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

*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

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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.

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

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.

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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.

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.

[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.

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.

2 Normative references

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

ISO 17511:2020, *in vitro diagnostic medical devices — Requirements for establishing metrological traceability of values assigned to calibrators, trueness control materials and human samples* 1151-2020

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

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

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

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.

4 Abbreviated terms and symbols

CV	coefficient of variation
IVD	in vitro diagnostic
MD	medical device
SI	<i>Système international.</i>

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.

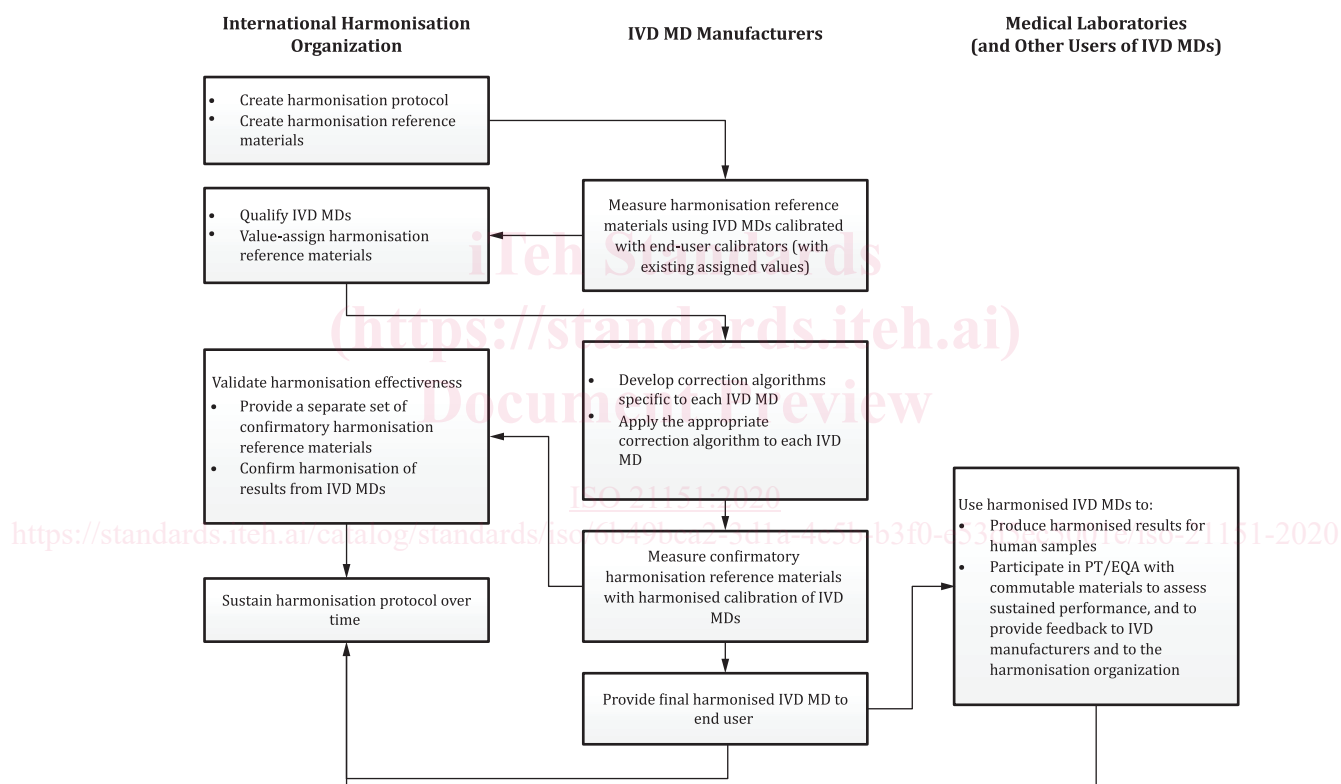


Figure 1 — Flowchart for steps in a harmonisation protocol

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.

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.

5.4 Harmonisation reference materials required for a harmonisation protocol

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.