BSI Standards Publication

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

bsi.

National foreword

This British Standard is the UK implementation of EN ISO 17511:2021. It is identical to ISO 17511:2020. It supersedes BS EN ISO 17511:2003, which is withdrawn.

The UK participation in its preparation was entrusted to Technical Committee CH/212, IVDs.

A list of organizations represented on this committee can be obtained on request to its committee manager.

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In vitro diagnostic medical devices - Requirements for establishing metrological traceability of values assigned to calibrators, trueness control materials and human samples (ISO 17511:2020)

Dispositifs médicaux de diagnostic in vitro - Exigences pour l'établissement d'une traçabilité métrologique des valeurs attribuées aux étalons, aux matériaux de contrôle de la justesse et aux échantillons humains (ISO 17511:2020)

In-vitro-Diagnostika - Anforderungen an die Ermittlung metrologischer Rückführbarkeit von Werten, die Kalibratoren, Richtigkeitskontrollmaterialien und Humanproben zugeordnet sind (ISO 17511:2020)

This European Standard was approved by CEN on 4 February 2020.

EUROPEAN COMMITTEE FOR STANDARDIZATION
COMITÉ EUROPÉEN DE NORMALISATION
EUROPÄISCHES KOMITEE FÜR NORMUNG

CEN-CENELEC Management Centre: Rue de la Science 23, B-1040 Brussels

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European foreword

This document (EN ISO 17511:2021) has been prepared by Technical Committee ISO/TC 212 "Clinical laboratory testing and in vitro diagnostic test systems" in collaboration with Technical Committee CEN/TC 140 “In vitro diagnostic medical devices” the secretariat of which is held by DIN.

This European Standard shall be given the status of a national standard, either by publication of an identical text or by endorsement, at the latest by December 2021, and conflicting national standards shall be withdrawn at the latest by June 2024.

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

This document supersedes EN ISO 17511:2003.

This document has been prepared under a standardization request/mandate given to CEN by the European Commission and the European Free Trade Association, and supports essential requirements of EU Directive(s).

For relationship with EU Directive(s), see informative Annex ZA, which is an integral part of this document.

NOTE In this European Standard the concept "accuracy of measurement" is not equivalent to "trueness of measurement" (see 3.47) nor to the "precision of measurement" (see 3.34) alone. Instead, accuracy is commonly used as a combination of trueness and precision, which is also used as a concept in the Regulation 2017/746/EU on in-vitro diagnostic medical devices.

The following referenced documents are indispensable for the application of this document. For undated references, the latest edition of the referenced document (including any amendments) applies. For dated references, only the edition cited applies. However, for any use of this standard ‘within the meaning of Annex ZA’, the user should always check that any referenced document has not been superseded and that its relevant contents can still be considered the generally acknowledged state-of-art.

When an IEC or ISO standard is referred to in the ISO standard text, this should be understood as a normative reference to the corresponding EN standard, if available, and otherwise to the dated version of the ISO or IEC standard as listed below.

NOTE The way in which these referenced documents are cited in normative requirements determines the extent (in whole or in part) to which they apply.

Table — – Correlation between normative references and dated EN and ISO standards

Normative references as listed in Clause 2 of the ISO standard	Equivalent dated standard	
	EN	ISO
ISO 18113-2:2009	EN ISO 18113-2:2011	ISO 18113-2:2009
ISO 15193	EN ISO 15193:2009	ISO 15193:2009
ISO 15194	EN ISO 15194:2009	ISO 15194:2009

According to the CEN-CENELEC Internal Regulations, the national standards organizations of the following countries are bound to implement this European Standard: Austria, Belgium, Bulgaria, Croatia, Cyprus, Czech Republic, Denmark, Estonia, Finland, France, Germany, Greece, Hungary, Iceland, Ireland, Italy, Latvia, Lithuania, Luxembourg, Malta, Netherlands, Norway, Poland, Portugal, Republic of North Macedonia, Romania, Serbia, Slovakia, Slovenia, Spain, Sweden, Switzerland, Turkey and the United Kingdom.

Endorsement notice

The text of ISO 17511:2020 has been approved by CEN as EN ISO 17511:2021 without any modification.

Annex ZA
(informative)

Relationship between this European Standard and the General Safety and Performance Requirements of Regulation (EU) 2017/746 aimed to be covered

This European standard has been prepared under a Commission's standardisation request to provide one voluntary means of conforming to the General Safety and Performance Requirements of Regulation (EU) 2017/746 of 5 April 2017 concerning in vitro diagnostic medical devices [OJ L 117].

Once this standard is cited in the Official Journal of the European Union under that Regulation, compliance with the normative clauses of this standard given in Table ZA.1 confers, within the limits of the scope of this standard, a presumption of conformity with the corresponding General Safety and Performance Requirements of that Regulation, and associated EFTA regulations.

NOTE 1 Where a reference from a clause of this standard to the risk management process is made, the risk management process needs to be in compliance with Regulation (EU) 2017/746. This means that risks have to be 'reduced as far as possible', 'reduced to a level as low as reasonably practicable', 'reduced to the lowest possible level', 'reduced as far as possible and appropriate', 'removed or reduced as far as possible', 'eliminated or reduced as far as possible', 'prevented' or 'minimized', according to the wording of the corresponding General Safety and Performance Requirement.

NOTE 2 The manufacturer's policy for determining **acceptable risk** must be in compliance with General Safety and Performance Requirements 1, 2, 3, 4, 5, 8, 10, 11, 13, 15, 16, 17, 18 and 19 of the Regulation.

NOTE 3 This Annex ZA is based on normative references according to the table of references in the European Foreword, replacing the references in the core text.

NOTE 4 When a General Safety and Performance Requirement does not appear in Table ZA.1, it means that it is not addressed by this European Standard.

Table ZA.1 — Correspondence between this European standard and Annex I of Regulation (EU) 2017/746 [OJ L 117]

General Safety and Performance Requirements of Regulation (EU) 2017/746	Clause(s)/sub-clause(s) of this EN	Remarks/Notes
9.1 (a)	4.3, 4.6.2	Covered with respect to analytical performance requirements resulting from a calibration hierarchy, and related uncertainty
9.3	4.1, 4.3, 4.4, 4.5, 4.6, 4.7, 4.8, 5	Covered
10.1	4.2, 4.5.4, 4.5.5	Covered with respect to definition of the measurand, corresponding performance characteristics and commutability during design and manufacturing processes
13.4	4.7, 4.8	Covered with respect to effectiveness and reliability of calibration
13.5	4.5.4, 4.5.5, 4.8	Covered with respect to commutability and traceability of end-user calibrator

General Safety and Performance Requirements of Regulation (EU) 2017/746	Clause(s)/sub-clause(s) of this EN	Remarks/Notes
14.1	4.3, 4.6.2	Covered with respect to analytical performance requirements resulting from a calibration hierarchy, and related uncertainty
20.1 (g)	4.3, 4.7.1	Covered with respect to uncertainty as a limitation and information to be provided by the manufacturer
20.4.1 (g)	4.7.1	Covered with respect to uncertainty of assigned values for end-user calibrator and information to be provided by the manufacturer
20.4.1 (u)	4.7.1, 4.9.1, 4.9.3	Partly covered with respect to uncertainty and assigned values of end-user calibrators and their associated metrological traceability as the kind of information to be provided by the manufacturer, but the requirement to provide this information in the IFU is not addressed by this European standard.
20.4.1 (w)	4.6.2, 4.7.1, 4.9.1	Partly covered with respect to analytical performance requirements resulting from a calibration hierarchy, assigned values for end-user calibrators and their associated metrological traceability as the kind of information to be provided by the manufacturer, but the requirement to provide this information in the IFU is not addressed by this European standard.

WARNING 1 Presumption of conformity stays valid only as long as a reference to this European Standard is maintained in the list published in the Official Journal of the European Union. Users of this standard should consult frequently the latest list published in the Official Journal of the European Union.

WARNING 2 Other Union legislation may be applicable to the product(s) falling within the scope of this standard.

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Foreword

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

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

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

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

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

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

This second edition cancels and replaces the first edition (ISO 17511:2003), which has been technically revised. The main changes compared to the previous edition are as follows:

— incorporation of the special requirements for metrologically traceable calibration hierarchies for measurement of catalytic concentration of enzymes (previously covered in ISO 18153:2003);

— to clarify that final reported values on human samples shall be metrologically traceable to the highest order available reference, the title and scope were modified to include metrological traceability of values assigned to human samples;

— updated normative references to remove International Vocabulary of Basic and General Terms in Metrology, 2nd edition, ISO, Geneva (1993) and ISO Guide 35:1989, Certification of reference materials — General and statistical principles;

— revision of Clause 4 to clearly define requirements of a manufacturer of an in vitro diagnostic medical device in establishing and documenting metrological traceability of assigned values (for calibrators, trueness controls and human samples), while incorporating requirements previously addressed in Clauses 6, 7 and 8 (thus eliminating those sections);

— revision of Clause 5 to incorporate additional models of metrologically traceable calibration hierarchies, especially 5.3 for measurement of catalytic concentration of enzymes (where the measurand is defined by a primary RMP; previously addressed in ISO 18153:2003), and 5.6 for an overview of the concept of assigned values of materials for measurands with metrological traceability to international harmonisation protocols (addressed in detail in ISO 21151).

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

Introduction

In laboratory medicine, the objective of examining a measurand in a human sample is to produce laboratory results that will enable a clinician to assess the risk of a disease, or to diagnose and make treatment decisions for a medical condition. To be clinically useful, the results obtained from a given human sample examined by different laboratories or among different in vitro diagnostic medical devices (IVD MDs) within a single laboratory should be equivalent, regardless of the measurement procedure employed. Equivalent results allow uniform application of medical decision limits and reference intervals, which can reduce the risk of harm caused by medical decisions based on non-equivalent examination results. Equivalence of results among different IVD MDs for the same measurand is also important for the analysis of results in medical records for the purpose of supporting clinical decisions and for conducting epidemiological investigations.

Equivalent results for human samples for a measurand can be achieved by establishing metrological traceability of the values assigned to the calibrators for a measurement procedure (MP) to the highest available reference system component for the measurand. Metrological traceability describes the calibration hierarchy and the sequence of value assignments, demonstrating an unbroken linkage between the measurement result for a human sample up to the highest available reference system component in the calibration hierarchy. The point at which metrological traceability begins (i.e. the highest level of metrological traceability in the calibration hierarchy) depends on the availability of higher order reference measurement procedures (RMPs), reference materials (RMs) or harmonisation protocols for the stated measurand.

Limitations in implementing metrologically traceable calibrations occur when different IVD MDs intended for the same measurand do not measure the same or very closely related measurable quantities. Some measurands of medical interest may be well-defined elements or molecules. An increasing number of medical decisions depend on measurands that consist of complex and variable mixtures of chemical structures, molecular species and molecular complexes in varying proportions, e.g. glycoproteins with multiple isoforms, variant amino acid sequences, nucleic acid sequences, and other complex molecular forms. When the selectivity of an IVD MD is not fit-for-purpose, sample-specific influence quantities in human samples due to factors including disease, drugs or other pathological conditions may lead to erroneous values for the intended measured quantity. Even with metrological traceability to higher order reference system components, the selectivity of MPs at all levels in the calibration hierarchy for a given IVD MD can influence its ability to achieve results for human samples that are equivalent to the results obtained with other IVD MDs for the same measurand.

This document presents requirements for manufacturers of IVD MDs in documenting the calibration hierarchy for a measured quantity in human samples using a specified IVD MD. The document includes various model calibration hierarchies offering potential technical solutions for different kinds of measurands in establishing metrological traceability of assigned values for human samples, calibrators and trueness control materials. Use of this document as part of a broadly-based risk management program for manufacturers of IVD MDs is consistent with the requirements of ISO 14971 and is expected to assist in the reduction of the risk of harm to patients due to non-equivalence of results among different IVD MDs.

INTERNATIONAL STANDARD ISO 17511:2020

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

1 Scope

This document specifies technical requirements and documentation necessary to establish metrological traceability of values assigned to calibrators, trueness control materials and human samples for quantities measured by IVD MDs. The human samples are those intended to be measured, as specified for each IVD MD. Metrological traceability of values for quantities in human samples extends to the highest available reference system component, ideally to RMPs and certified reference materials (CRMs).

All parties having a role in any of the steps described in a calibration hierarchy for an IVD MD are subject to the requirements described. These parties include but are not limited to manufacturers (of IVD MDs), RMP developers (see ISO 15193), RM producers (see ISO 15194), and reference/calibration laboratories (see ISO 15195) supporting calibration hierarchies for IVD MDs.

NOTE 1 Producers of RMs intended for use in standardization or calibration of IVD MDs include commercial and non-commercial organizations producing RMs for use by many end-users of IVD MDs and/or calibration laboratories, or for use by a single end-user medical laboratory, as in the case of a measurement standard (calibrator) intended to be used exclusively for calibration of a laboratory-developed MP.

This document is applicable to:

a) all IVD MDs that provide measurement results in the form of numeric values, i.e. rational (ratio) and/or differential (interval) scales, and counting scales.

b) IVD MDs where the measurement result is reported as a qualitative value established with a ratio of two measurements (i.e. the signal from a specimen being tested and the signal from a RM with a specified concentration or activity at the cut-off), or a counting scale, with corresponding decision threshold(s). This also includes IVD MDs where results are categorized among ordinal categories based on pre-established quantitative intervals for a quantity.

c) RMs intended for use as trueness control materials for verification or assessment of calibration of IVD MDs, i.e. some commutable CRMs and some external quality assessment (EQA) materials (if so indicated in the RM's intended use statement).

d) IVD MD-specific calibrators and trueness control materials with assigned values, intended to be used together with a specified IVD MD.

e) IVD MDs as described in a) and b), where no end-user performed calibration is required (i.e. when the manufacturer performs a factory calibration of the IVD MD).

This document is not applicable to:

a) calibrators and trueness control materials for IVD MDs which, due to their formulation, are known to have zero amount of measurand;

b) control materials that are used only for internal quality control purposes in medical laboratories to assess the imprecision of an IVD MD, either its repeatability or reproducibility, and/or for assessing changes in IVD MD results compared to a previously established calibration condition;

c) control materials that are used only for internal quality control purposes in medical laboratories and which are supplied with intervals of suggested acceptable values that are not metrologically traceable to higher order reference system components;