Harmonization as a method for standardization in Laboratory Medicine

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Harmonization is the “achievement of equivalent measured quantity values (within clinically meaningful limits) for human samples examined for a stated measurand among two or more in-vitro diagnostic measurement devices 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” (1).

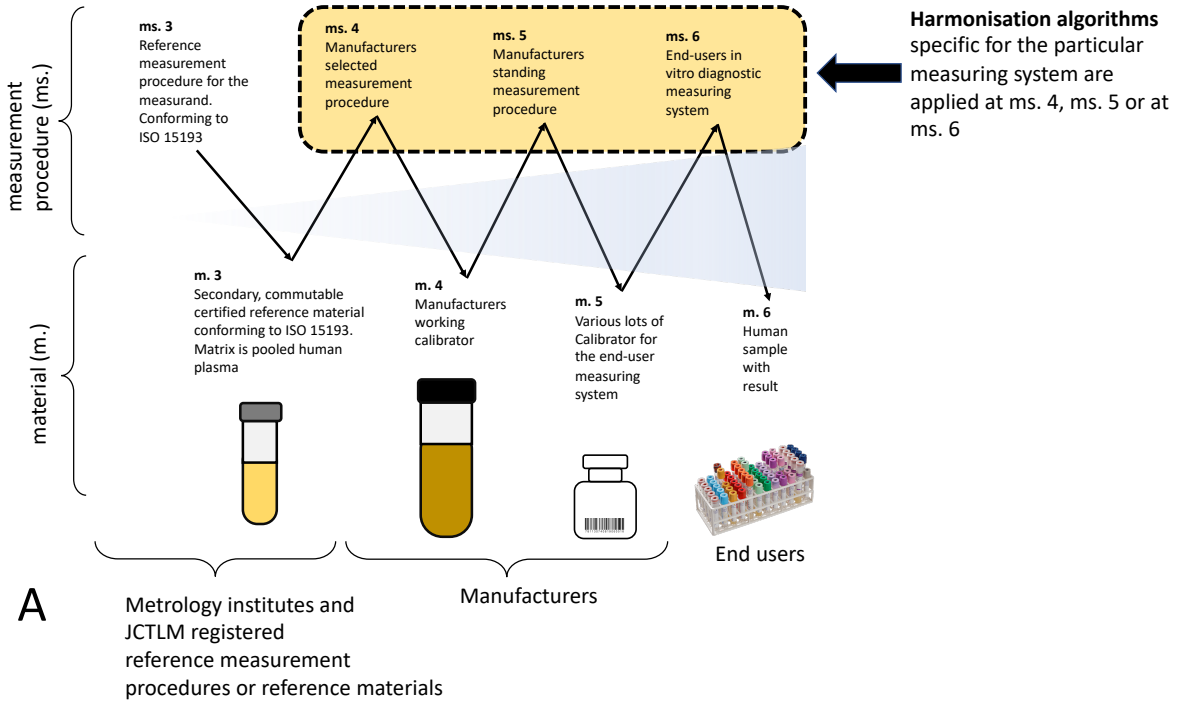
There is no need for harmonization when the different measuring systems provide equivalent results. The reference can be a definition of a SI unit, a certified value of reference material, a result of a reference measuring system, a value assigned to international conventional reference material, or values assigned to global harmonization reference materials.

Harmonization is needed when appropriate references are not available, or matrix effects leading to lack of traceability are found in traceability hierarchies where a proper reference is available.

Optimal *experimental design* dictates that all known controllable confounding factors influencing the results should be controlled. The possible effects of all remaining confounding factors are neutralized by proper randomization. Metrological standardization represents an obvious parallel to good experimental design where all known controllable confounding factors are controlled for optimal traceability hierarchy. Harmonization is a direct parallel to randomization in classical experimental design when confounding factors, including matrix effects, contribute to a lack of

traceability. Harmonization uses a substantial number of native samples from healthy and sick people to ensure that the effects of confounding factors are distributed evenly – randomized – amongst the measuring systems/methods whose traceability hierarchies are being harmonized (1).

Matrix effects are the remaining "dark horses" in the traceability hierarchy when all known effects have been elucidated and controlled for (2, 3). Like an optimal experimental design, all possible influencing factors that can be controlled need to be controlled to eliminate known systematic effects. When that is done, the potential effects of all remaining unknown confounders need to be randomized to make them influence equally the different facets of the experimental setup. It is similarly crucial that commutable reference materials are used in all relevant steps of the traceability hierarchy. Any non-commutable reference material risks introducing bias, thereby increasing measurement uncertainty and diagnostic uncertainty.



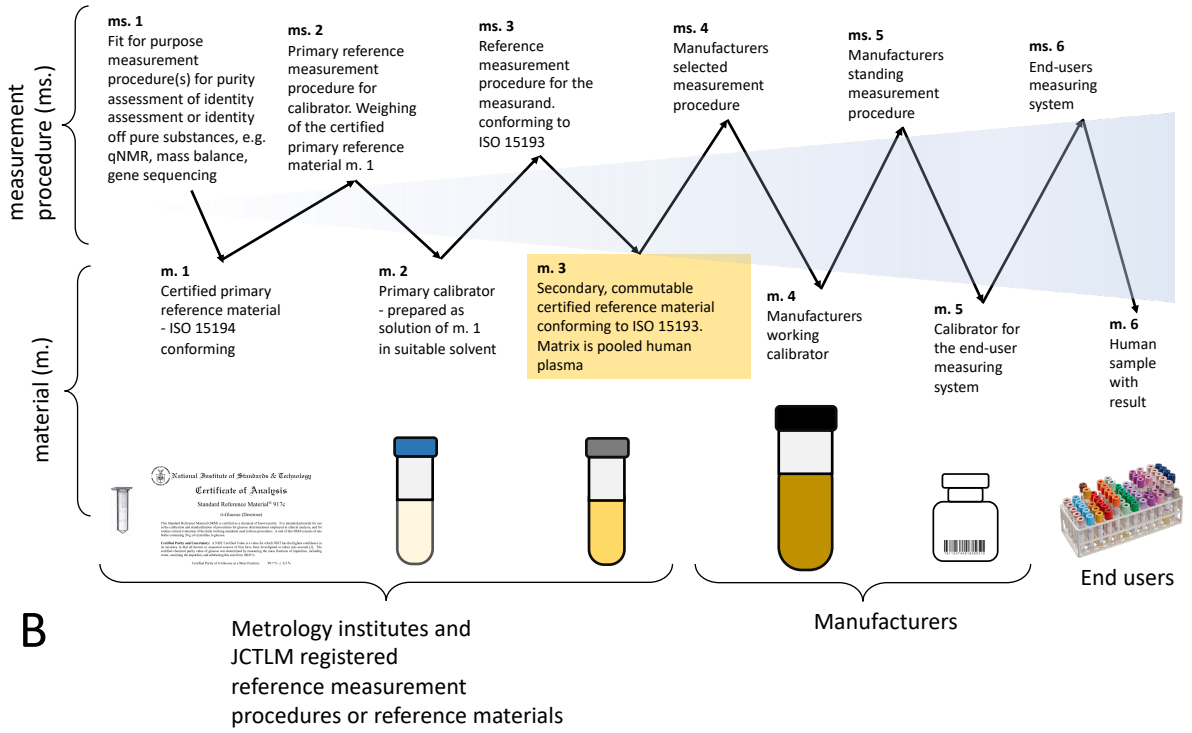


Figure 13: A. In the absence of a proper reference, a harmonization is needed for measuring systems/procedures from different manufacturers to give equivalent results when measuring patient samples.
B. When a pooled human plasma is introduced in stage m.3 of the traceability hierarchy, there may be a risk of matrix effects that may need to be randomized by harmonization.

Classic harmonization (1) (Figure 13 A) is needed when a proper reference is unavailable. Harmonization due to matrix effects is required when the intended sample matrix is introduced in the traceability hierarchy (Figure 13 B). There is an evident risk of matrix effects that cannot be controlled and may vary between samples from different persons in health and disease.

Improvements in measurement quality in Laboratory Medicine

Medical Laboratories have become accustomed to steady improvements in repeatability imprecision and improvements of detection limits for measuring systems. The most significant performance improvements are improved selectivity due to fundamental advances in the physicochemical methods used for measuring the measurand, e.g., when changing from colorimetric- to enzymatic procedures or from immunochemical methods isotope- dilution mass spectrometry. Even though improved selectivity can be obtained, practical fitness matters for the intended use can be reached. Such as turnaround time and cost may mean that less costly, faster, and more miniaturized measuring systems are chosen over more selective ones.

When a compromise is reached between selectivity, sensitivity cost, turnaround time, and ability to miniaturize, it is crucial to achieving an optimum standardization for the available combination of all possible influence factors. The fewer steps there are in the traceability hierarchy from the highest reference material to the end-user calibrator, the more limited the effect on the overall uncertainty there is from the traceability hierarchy.

There are seven base quantities in the current SI system, the "amount of substance" being the most used unit in Laboratory Medicine. This unit is used to express measurements of thousands of molecules occurring naturally in the human organism, microbes, pharmaceuticals, and chemicals in the environment. The field of Laboratory Medicine is enormous regarding the number of commonly used measurands (about 700 in common University Hospitals) and the number of samples processed every day.

The well-established standardization system through national metrology institutes has served physical metrology so well for more than 100 years. This system can hardly be expected to establish the competency, measuring systems, and reference materials for all conceivable measurands in Laboratory Medicine because only a minority of the measurands in Laboratory Medicine are traceable to SI due to the substantial matrix effects frequently influencing measurement results in calibrators and patient samples. Patient samples are crucial for harmonization efforts, and patient samples are primarily available in healthcare organizations. Harmonization using natural patient samples has the potential to create a paradigm shift in the traceability and measurement uncertainty in Laboratory Medicine. This will be followed by much slower, focused, and deliberate improvements in selectivity and the study of the medical diagnostic properties of methods in Laboratory Medicine.

The availability and use of big data from healthcare organizations for quality control is also a promising tool for controlling the equivalence of measurement results locally and globally (4-9). Such patient-sample and patient data-dependent techniques are only available in Medical Laboratories.

The International Consortium for Harmonization of Clinical Laboratory Results

Global standardization using a harmonization protocol requires extensive engagement and collaboration between manufacturers of in vitro diagnostic measuring systems and reagents, metrology institutes, regulatory agencies, standardization- and guidelines organizations, professional organizations, and healthcare organizations to function fully. Therefore, the availability of an international organization mandated by regulatory authorities to coordinate projects to facilitate the equivalence of measurement results of all such methods, including in these challenges, is in demand.

Such an organization currently does not exist. An international consortium likely to remain a cornerstone in this process is *The International Consortium for Harmonization of Clinical Laboratory Results*, ICHCLR, (https://www.harmonization.net) with its secretariat at the International Federation of Clinical Chemistry and Laboratory Medicine (IFCC) (10). The Consortium maintains a list of measurands that may prioritize harmonization projects, provides information on active harmonization projects being conducted by organizations with a global reach, facilitates coordination and avoidance of duplication of efforts, and provides information on resources available for harmonization and standardization projects. In addition, the consortium promotes administrative and regulatory advances to support harmonization for measurands in Laboratory Medicine.

A council governs the ICHCLR. The current (2021-02-04) council members are The American Association for Clinical Chemistry, The College of American Pathologists, The International Federation of Clinical Chemistry and Laboratory Medicine, The Japanese Committee for Clinical Laboratory Standards, and The Korean Society for Laboratory Medicine.

A database of standardization including harmonization status for measurands including both harmonization and classical standardization protocols for standardization can be reached at https://www.harmonization.net/measurands/. It currently (2021-02-04) includes 131 entries. Notably, the database also evaluates the medical impact of harmonization and the harmonization status.

The ICHCLR has published a "Toolbox of technical procedures to be considered when developing a process to achieve harmonization for a measurand" available (2021-02-05) at https://www.harmonization.net/media/1004/tool_box_2013.pdf . A very substantial part of this toolbox has become the seed to an even more comprehensive ISO standard 21151:2020.

A *Council* is responsible for governance and administrative oversight of the ICHCLR. It consists of international organizations that contribute financially to the program's administration. A Harmonization Oversight Group (HOG) manages the harmonization activities of the consortium; the Council appoints its members. The HOG maintains communication with the Stakeholder Members and other international groups who are active in harmonizing or standardizing results in Laboratory Medicine. The HOG reviews measurand submissions for prioritization based on medical importance and technical feasibility for harmonization and cooperates with other organizations to coordinate harmonization activities and avoid duplication of effort. The HOG maintains a website to inform stakeholders of the status of harmonization or standardization

activities being managed by organizations worldwide. The stakeholder members support the harmonization of clinical laboratory results and support the ICHCLR by proposing measurands in need of harmonization provide feedback on the direction and activities of the ICHCLR. Stakeholder members receive all updates and reports on efforts by the ICHCLR for the international promotion of the importance of and approaches for harmonization. Interested individuals and groups can apply for funding for harmonization projects.

The current role of ICHCLR or a corresponding international body needs to be formally and more widely recognized and supported, enabling it to shoulder the responsibility it needs to apply the application of the ISO-17511:2020 (11) and ISO-21151:2020 standards. Standardization with traceability to SI units is ideal, but when not possible, harmonization has the potential of substantially improving the equivalence of measurement results in Laboratory Medicine.

The standard *ISO-21151:2020* - In vitro diagnostic medical devices – Requirements for international harmonization protocols establishing metrological traceability of values assigned to calibrators and human samples details requirements for protocols implemented by an international body to achieve equivalent results among two or more in-vitro measuring systems for the same measurand when there is no available reference measuring systems, no certified reference materials nor international conventional calibrators. When applied according to this standard, the harmonization protocol defines an acceptable level of the calibration hierarchy of the metrological traceability for a particular measurand. The standard can also be used when certified reference materials or international conventional calibrators exist but are not fit for the intended use, e.g., because they are not commutable with human samples.

The harmonization protocol can also be used if the equivalence of measurement results is not obtained for heterogeneous measurands.

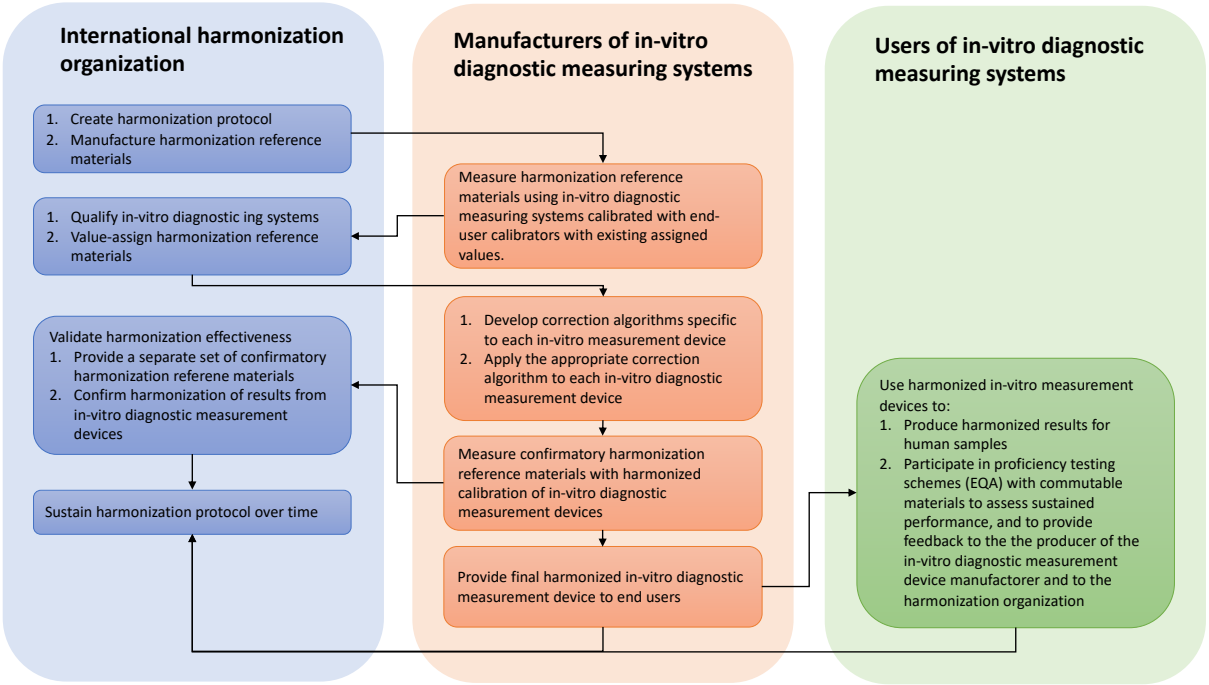


Figure 14: The roles of an international harmonization organization, manufacturers, and users of in-vitro diagnostic measuring systems in establishing and maintaining standardization through harmonization protocols when necessary.

Harmonization protocols

The agreed harmonization protocol must state the criteria for inclusion or exclusion of the measuring systems in the specific harmonization efforts.

The criteria must specify the following performance characteristics:

1. The repeatability imprecisions of the included measuring systems
2. The proportional recovery of the measurand is a set of samples with known proportions of the measurand present in the measuring interval.
3. Selectivity for the measurand, for example, demonstrated as proportional and linear relationships for measured values from different in-vitro diagnostic measuring systems for a panel of individual human samples that cover a substantial portion of the measuring interval and other relevant performance characteristics as applicable.
4. How results from the measuring systems influence medical decisions

A possible decision to reject a measuring system on the grounds of apparent poor selectivity should be carefully considered since a measuring system that appears to result in outliers compared to results from other in-vitro diagnostic measuring systems claiming to measure the same measurand may have superior diagnostic performance in medical decisions. In such cases, the definition of the measurand and the quantity measured as a reflection of the “analyte” should be re-considered

The analytical performance of some measuring systems may be inadequate and can require corrective action before inclusion in a harmonization protocol. For example, the selectivity or imprecision of a measuring system could need improvements before it can be included.

Harmonization reference materials

The harmonization reference materials can be a panel of human samples with limited shelf life and a limited amount of material. Due to limited shelf-life and limited supply, the materials are likely to be available only for a limited time as a foundation for the original harmonization protocol. Other materials can include pools of human samples, individual human samples or collections of human samples supplemented with the measurand, or other preparations containing the measurand that do not fulfill the requirements for certified reference material or of an international conventional calibrator. When such materials are used, they should be as similar (matrix-matched) to the types of samples intended to be measured by end-user measuring systems.

The number and quantity values of the harmonization reference materials must be appropriate for the measuring intervals of the measuring systems used, as needed to implement the harmonization protocol. The preparation of the harmonization reference materials must be described in sufficient detail so that replacement batches with similar characteristics can be prepared.

Criteria for selecting the human samples for harmonization protocols

When human samples or materials derived from human samples are used, the description must provide characteristics and criteria used for selecting the human samples.

Such characteristics and criteria must detail

1. The population from which the donors are selected
2. Health or disease conditions of the donors
3. Requirements for sample collection that the donors must fulfill
4. Procedures for collection, processing, storage, and transportation of materials used for producing the harmonization reference material
5. The source and purity of any added components (for example, measurand, a substance similar to the measurand, stabilizers)

Changes in temperature, including freezing and thawing, commonly influence the quantity measured when examining the measurand of interest. Therefore, stability characteristics must be established and ensured over the intended time of use for the

materials. The influence of any stabilization and storage procedure(s) must be validated to be suitable for the intended use.

The procedures used to prepare the harmonization reference materials and their aliquots must be designed to maximize the probability of *homogeneity*. A statement regarding procedures, for example, *mixing* or *filtration* to ensure homogeneity among aliquots of the harmonization reference materials, must be provided.

A statement regarding the *commutability* (12-15) of the harmonization reference materials with corresponding natural human samples must be provided, and a commutability assessment should have been performed (12). Validation of commutability may not be required when a panel of individual human samples is used since they are by definition commutable. However, the potential influence of any stabilization procedure on commutability must be evaluated. The possibility of sample-specific influences, such as interfering substances, should be considered because such influences can affect the suitability of one or more individual human samples as harmonization reference materials. Criteria should be defined to exclude results from such individual human samples. The use of additives and pooling of samples for harmonization reference materials risk altering the matrix of the materials and influence their suitability in harmonization protocols used in standardization. Commutability must therefore be verified when additives are used for stabilization or to supplement the quantity value (for example, concentration) of the measurand or when a preparation process such as pooling human samples is used.

Commutability validation may be performed for a different batch of international harmonization reference materials when limited quantities of the materials are available, and commutability of a subsequent batch can be assumed to be acceptable, e.g., for single-donor samples.

Commutability must also be verified when harmonizing reference materials other than human samples.

Measuring the quantity values of harmonization reference materials by participants in a harmonization calibration hierarchy

The procedure for handling samples and measuring the quantity values in the samples of the materials used in the harmonization protocol must be detailed, including storage and pre-analytical processing. The experimental designs and templates calculating repeatability and reproducibility components of variation must be documented and provided.

A possible inability of a specific in-vitro measuring system to reach agreed criteria may constitute a reasonable cause for its exclusion from the harmonization process.

Procedure for assigning a single quantity value to the harmonization reference materials used in a harmonization protocol.

The harmonization process aims to achieve equivalence of results for patient samples from two or more end-user in-vitro diagnostic measuring systems. Procedures, including statistical and mathematical algorithms used for assigning quantity values to the materials used in a harmonization protocol, must be described, including the scientific rationale for finding them fit for the intended use.

Each intended measuring system must already have a completed *conventional calibration hierarchy*. The harmonization protocol describes the general approach for modifying the calibration hierarchy for in-vitro measuring systems that will be used to assign quantity values to patient samples to make them equivalent to the quantity values from other measuring systems in the harmonization protocol.

Each manufacturer engaged in the harmonization scheme applies the specific details of the developed harmonization to modify the calibration hierarchy as appropriate for their manufacturing process. This means that harmonization algorithms may differ amongst manufacturers.

The following approaches can be considered to apply the harmonization algorithm for assigning results to human samples to achieve harmonized results:

1. A calibration correction based on the harmonization algorithm can be applied to the current results by measuring systems with no change to the values assigned to the existing end-user calibrators. This correction will add a step in the calibration hierarchy between the end-user calibrator and the value assigned to the human sample.
2. According to the harmonization algorithm, a manufacturer can reassign the value(s) of their end-user calibrator(s). This reassignment will add a step in the calibration hierarchy between the standing measurement procedure and the end-user calibrator(s).
3. A manufacturer can reassign the value(s) of their working calibrator(s) according to the calibration algorithm that will then be propagated to new values assigned to the end-user calibrators. This reassignment adds a step in the calibration hierarchy between the selected measurement procedure and the working calibrator(s).
4. The assignment of measurement uncertainty to the working calibrator must be re-calculated as described in ISO-21151:2020. The added uncertainty caused by the

harmonization process must be included when determining the combined standard uncertainty of the end-user calibrators.

5. The end-user documentation published by the manufacturer must detail the approach taken to achieve harmonization of human sample results.
6. The approach used to assign quantity values to human samples shall be transparent to the end-user and be an automated component of the end-user calibration process for the in-vitro diagnostic measuring systems.

Assigning quantity values to control samples = calibration verification controls

Control samples serving as calibration verification should be included in the measuring systems, enabling the end-user to control the calibration. The same procedure used for assigning harmonized values to end-user calibrators can be used to assign values to end-user samples for internal quality control and samples for proficiency testing.

The effectiveness of the harmonization protocol to achieve equivalent results among different measuring systems must be validated based on results from individual human samples or other commutable samples.

Samples used for validation that equivalent results were achieved among different measuring systems must be other than those used as harmonization reference

materials.

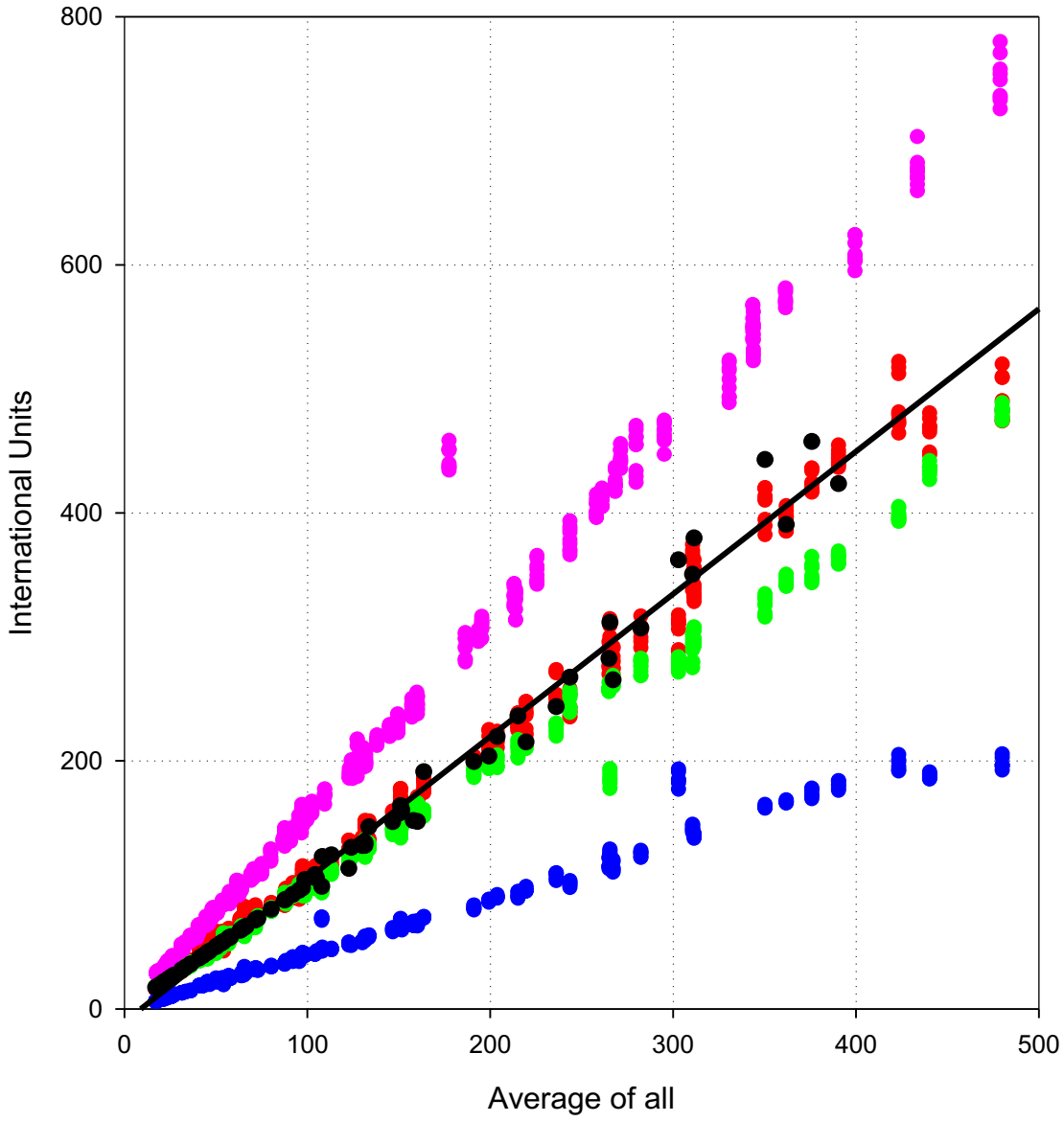


Figure 15: The measurements of 80 natural patient samples with four different measuring systems (color blue, green, red, and magenta) calibrated with the same international conventional reference material. After removing outliers and Deming regression analysis, the 80 samples were allocated. Data from ISO 21151:2020 (1). (https://standards.iso.org/iso/21151/ed-1/en/)

Traceability uncertainty caused by the harmonization protocol

ISO 21151:2020 and, in particular, its published (https://standards.iso.org/iso/21151/ed-1/en/) calculation example discusses and shows the measurement uncertainty calculation due to the harmonization protocol.

Deming regression is used to calculate re-calibration functions y=a*x + b (where a is the slope and b is the intercept on the y-axis) for each measuring system A-D for use in the individual measurement equations the measuring systems which calculate a harmonized measurement result for each measuring systems actual result when calibrated using, e.g., international conventional reference materials. The harmonized measurement result is shown in black in Figure 15. Harmonized end-user reference materials are allocated values

The harmonization uncertainty is not calculated using the results from the 80 original harmonization reference samples but from 40 additional single donor samples handled in the same way.

1. The average values (*harmonization reference material values*) assigned to the 40 reference materials are estimated in the same process as when the 80 initial reference materials were subjected to the harmonization procedure.
2. Each measuring system is harmonized using the 80 initial harmonization samples and a measuring equation established for each measuring system.
3. The average values of triplicate measurements of each of the 40 test materials are measured by each of the four measuring systems and plotted on the Y-axis with the average values on the X-axis.
4. The percent difference between the average value of the concentrations of the 40 test materials and the harmonization reference material values are calculated for each measuring system.
5. The standard deviations of the percentage differences are calculated

After the harmonization equations have been established

The underlying assumptions are that:

- the variability is proportional to concentration, and thus the relative uncertainty is constant over the measuring interval of each measuring system
- The harmonization process effectively provides a proportional adjustment resulting in a zero intercept. Any remaining bias after adjustment plays no role in the uncertainty estimation if the remaining bias meets the harmonization protocol requirements.

Under these assumptions, the standard error of the bias for a measuring system uses the distribution of sample % difference results (mean of three replicates per sample) to determine the standard uncertainty of the harmonization step for that measuring system.

Sustainability of the harmonization protocol

The detailed practical plans for *sustaining harmonization over time* must be described in sufficient detail that a competent organization can implement the strategies.

A commitment is essential from one or more organizations to provide surveillance of harmonization for a particular measurand for years and decades. A formal commitment from at least one organization must be secured for sustaining the resources needed. Preparation and qualification of replacement batches of materials used for harmonization must be described.

The type of samples used for sustainability can differ from the type of samples used for the original harmonization process. However, the metrological traceability to the original harmonization protocol must also be specified. Guidance for estimating the uncertainty of values assigned to replacement batches of harmonization materials must be provided. We must consider the combined uncertainty of the processes to ensure consistency from batch to batch.

Recommendations must be provided for surveillance that harmonization has been maintained over time. A surveillance program should primarily be made available by the organization that initially developed the harmonization protocol or a collaborating organization. Samples used for surveillance must be human samples or samples commutable with human samples. Recommendations regarding materials suitable for surveillance must be provided to include: preparation instructions, target quantity values (e.g., concentrations), assignment of quantity values, criteria to evaluate the surveillance results to determine that harmonization has been sustained, and instructions for notification of providers of in-vitro diagnostic measuring systems that do not meet the evaluation criteria.

It is optimal to include as many in-vitro diagnostic measuring systems as possible when implementing a harmonization protocol. Therefore, a process should be created to harmonize in-vitro diagnostic measuring systems not initially included in the group that participated in the initial development and validation of a harmonization protocol.

The standard *ISO-18113:2009* on labeling in-vitro diagnostic systems is used to document a harmonization protocol used in the calibration hierarchy and identify the international organization responsible for the harmonization protocol.

Are you maintaining and evaluating the integrity of the metrological traceability chain?

Laboratories making claims of traceability must monitor that it is intact by participation in appropriate proficiency testing schemes (16-20).

If there is a need for further verification of maintained traceability, certified reference materials can be used or natural patient samples sent to providers of reference measurement services (21-28). Use of the NIST publication Standard Reference Materials for Decisions on Performance of Analytical Chemical Methods and Laboratories (29) is recommended for determining the number of samples used for the level of probability required.

Traceability and fitness for the intended use of measuring systems

The end-users of the results of the measuring systems and measurement methods are the proper judges of its fitness for that intended use. Dialogs with the end-users are necessary when novel in-house methods are contemplated.

If the measurand is well-known and widely used, there are likely to be several commercially available measuring systems. There is a current highly active international dialog on criteria for appropriate performance specifications in Laboratory medicine (30-34). The most recent general- and measurand-specific literature in the diagnostic area of interest should be consulted for the appropriate performance specification for the measurands of interest.

Traceability and measurement uncertainty

The requirements regarding measurement uncertainty for a measurand in Laboratory Medicine are determined at the stage of the investigation of the set of fit for the intended use investigation. The determining factor is the analytical quality specifications defined by the clinical need, taking biological variation preanalytical uncertainty into account. Due to the traceability hierarchy added to the uncertainties mentioned above, the measurement uncertainty must at least limit the total uncertainty to the upper limit determined by the chosen analytical quality specification (32-38).

A particular challenge for traceability in Laboratory Medicine is the commutability of the calibrators in the various steps of the calibration hierarchy. The patient sample in the lowest step of the calibration hierarchy is commutable - by definition. Possible non-commutable materials in the higher steps will add to the measurement and diagnostic uncertainty.

A particular manufacturer’s product calibrator for a certain measurand is intended for use with the manufacturer's measurement procedure and should not be expected to work with other measuring systems.

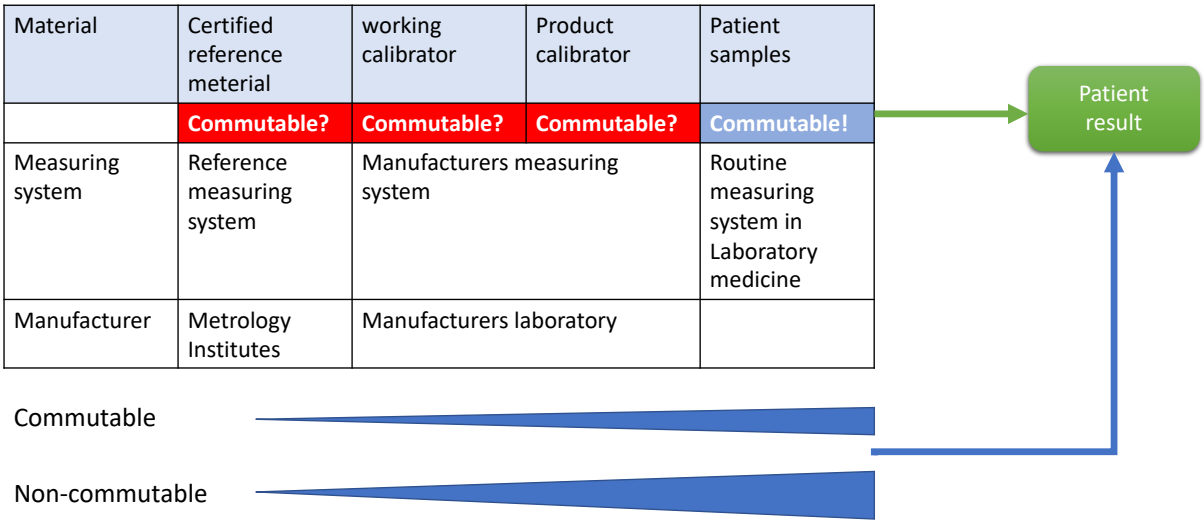


Figure 16: The commutability or lack thereof of the reference materials in the calibration hierarchy of a measurement method is crucial for the traceability and uncertainty in the measurement hierarchy of the traceability chain.

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