The purpose of the user performance evaluation is to demonstrate that users are able to operate the oral-anticoagulation monitoring system and obtain acceptable results, given only the instructions for use and training routinely provided by the manufacturer.

The user performance evaluation shall be performed according to a written protocol. The protocol shall, as a minimum, specify the training and education, evaluation sites, data collection and analysis procedures and acceptance criteria. The results of the user performance evaluation shall be documented in a report.

Results obtained by the lay user shall be compared to results obtained by experienced technicians, using the same oral-anticoagulation monitoring system, and may be compared to results obtained by the manufacturer's standing/selected measurement procedure.

### 9.2 Study sites

User studies shall be conducted at three professional sites. The setting shall allow the lay user to perform the measurements using only the instructions for use and training routinely provided to users by the manufacturer. Rationale for the selection of the evaluation sites shall be documented.

NOTE The manufacturer is encouraged to select sites that represent the actual use of the product (e.g., anticoagulation clinics).

## 9.3 Subjects

At least 60 users, 20 per site, shall be included, with age, gender and education level representative of the intended user population. Subjects shall have a target INR interval between 2,0 and 4,5, and shall meet the requirements of the oral-anticoagulation self-testing system (e.g., the value for the volume fraction of erythrocyts shall fall within the interval specified in the instructions for use).

Subjects shall complete the manufacturer's education program, but shall not receive additional training, instructions, assistance or training materials other than those routinely provided with the oral-anticoagulation self-testing system.

Once the subjects have completed the manufacturer's education program and are deemed qualified to perform self-measuring, they may perform the user study.

If the training program requires users to take the self-testing systems home, the subjects shall be instructed not to use the results for any medical purpose. The devices shall be labelled appropriately (e.g., "For Performance Evaluation Only", "For Investigational Use Only").

## 9.4 Instruments and materials

User studies shall be conducted using one reagent lot.

## 9.5 Evaluation of user proficiency

At the evaluation site, the subjects shall perform their own finger punctures and measure their blood value using the oral-anticoagulation self-testing system. Each subject shall perform the measurement twice, obtaining two INR results.

The site's trained healthcare provider shall also measure the subject's blood value using the same oral-anticoagulation self-testing system and the same lot of reagent. The healthcare professional shall measure the subject's blood twice, obtaining two INR results.

Immediately thereafter, the healthcare provider may obtain a venous blood sample from the subject for measurement by the reference measurement procedure.

In order not to introduce bias, the order of measurement by the users and the healthcare providers should be randomized or alternated.

NOTE 1 If two instruments are available, and if allowable by the self-testing system, the two measurements may be taken from a single finger puncture, using two sequential drops of blood.

User techniques in operating and maintaining the system, applying the sample and reading the result shall be evaluated by the site's trained healthcare provider. Results of the evaluation shall be documented.

Subjects may be given a questionnaire to evaluate their understanding of the system.

After completion of the program, users shall be instructed to perform measurements at home.

Each subject shall be instructed to complete at least ten measurements spanning at least ten days, but no more than 30 days and no more than one measurement per day, following the manufacturer's instructions for use, including the measurement of control materials as applicable.

Each subject shall be instructed to measure two control samples with each measurement, obtaining a total of ten values for each level of control material, if applicable.

Manufacturers shall provide the subjects with data forms for documentation of their self-testing results and control results.

After the home measurement period, each subject shall return to the healthcare provider's site to complete the user evaluation. At the healthcare provider's site, the subjects shall perform their own finger punctures and measure their blood samples using the oral-anticoagulation self-testing system.

Immediately after the subject's self-testing, the site's trained healthcare provider shall measure the subject's blood with the same oral-anticoagulation self-testing system.

Immediately thereafter, the healthcare provider may obtain a venous blood sample from the subject, for measurement by the reference measurement procedure.

User techniques in operating and maintaining the system, applying the sample, and reading the result shall be evaluated by the trained healthcare provider participating in the study. Results of the user evaluation shall be documented in the report.

NOTE 2 Subjects may be given a questionnaire designed to evaluate their understanding of the system.

NOTE 3 Linear regression and/or t-tests may be used to calculate the relationships of the patient and professional results.

## 9.6 Acceptance criteria and data assessment

From the user's duplicate results, and the healthcare provider's duplicate results, repeatability of the duplicate measurements shall be calculated as described in 8.4.4.1.

From the user's control results, if applicable, the intermediate precision SD shall be calculated using an analysis-of-variance procedure for each level of control material.

Using the first result from each set of duplicate results, agreement of the user's results with the healthcare provider's results shall be calculated as described in 8.5.8.

The same analysis shall be performed using the first user result and the corresponding reference measurement result, if applicable.

For the users' and the healthcare provider's results, 95 % of all results in the INR interval of 2,0 to 4,5 shall be within $\pm$ 0,5 INR.

The average difference between the users' results and the healthcare provider's results shall be $\leqslant$ 10 % of the healthcare provider's results.

Similarly, agreement of the users' results with their corresponding reference measurement results shall be calculated, if applicable.

The results of the study shall be reported in the format described in 8.6.3.

NOTE Annex F contains a survey of published performance evaluations to which these performance criteria have been applied retrospectively.

## 9.7 Evaluation of instructions for use

Instructions for use shall be evaluated by the study participants. The lay users and healthcare providers shall be requested to review and provide comments regarding the ease of understanding of the instructions for use.

This evaluation may be combined with the study described in 9.3, or may be conducted separately.

User comments may be collected via questionnaires, or as part of human factors studies.

The manufacturer shall establish acceptance criteria for the results of the evaluation of the instructions for use. If the users' results fail to meet the acceptance criteria, then the manufacturer shall consider the need to revise sections of the instructions and repeat the evaluation.

# Annex A
(normative)

# Additional requirements for electromagnetic compatibility

## A.1 General

This annex specifies minimum requirements for immunity and emissions regarding electromagnetic compatibility (EMC) for oral-anticoagulation monitoring devices intended for self-testing, in addition to the requirements of 6.4.

If risk analysis (see 4.4) shows that exposure to higher levels of radiation or electrostatic discharge presents an unacceptable risk to the user, then the device shall be tested at these higher levels.

## A.2 Immunity test requirements

### A.2.1 Radiated immunity

The requirements specified in IEC 61000-4-3 apply.

In addition, immunity against radiated frequencies shall be extended to the frequency range up to 2,5 GHz, at a test level of 3 V/m.

### A.2.2 Electrostatic discharge immunity

The requirements specified in IEC 61000-4-2 apply.

For air discharge, electrostatic discharge immunity shall be demonstrated at test levels of ± 2 kV, ± 4 kV and ± 8 kV.

For contact discharge, electrostatic discharge immunity shall be demonstrated at test levels of ± 2 kV, ± 4 kV and ± 6 kV.

## A.3 System test requirements

If other equipment is connected to the instrument or can be connected to the instrument, the resulting system shall also fulfill the EMC requirements.

When determining system testing requirements, the manufacturer shall consider whether or not it is possible to perform a measurement while the system is connected. System configurations specified by the manufacturer, or foreseeable system configurations identified by risk analysis, shall be tested as described in A.2 if they allow the user to perform an INR measurement.

System test requirements may not apply if the design of the device prevents the user from performing INR measurements when the instrument is connected to other equipment.

## A.4 Instructions for use

The instructions for use (see 5.3) shall include the following information:

a) a statement that the equipment complies with applicable EMC emission requirements, and that emissions of the energy used are low and not likely to cause interference in nearby electronic equipment;

b) a statement that the equipment is tested for immunity to electrostatic discharge, as specified in IEC 61000-4-2;

c) recommended mitigation measures that should be taken by the user to avoid incorrect operation or damage to the device;

EXAMPLE 1 “Do not use this instrument in a dry environment, especially if synthetic materials are present. Synthetic clothes, carpets, etc., may cause damaging static discharges in a dry environment.”

d) a statement that the equipment is tested for immunity to radio frequency interference at the frequency range and test levels specified in this International Standard;

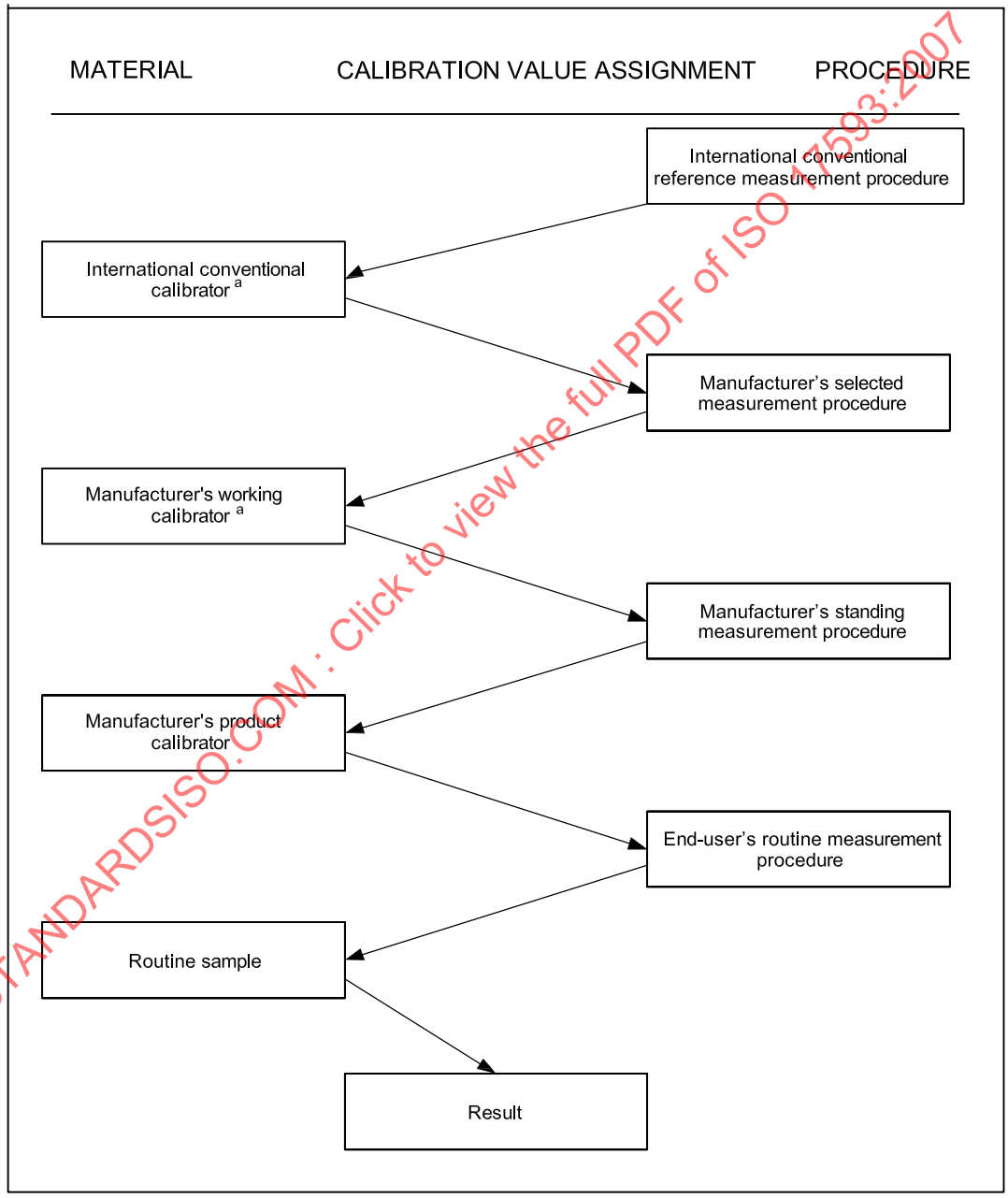
e) recommended mitigation measures that should be taken by the user to avoid radio frequency interference, with specific examples.

EXAMPLE 2 “Do not use this instrument near cellular or cordless telephones, walkie talkies, garage-door openers, radio transmitters, or other electrical or electronic equipment that are sources of electromagnetic radiation, as these may interfere with the proper operation of the instrument.”

# Annex B
(informative)

# Traceability chain examples

The diagram in Figure B.1 is adapted from ISO 17511 to show a full traceability chain for calibration of an oral anticoagulation monitoring system by the manufacturer.

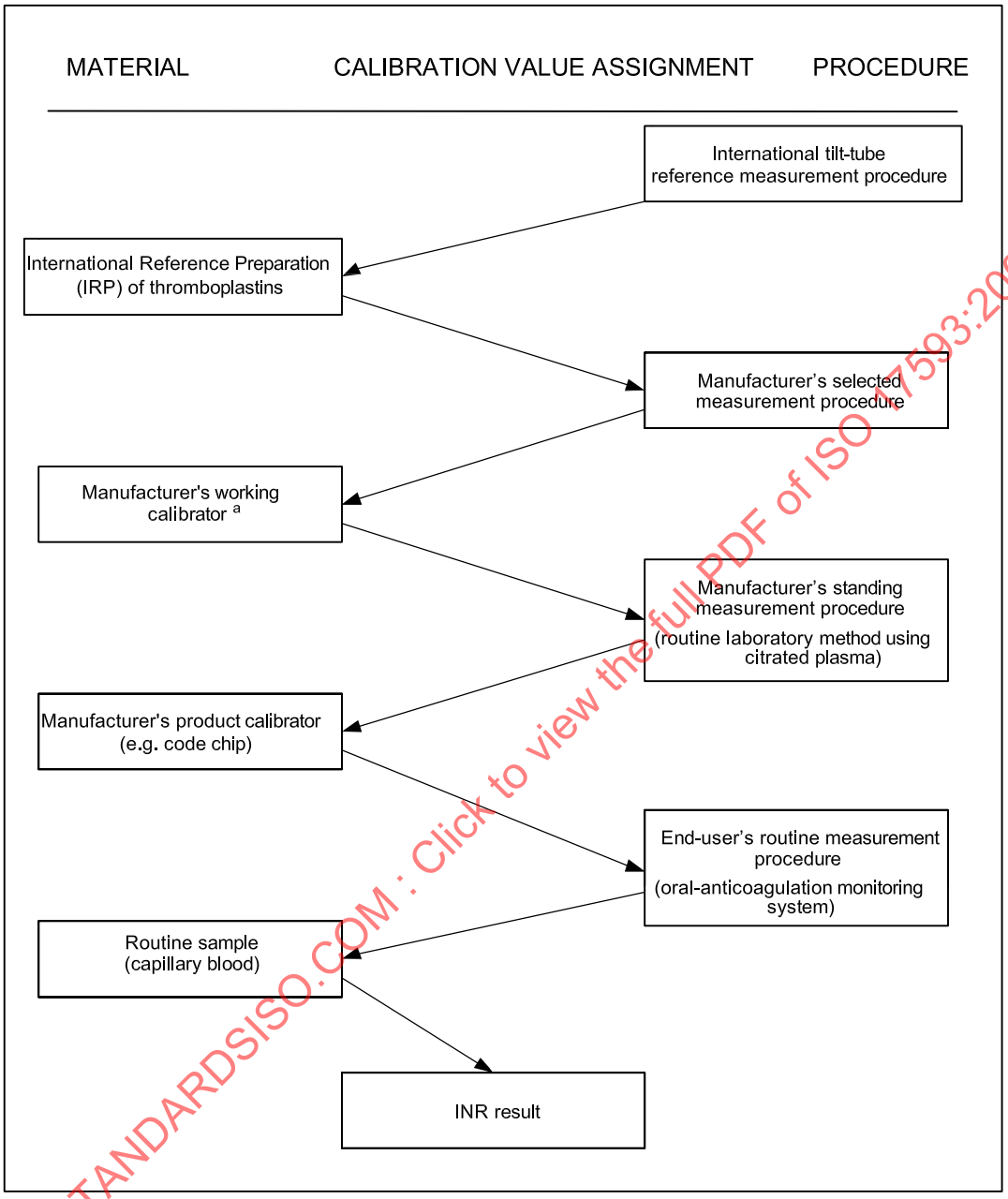





[a] The calibrator can be an appropriate surrogate reference material or human sample.

**Figure B.1 — Example of a traceability chain for a measurement result of an oral-anticoagulation monitoring system**

The example in Figure B.2 shows a traceability chain for INR results to the WHO tilt-tube reference measurement procedure and the International Reference Preparation (IRP) of thromboplastins using the "one-step procedure" described in 8.5.7.2.

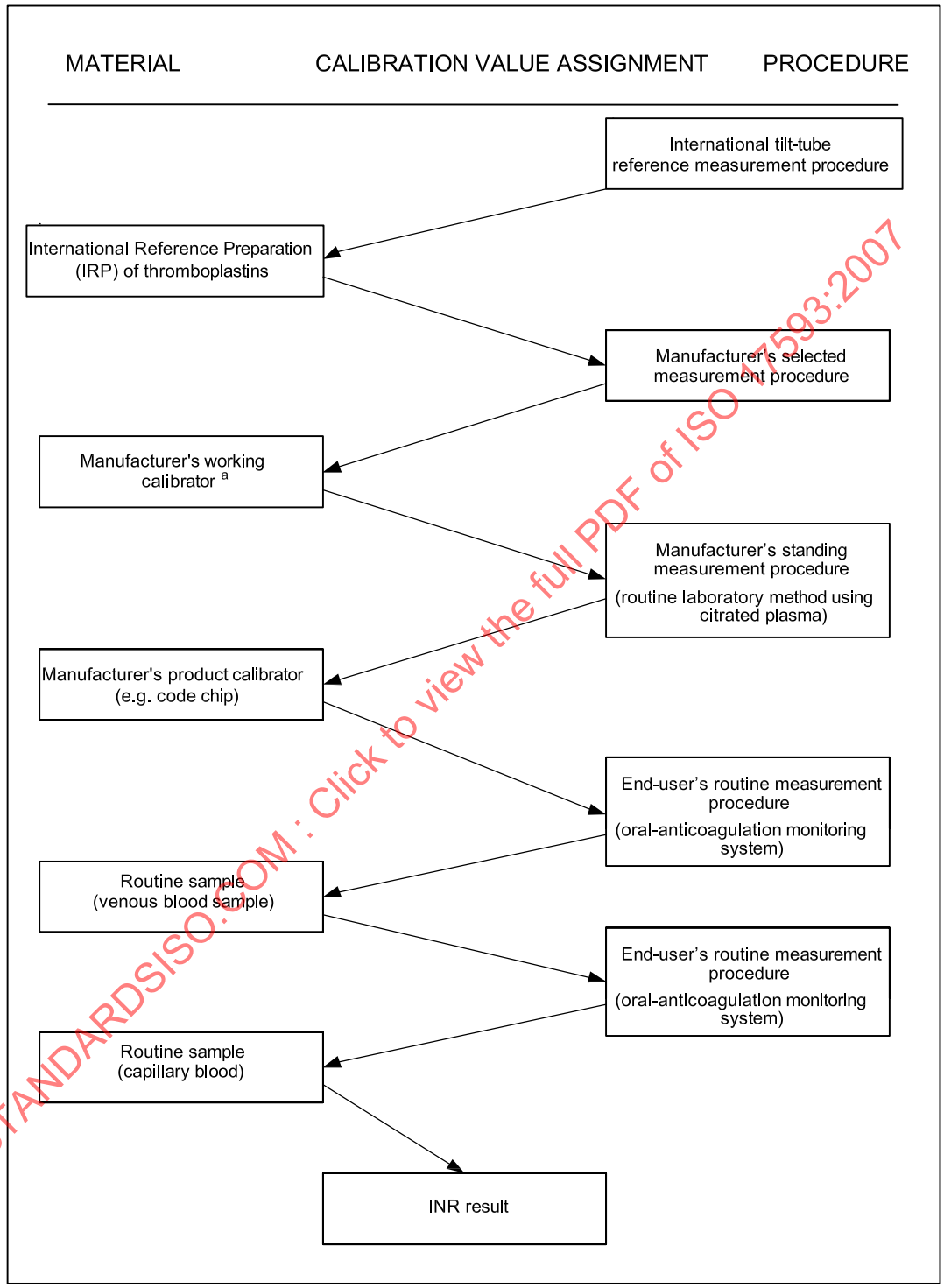





a The calibrator can be an appropriate surrogate reference material or human sample.

**Figure B.2 — Example of a traceability chain for the system accuracy verification study of an oral-anticoagulation monitoring system following the one-step procedure**

The example in Figure B.3 shows a traceability chain for INR results to the WHO tilt-tube reference measurement procedure and the International Reference Preparation (IRP) of thromboplastins using the "two-step procedure" described in 8.5.7.3.






[a] The calibrator can be an appropriate surrogate reference material or human sample.

**Figure B.3 — Example of a traceability chain for the system accuracy verification of an oral-anticoagulation monitoring system following the two-step procedure**

# Annex C
(informative)

## Sample size calculation to estimate bias ([42] in the Bibliography)

In accordance with Table 2 in 8.5.3, at least 150 samples will be examined in the interval of INR 2,0 to 4,5.

A coefficient of variation of 5 % will be postulated for the oral-anticoagulation monitoring system and for the manufacturer's selected measurement procedure.

For an average INR of 3,0, an $SD_E = 0{,}15$ follows.

Because duplicate measurements are performed, the effective SD is reduced by $SD_{dup} = SD_E/\sqrt{2} = 0{,}106$.

If the allowable bias is 0,3 INR, the 95 % confidence interval, CI [$u(1 - \alpha/2) \approx 2$] may be calculated as follows:

$$CI = \text{bias} \pm 2\sqrt{2}\,SD_{dup}/\sqrt{150}$$

only the length of the interval

$$CI = \pm\sqrt{2} \times 0{,}106 / \sqrt{150}$$

$$CI = \pm 0{,}3/12{,}24$$

$$CI = \pm 0{,}025$$

or 0,3 ± 0,025 INR.

Therefore, a sample population of 150 samples in the interval of 2,0 to 4,5 INR results in a confidence interval of ± 0,025 INR, which is sufficient to verify that the performance of the system conforms to the allowable bias of 0,3 INR.

# Annex D
(informative)

# Example of an uncertainty calculation for a prothrombin INR determination using an oral anticoagulation monitoring system

**Table D.1**

| Influence Name | Magnitude at INR 3,0 | Type | Probability Distribution | Divisor | Quotient | Square | Comments |
|---|---|---|---|---|---|---|---|
| **Step 1 – Manufacturer's Standing Measurement Procedure: ISI determination of master lot** | | | | | | | |
| International Reference Preparation | Zero (by definition) | | | | | | |
| • Analytical error of WHO process<br>• Operator dependant variability<br>• Sample collectives<br>• Manufacturer's Standing Measurement Procedure variability | CV 5 % or 0,15 INR (standard deviation) | A | Normal | 1 | | 0,0225 | Interlaboratory CV of ISI determination 4,5 to 5,7 % [44-46]<br>Prerequisites: intralaboratory CV of ISI determination < 3 %, as requested by WHO procedure [44]<br>Because 3 labs are involved, standard deviation should be divided by 1,73. However, a conservative approach was employed. |
| • Algorithm variability | ± 0,03 INR interval | B | Rectangular | 1,73 | | - | Effect is negligible [45]. |
| **Step 2 – End-user's routine measurement procedure: Factory calibration** | | | | | | | |
| • Analytical error of calibration procedure<br>• Sample collectives for calibration<br>• Instrument collective<br>• Stability of masterlot/ reagent | 0,10 INR (standard deviation) | A | Normal | 1 | | 0,01 | The 4 causes were estimated in total using 8 reagent lots produced over a time period >1 year, venous blood sample [46]. |
| • Stability of reagent | 0,10 INR (standard deviation) | A | Normal | 1 | | 0,01 | Product claim considered as standard deviation. Even though stability of reagents is already included in Step above, by the conservative approach chosen, this variability is added separately. |

**Table D.1** (*continued*)

| Influence Name | Magnitude at INR 3,0 | Type | Probability Distribution | Divisor | Quotient | Square | Comments |
|---|---|---|---|---|---|---|---|
| **Step 3 – End-user's routine measurement procedure: User INR determination** | | | | | | | |
| • Influence of patient sample matrix<br>• Analytical error of user determination | CV 5,5 % or 0,16 INR (standard deviation) | A | Normal | 1 | | 0,0256 | Imprecision in patients' hands ranges between 5,2 and 5,5 % [47-49]. |
| • Instrument variability | CV 1,5 % or 0,045 INR (standard deviation) | A | Normal | 1 | | 0,002 | CV 1,5 % using 657 instruments [50]. |
| | | | | | **Sum of squares** | **0,0701** | |
| | | | | | **Combined standard uncertainty** | **± 0,265 INR (Standard deviation)** | |

Source: R. Leinberger, W. Plesch, B. Scheffler, C. Berding, and S. Arends, Roche Diagnostics GmbH, Mannheim GERMANY (unpublished).

The Manufacturer's Standing Measurement Procedure may not have been calibrated directly against the International Reference Preparation (IRP) as shown in the cause and effect diagram, but against a Manufacturer's Selected Measurement Procedure as shown in Figure B.1. The additional Step in the uncertainty chain, the calibration of the Manufacturer's Selected Measurement Procedure against the IRP, will add uncertainty. The magnitude of uncertainty added will be identical to Step 1 in Table D.1, respectively 0,15 INR standard deviation.

The inclusion of a Manufacturer's Selected Measurement Procedure in the calibration chain may be necessary, when not enough IRP reagent is available.

NOTE 1 For the use of a cause and effect diagram to identify contributors to measurement uncertainty, see Figure D.1.

NOTE 2 For additional information, see [50-54] in the Bibliography.