INTERNATIONAL STANDARD

ISO 21151

First edition
2020-05

In vitro diagnostic medical devices — Requirements for international harmonisation protocols establishing metrological traceability of values assigned to calibrators and human samples

iTeh STANDARD PREVIEW
(standards.iteh.ai)

Dispositifs médicaux de diagnostic in vitro — Exigences relatives aux protocoles d'harmonisation internationaux établissant la traçabilité métrologique des valeurs affectées aux étalons et aux échantillons humains

ISO 21151:2020
https://standards.iteh.ai/catalog/standards/sist/6b49bca2-3d1a-4c5b-b3f0-e53d5ec5001e/iso-21151-2020

Reference number
ISO 21151:2020(E)

© ISO 2020

iTeh STANDARD PREVIEW
(standards.iteh.ai)
ISO 21151:2020
https://standards.iteh.ai/catalog/standards/sist/6b49bca2-3d1a-4c5b-b3f0-e53d5ec5001e/iso-21151-2020

COPYRIGHT PROTECTED DOCUMENT

© ISO 2020

All rights reserved. Unless otherwise specified, or required in the context of its implementation, no part of this publication may be reproduced or utilized otherwise in any form or by any means, electronic or mechanical, including photocopying, or posting on the internet or an intranet, without prior written permission. Permission can be requested from either ISO at the address below or ISO's member body in the country of the requester.

ISO copyright office
CP 401 • Ch. de Blandonnet 8
CH-1214 Vernier, Geneva
Phone: +41 22 749 01 11
Fax: +41 22 749 09 47
Email: copyright@iso.org
Website: www.iso.org

Published in Switzerland

© ISO 2020 – All rights reserved

Contents

Page

iTeh STANDARD PREVIEW
(standards.iteh.ai)
ISO 21151:2020
https://standards.iteh.ai/catalog/standards/sist/6b49bea2-3d1a-4c5b-b3f0-e53d5ec5001e/iso-21151-2020

© ISO 2020 – All rights reserved

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.

iTeh STANDARD PREVIEW
(standards.iteh.ai)

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

ISO 21151:2020
https://standards.iteh.ai/catalog/standards/sist/6b49bca2-3d1a-4c5b-b3f0-e52b5ea1801e/iso-21151-2020

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.

© ISO 2020 – All rights reserved

Introduction

Results for a measurand in a human sample should be numerically equivalent, within clinically meaningful limits, among different laboratories using different in vitro diagnostic (IVD) medical devices (MDs). Clinical practice guidelines for diagnosis and treatment decisions that use fixed decision limits for interpreting laboratory results can only be appropriately applied when results are equivalent irrespective of the IVD MD used. Laboratory medicine has adopted the principle of metrological traceability of IVD MD calibration to higher order references as the basis to achieve equivalent results for the same measurand that are independent of the IVD MD, location or time the measurements were made.

ISO 17511:2020, describes 6 calibration hierarchies of reference measurement systems (referred to as cases in 5.2 to 5.7 of ISO 17511:2020) that fulfil the requirement for metrological traceability of a calibration to higher order references. Metrological traceability of calibrator assigned values for particular IVD MDs for measurands in cases 5.2, 5.3 and 5.4 are based on the availability of a reference measurement procedure. Case 5.5 includes measurands for which a certified reference material or an international conventional calibrator with a consensus-based protocol for value assignment is available but there is no reference measurement procedure. Cases 5.6 and 5.7 include measurands for which neither a reference measurement procedure nor a certified reference material or international conventional calibrator is available. Case 5.6 achieves standardization based on a consensus harmonisation protocol. The requirements for such a harmonisation protocol are described in this document. Case 5.7 includes measurands that are not addressed by traceability schemes in the preceding categories. For such measurands, metrological traceability is to the calibrator chosen by the manufacturer of an IVD MD but there is no traceability to a common reference. In case 6 the results from different IVD MDs can be different and not comparable to each other or to decision limits used in guidelines for making medical decisions.

iTeh STANDARD PREVIEW
(standards.iteh.ai)

Higher order references for measurands in case 5.6 have been technically difficult to develop thus requiring an approach for standardization based on a protocol for achieving equivalence of results among two or more IVD MDs. Research to develop suitable processes for harmonisation of case 5.6 measurands forms the basis for the requirements in this document[5][11]. Standardization of results based on a harmonisation protocol provides metrological traceability of particular IVD MD calibrators to that protocol. A harmonisation protocol is developed and administered by an international body to achieve equivalence among results for different IVD MDs thus meeting requirements for use of the results in medical decisions.

ISO 21151:2020

Annex A provides a worked example to illustrate the principles of a harmonisation protocol and one possible approach to implementing a harmonisation protocol. Other approaches are also possible and will likely be developed for particular measurands and IVD MDs.

© ISO 2020 – All rights reserved

iTeh STANDARD PREVIEW
(standards.iteh.ai)

ISO 21151:2020
https://standards.iteh.ai/catalog/standards/sist/6b49bca2-3d1a-4c5b-b3f0-e53d5ec5001e/iso-21151-2020

In vitro diagnostic medical devices — Requirements for international harmonisation protocols establishing metrological traceability of values assigned to calibrators and human samples

1 Scope

This document specifies requirements for a protocol implemented by an international body to achieve equivalent results among two or more IVD MDs for the same measurand for cases where there are no reference measurement procedures and no fit-for-purpose certified reference materials or international conventional calibrators. In this case, the harmonisation protocol defines the highest level of metrological traceability for the stated measurand.

This document can be applied in cases when certified reference materials or international conventional calibrators exist but are not fit-for-purpose because, for example, they are not commutable with human samples.

NOTE This document addresses one case of traceability of assigned and measured values described in 5.6 in ISO 17511:2020.

iTeh STANDARD PREVIEW

2 Normative references

(standards.iteh.ai)

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

ISO 21151:2020
https://standards.iteh.ai/catalog/standards/sist/6b49bca2-3d1a-4e5b-b3f0-e33d5ec3001e/iso-21151-2020

ISO 17511:2020, *in vitro diagnostic medical devices — Requirements for establishing metrological traceability of values assigned to calibrators, trueness control materials and human samples*

3 Terms and definitions

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

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

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

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

3.1
aliquot
known amount of a homogeneous material, assumed to be taken with negligible sampling error

[SOURCE: ISO 11074:2015]

3.2
calibration verification control
control provided by a manufacturer for use with a stated IVD MD to confirm that a satisfactory calibration was achieved using the end-user calibrator(s) intended for use with that IVD MD

© ISO 2020 – All rights reserved

3.3
harmonisation
harmonised
achievement of equivalent measured quantity values (within clinically meaningful limits) for human samples examined for a stated measurand among two or more IVD MDs by applying an international consensus protocol in their calibration hierarchies when fit-for-purpose higher order reference materials or reference measurement procedures are not available

Note 1 to entry: Harmonisation is one of the calibration hierarchy models described in ISO 17511:2020 to achieve metrologically traceable quantity values for human samples.

Note 2 to entry: Harmonisation is a special case of non-SI traceable standardization where the calibration of two or more IVD MDs is traceable to an international harmonisation protocol that defines the highest level of metrological traceability for the stated measurand, but with no traceability to SI.

Note 3 to entry: Harmonised is the condition in which harmonisation (equivalence among quantity values) is achieved among two or more IVD MDs.

3.4
harmonisation reference material
reference material used as a calibrator for an international *harmonisation* (3.3) protocol

Note 1 to entry: Specifications for these materials are included in the harmonisation protocol.

3.5
international harmonisation protocol
harmonisation protocol
iTeh STANDARD PREVIEW
(standards.iteh.ai)
standardization process implemented by an international body to achieve equivalence among measured quantity values for two or more IVD MDs intended for examination of the same measurand for cases where there are no higher order reference measurement procedures and no fit-for-purpose certified reference materials or international conventional calibrators
ISO 21151:2020
https://standards.iteh.ai/catalog/standards/sist/6b49bca2-3d1a-4c5b-b3f0-e53d5ce3001e/iso-21151-2020

Note 1 to entry: A harmonisation protocol can be used to achieve standardization of measured values for a stated measurand when there are no other higher order reference system components that are suitable for use.

Note 2 to entry: A harmonisation protocol defines the highest level of metrological traceability for the stated measurand.

3.6
standardization
standardized
achievement of equivalent measured quantity values (within clinically meaningful limits) for human samples examined for a stated measurand among two or more IVD MDs, where each “standardized” IVD MD is calibrated according to a defined hierarchy of relationships to higher order references (materials and/or measurement procedures)

Note 1 to entry: Standardization of an IVD MD is achieved preferably by implementation of a calibration system that is traceable to higher order references, ideally with traceability to SI.

Note 2 to entry: Not all standardization approaches result in traceability of final measured values to SI but may be the best available means for achieving equivalent results for human samples among different IVD MDs. Such standardization approaches should be replaced when an approach becomes available that provides traceability to SI.

Note 3 to entry: Standardized is the condition in which standardization of results for human samples is achieved among two or more IVD MDs.

© ISO 2020 – All rights reserved

4 Abbreviated terms and symbols

CV coefficient of variation

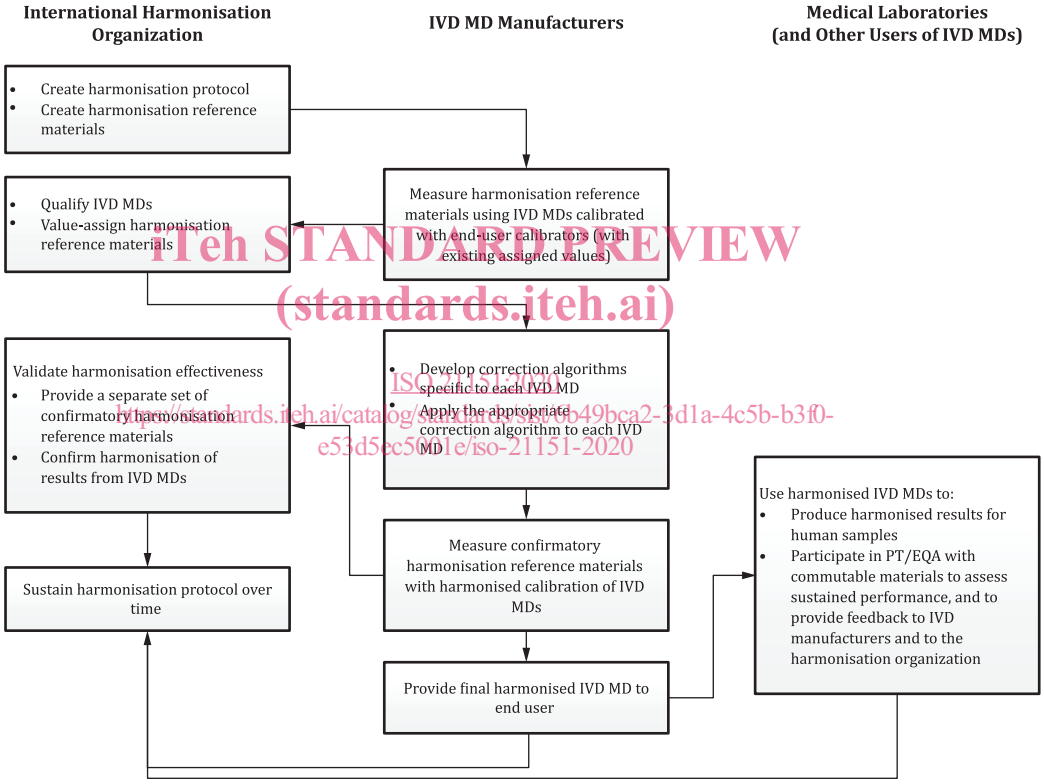
IVD in vitro diagnostic

MD medical device

SI *Système international.*

5 Requirements for a harmonisation protocol

Figure 1 shows a flowchart for the main steps in a harmonisation protocol as described in this document. Subsequent subclauses provide the detailed requirements and considerations to implement a harmonisation protocol. Development and implementation of a harmonisation protocol is a collaboration among one or more harmonisation organizations, IVD MD manufacturers and regulatory bodies.



iTeh STANDARD PREVIEW
(standards.iteh.ai)
ISO 21151:2020
https://standards.iteh.ai/catalog/standards/sist/b49bca2-3d1a-4c5b-b3f0-e53d5ec5041e/iso-21151-2020

Figure 1 — Flowchart for steps in a harmonisation protocol

5.1 Description of the measurand

The measurand shall be defined as described in 4.2 of ISO 17511:2020.

5.2 Specifications for agreement among results from different IVD MDs

5.2.1 Specifications for agreement among results from different IVD MDs shall a priori be defined based on medical usefulness of decisions based on those results.

5.2.2 Specifications for agreement shall be defined at different amounts of the measurand when applicable.

© ISO 2020 – All rights reserved

NOTE The specifications set the criteria for a decision whether the harmonisation protocol achieves equivalent results[12][13].

5.3 Inclusion or exclusion of IVD MDs

5.3.1 Criteria for inclusion or exclusion of IVD MDs in the harmonisation protocol shall be stated.

5.3.2 Criteria shall specify the following performance characteristics: precision; proportional recovery of the measurand in a set of samples with known proportions of measurand present over the measuring interval; selectivity for the measurand, for example demonstrated as proportional and linear relationships for measured values from different IVD MDs for a panel of individual human samples that cover a substantial portion of the measuring interval; and other relevant performance characteristics as applicable.

5.3.2.1 Criteria should consider how results from an IVD MD influence a medical decision.

5.3.2.2 The decision to reject an IVD MD due to apparent poor selectivity should be carefully considered. An IVD MD that appears to generate outliers when compared to results from other IVD MDs purporting to measure the same measurand can have superior effectiveness in medical decisions. In such cases the definition of the measurand and the quantity actually measured should be re-considered.

5.3.2.3 The analytical performance of some IVD MDs may be inadequate and can require corrective action before inclusion in a harmonisation protocol. For example, the selectivity or imprecision of an IVD MD could need improvement before an IVD MD can be included in a harmonisation protocol.

iTeh STANDARD PREVIEW
(standards.iteh.ai)

5.4 Harmonisation reference materials required for a harmonisation protocol

ISO 21151:2020
https://standards.iteh.ai/catalog/standards/sist/40b...e53d5ec5001e/iso-21151-2020

5.4.1 Materials required for a harmonisation protocol and its sustainability shall be specified.

5.4.1.1 These materials can be a panel of human samples with limited shelf life and limited amount of material. The materials can be available only for a limited time period for performing the harmonisation protocol.

5.4.1.2 Other types of materials can include: pools of human samples, human samples or pools supplemented with the measurand, or other preparations containing the measurand that do not fulfil the requirements for a certified reference material or an international conventional calibrator. When such materials are used, they should be as similar as possible (matrix-matched) to the types of samples intended to be measured by end-user IVD MDs. (See 5.4.9 regarding commutability requirements for harmonisation reference materials).

5.4.2 The number and quantity values of the harmonisation reference materials shall be appropriate for the measuring intervals of the IVD MDs as needed for implementation of the harmonisation protocol.

5.4.3 Preparation of the materials shall be described with sufficient detail that replacement batches with similar characteristics can be prepared.

5.4.4 When human samples or materials derived from human samples are used, the description shall provide characteristics and criteria used for selecting the human samples. Such characteristics and criteria shall consider the population from which the donors are selected, health or disease conditions and requirements for sample collection that the donors shall fulfil.

5.4.5 Procedures for collection, processing, storage and transportation of materials used in a harmonisation protocol shall be described.

 © ISO 2020 – All rights reserved

5.4.6 The source and purity of any added components (e.g. measurand, substance similar to the measurand, stabilizers) shall be stated.

5.4.7 Stability characteristics shall be established and ensured over the intended use period for the materials. The influence of any stabilization and storage procedure(s) shall be validated to be suitable for the intended use.

NOTE 1 Freezing and thawing can alter the quantity or matrix from that in the human samples intended to be measured.

NOTE 2 Stability of harmonisation reference materials during transport and storage at the user location is also to be considered.

5.4.8 The procedures used to prepare the materials and their aliquots shall be designed to ensure a high probability of homogeneity. A statement regarding procedures to ensure homogeneity among aliquots of the materials shall be provided.

NOTE Homogeneity validation by sampling aliquots may not be practical for materials such as aliquots of individual human samples because of the limited amounts available. The procedures used to prepare the materials and their aliquots can be designed to ensure a high probability of homogeneity, for example by mixing a bulk quantity of serum during the aliquoting process.

5.4.9 A statement regarding the commutability of the materials with human samples shall be provided. Commutability assessment shall be performed when applicable[14].

iTeh STANDARD PREVIEW
(standards.iteh.ai)

5.4.9.1 Commutability validation may not be required when, for example, a panel of individual human samples is used. However, the potential influence of any stabilization procedure on commutability should be considered. The possibility of sample specific influences, for example from interfering substances, should be considered because such influences can affect the suitability of one or more of the individual human samples as harmonisation reference materials. Criteria should be included for exclusion of results from such individual human samples.

ISO 21151:2020
https://standards.iteh.ai/catalog/standards/sist/6b496ca2-3d1a-4c36-b510-e53d5ec5001e/iso-21151-2020

5.4.9.2 Commutability validation may be performed for a different batch of materials when limited quantities are available and commutability of a subsequent batch can be assumed to be acceptable. This assumption implies appropriate control of the production process to ensure consistency with specifications for the batch for which commutability was validated. Various characteristics of materials can be different for different batches or can become altered during material storage, thus representing conditions when reassessment of commutability can be applicable.

5.4.9.3 Commutability shall be validated when additives are used for stabilization or to supplement the quantity value (e.g. concentration) of the measurand or when a preparation process such as pooling human samples is used.

NOTE Additives or pooling can alter the matrix from that expected for human samples of the type intended to be measured.

5.4.9.4 Commutability shall be validated when harmonisation reference materials other than human samples are used.

© ISO 2020 – All rights reserved