ISO 21151 Harmonization Protocol

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Harmonization

One of the most important challenges
in laboratory medicine
What is harmonization

Equivalent results among different measurement procedures for the same laboratory test
Clinical decisions need equivalent results from different measurement procedures

- Equivalent does not mean identical
- Equivalent means within an allowable error consistent with an acceptable risk of harm from decisions based on a lab test result
How to achieve equivalent results

1. Calibration of all measurement procedures is traceable to a common reference system

2. All measurement procedures measure the same quantity (the same molecule)
Standardization:

equivalent results are achieved by metrological traceability to a fit-for-purpose higher order reference system
92 analytes

WHO 400+

107 measurands

Many not validated for commutability

86 analytes (103 measurands)

41 with ref lab service

Metrological Traceability

Primary Reference Material (pure substance)

Secondary Reference Material (matrix)

Manufacturer’s End-user Calibrator

Patient’s Sample Result

Pure Substance Calibrator

Manufacturer’s Measurement Procedures

Medical Laboratory Procedure

Reference Measurement Procedure (e.g. IDMS)

Reference Measurement Procedure (e.g. Gravimetry)

Procedures for identity and mass balance

Assign value

Calibrate

Assign value

Assign value

Assign value
Situation in 2019:

1. Higher order reference systems for ~100 measurands

2. Metrological traceability to some non-commutable CRMs

3. How can we improve this situation?
FDIS 17511:2019  Requirements for establishing metrological traceability of values assigned to calibrators, trueness control materials and human samples

✓ includes a harmonization protocol as one approach to achieve metrological traceability
2010: AACC Workshop on issues in harmonization

2013: ICHCLR formed

2020: ISO 21151
DIS 21151:2019 Requirements for international harmonisation protocols establishing metrological traceability of values assigned to calibrators and human samples

FDIS not required (no technical comments on DIS vote)
Replace these inadequate calibration hierarchies ...
... with metrological traceability to a harmonization protocol

Harmonization reference material (e.g. a panel or pools of clinical samples)

Manufacturer’s working calibrator (master lot)

End-user calibrator

Clinical sample result

International harmonization protocol for a calibration hierarchy

Manufacturer’s selected measurement procedure

Manufacturer’s standing measurement procedure

End-user IVD medical device
Requirements in ISO DIS 21151:2019

Publication of the final 17511 and 21151 standards is expected in 2020
Qualify measurement procedures for inclusion

1. Measure the same quantity (molecular form)
   - Correlated measurement responses
   - Similar specimen specific influences = similar selectivity for the measurand

2. Adequate performance
   - Precision
   - Proportional response over concentration
Specify reference materials, e.g. clinical samples

Clinical samples as harmonization reference materials

1. Specification for the clinical samples (patient characteristics, storage, pooling, supplementation, commutability, etc.)

2. Process for value assignment of the clinical samples
Describe how to derive correction: e.g. initial results

Clinical samples as harmonization reference materials

End-user product calibrator

Medical lab measurement procedures

Initial results for harmonization reference materials
Describe how to derive the method-specific correction

Each IVD manufacturer develops a method-specific correction algorithm to achieve equivalent results for clinical samples. Can apply the correction to:

1. Working (master) calibrator, or
2. End-user calibrator, or
3. Clinical sample result

Clinical samples as harmonization reference materials

Medical lab measurement procedures

Initial results for harmonization reference materials
Apply the method-specific correction

Clinical samples as harmonization reference materials

End-user product calibrator

Medical lab measurement procedures

Each IVD manufacturer applies their method-specific correction algorithm

Equivalent results for clinical samples
Describe validation and sustainability

Clinical samples as harmonization reference materials

Process for value assignment

Reserve set of clinical samples for validation & sustainability
Validate the harmonization protocol

Validate the protocol with a different set of clinical samples

Reserve set of clinical samples for validation & sustainability

End-user product calibrator

Each IVD manufacturer applies their method-specific correction algorithm

Medical lab measurement procedures

Equivalent results for clinical samples
Surveillance over time (sustained validation)

1. Feedback to labs and IVD manufacturers
2. Repeat harmonization protocol if needed (reserve set)
3. Provision for harmonization of new or improved measurement procedures

Surveillance of harmonized results
- **EQA/PT** (commutable samples)
- Other scheme; e.g. patient medians

Equivalent results for clinical samples
EQA data aggregation project (ICHCLR / EQALM)

- Commutable samples
- Aggregate results from global providers
- Feedback to IVD and laboratories
- Pilot from 4 EQA providers
ISO 21151 will enable JCTLM to list harmonization protocols
Conclusions

- Metrological traceability to higher order CRMs or RMPs is preferred.

- A harmonization protocol provides metrological traceability when:
  - higher order CRMs or RMPs do not exist,
  - are technically inadequate,
  - or are difficult to develop.

- JCTLM will be able to list harmonization protocols in its database