Standardization and Harmonization

Hello and welcome to this JCTLM webinar on standardization and harmonization,

Elvar Theodorsson speaking

It is truly crucial to be able to measure results with a minimum of bias and consistently at different times and in different places regionally and globally. From the patient´s perspective it is important that the two primary health care facilities shown at the bottom are consistent with the results from the two hospitals that the patient pays visit to during her/his diagnosis and treatment. Otherwise a well-functioning treatment risks to be changed unnecessarily and in a manner confusing to the patient.

Bias between measurement methods is also crucial from the perspective of the healthcare regarding

- The ability to compare results from research studies over time, e.g. comparing the plasma concentrations of lipids in studies of risk for atherosclerotic hearth disease across generations of people
- For the ability to share common reference intervals, decision limits and guidelines between measurement methods

A positive bias of 5 units in the measurement method depicted in the present example will shift the results five units to the right, which means that a larger number of the healthy will be falsely diagnosed as sick.

The measurement uncertainty that needs to be counted in for a measurement result of a patient sample that is randomly distributed between different laboratories, measurement systems, reagent batches and operators is larger than the uncertainty encountered when the sample from a certain patient is sent to the same laboratory, measurement system and operator. However, the better standardized all measurement systems, reagents and procedures in the laboratories are, the smaller is the additional uncertainty induced when samples from the same patient are analysed by different laboratories using various measurement systems.

If different measurements systems result in different results for the same patient sample

- Physicians and patients will become confused

- Clinical guidelines will become less useful

- Suboptimal treatments and monitoring practices may be implemented

However, a measurement result is not only influenced by the properties of the measurement systems. They are also substantially influenced by all other phases of the total testing chain including biological variation and the pre- and postanalytic phases. There are currently numerous practicable options and standards to standardize and harmonize the pre- and postanalytic phases and substantial interest in using the pre- and postanalytic options for quality improvements.

Metrological standardization means implementing and developing measurement standards and reference measurement procedures to achieve comparability and interchangeability of laboratory results amongst a multitude of measurement systems.

Standardization in general is also important. It means agreeing on and implementing quality systems, concepts, terms and codes for information exchange, standardizing preanalytic- and postanalytic approaches based on research findings.

Traceability is a nominal property – that is – it expresses whether a measurement result is traceable or not and to what international standard, preferably an SI standard. It also implies an unbroken chain of measurements comparisons to carry the results of the measurements between successive calibrators from the weighed pure and homogenous material through to the matrix-based calibrators used for routine measurements.

A crucial question for the traceability chain of a calibrator is whether the calibrators at the different links in the traceability chain are commutable or not. In case of lack of commutability at any link in the traceability chain, the uncertainty increases correspondingly and may eventually risk substantial bias between routine measurement methods measuring patient samples. The earlier in the traceability chain commutable materials, e.g. natural patient samples are introduced in the traceability chains aimed for laboratory medicine – the better.

Harmonization aims for equivalence of measurement results among different routine measurement procedures over time and space according to defined analytical and clinical performance goals. It is obtained through any process that enables the establishment of equivalence of reported values produced by different measurement procedures for the same measurand. Harmonization is not dependent on the availability of pure and homogenous primary reference material nor of primary reference measurement procedures.

Harmonization includes standardization and also caters for those tests that can't be calibrated by traceability to a primary reference measurement standard and reference measurement procedure.

Standardization is preferable to harmonization, but it is not always possible even when an internationally accepted calibrator is available. Why then is standardization preferable to harmonization? It is because it is based on pure and homogenous substance primary references that can be reproduced in different laboratories around the globe over decades of time and on primary reference measurement procedures. It is preferable due to its traceability to primary reference materials and primary reference measurement procedures.

Harmonization has a broader scope than standardization and includes

- Quality systems, ISO standards
- Concepts, terms, unit of measurement and coding systems
- Preanalytical procedures
- Patient preparation
- Specimen collection and handling

- Harmonizing measurement results
- Interpretation of results in medical contexts
- Reference intervals

Laboratory results should be comparable and interchangeable regionally and round the globe over time. The availability of multitude of standards, guidelines, directives etc. for medical laboratories suffer from the fact that these standards, guidelines, directives are seldom harmonized. Furthermore e.g. the EU IVD directive e.g. does not clarify which reference measurement system should be used to fulfil its requirements and organizations at the pinnacle of metrology, including the BIPM and the JCTLM lack the necessary legal authority to fulfil the expectations that healthcare in general and medical laboratories specifically have on them.

Greenberg has listed the following harmonization strategies – method 1 and method 2, primarily according to the availability of reference materials and or reference measurement procedures.

It is crucial to note that the traceability chain of reference materials only includes the calibration phase of the total testing chain. Standardization and harmonization of all other parts of the chain inevitably also influence the uncertainty and clinical usefulness of the laboratory results.

There are several international harmonization projects or efforts being implemented, three of them specifically mentioned here.

The American Association of Clinical Chemistry lunched the international consortium for harmonization of clinical laboratory results in 2010 and has published operation procedures for its consortium.

The Empower project of Dietmar Stöckl and Linda Thienpont uses the Percentiler and Flagger application for retrieving medians of stratified measurement results of the measurement of patient samples

- Provides evidence about stability of performance & the reasons for assay variation (manufacturer, lot-to-lot, calibration, instrument)

- Provides basis for comparison across manufacturers

The IFCC has from the outset had a focus on standardization, but now also runs harmonization project exemplified by the harmonization project for thyroid hormones under the leadership of Linde Thienpont

Local and regional harmonization systems have also been implemented using natural patient samples sent in from peripheral (adept) laboratories to central (mentor) laboratories systematically estimating biases.

Using this comparative data/information it is possible to calculate using variance component analysis which of the following

- Measuring system
- Reagents

- Laboratory
- Operator

Contributes most to the overall diagnostic uncertainty

This enables involved laboratory organization to identify and rectify or improve the measurement systems, reagents, laboratories or operators contribute most to the measurement uncertainty of the laboratory organization. A crucial consequence of this is Europe is that the laboratory as far as possible respects the privilege and responsibility of the producer to properly calibrate their measurement systems.

Keywords
Standardisation, Harmonisation, Total testing chain

Learning objectives

1. Standardisation in the analytical phase and in the pre-and postanalytical phases of the total testing chain
2. Harmonisation and the importance of commutability
3. Standardisation as a top-down regulatory process which is stable in time and space
4. Harmonisation as a bottom up consensus process based on commutable patient samples and with less stability than standardisation in time and space
5. Examples of harmonisation projects

Multiple choice questions

Consistent laboratory results are important for

 a) Comparing results from research studies over time
 b) Avoiding unnecessarily changing treatment strategies
 c) For the ability to share common reference intervals, decision limits and guidelines between measurement methods
 d) Facilitating competition between producers of measurement systems and reagents

Answer(s): a), b), c)

Why is the availability of pure and homogenous reference materials crucial in the metrology of chemistry?

 a) They can be weighed (gravimetry) accurately and the number of mol estimated
 b) It avoids counting in variants of the molecules, e.g. posttranslational processing
 c) Other molecules are confounders in this context
 d) Purity is fundamental to the ability to reproduce the material over extended periods of time

Answer(s): a), b), c), d)

The difference between standardisation in general and standardisation in the metrology is

 a) The consensus processes
 b) The use of reference materials and reference measurement procedures
 c) Traceability
 d)

3) 5 multiple choice questions to assess knowledge gained (see example attached)