Traceability and the IVD Regulation

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Laboratory Medicine exists within a complex web of triangular inter-relationships
Adding value for Patients

Accrediting bodies
- standards

EQA providers
- trueness, traceability

JCTLM, NMIs

Labs
- comparability

Industry
- safety

Healthcare Provider
- troubleshooting, best practice, audit

Professions
- policy, national standards

Clinicians

Scientists

Regulator
- funding

Government
- funding

Funding

Healthcare Provider

Professions

Scientists

Industry

Notified Bodies

Labs

EQA providers

JCTLM, NMIs

Accrediting bodies

Labs

EQA providers

JCTLM, NMIs

Funding

Healthcare Provider

Professions

Clinicians

Scientists

Regulator

Government
Key Assertions

• The most important task we undertake in laboratory medicine is to make measurements of **clinically important measurands**

• **Clinicians** rely on them to **aid diagnosis** and to **monitor treatment** and thereby **improve patient outcomes**

• **Patients** have **implicit trust** that their **results are correct** and will be interpreted **appropriately** and **consistently** by clinicians

• Results of measurements must therefore be **accurate** and **comparable** across **time & geography**, and **proven to add value** to the clinical episode

• For these requirements to be realised, a **reference measurement system** must exist which enables suppliers of analytical methods to create products which are **metrologically traceable** to an established **standard** and are **clinically valid**
VIM 3.0 definition

2.41 (6.10)  
**metrological traceability**  
property of a measurement result whereby the result can be related to a reference through a documented unbroken chain of calibrations, each contributing to the measurement uncertainty

**NOTE 2**  
Metrological traceability requires an established **calibration hierarchy**.

2.43  
**metrological traceability to a measurement unit**  
metrological traceability to a unit  
metrological traceability where the reference is the definition of a measurement unit through its practical realization

**NOTE**  
The expression “traceability to the SI” means 'metrological traceability to a measurement unit of the International System of Units'.
Four things to start with ...
1. The Traceability Chain

- **SI-Unit (definition)**
- **Primary reference measurement procedure**
  - **Primary calibrator**
  - **Secondary reference measurement procedure**
    - **Secondary calibrator**
    - **Mf.'s selected measurement procedure**
      - **Mf.'s working (master) calibrator**
      - **Mf.'s standing measurement procedure**
        - **Mf.'s product calibrator**
          - **End-user's routine measurement procedure**
            - **Routine sample**
              - **RESULT**

**CGPM**
- General Conference on Weights and Measures

**IOs**
- International Scientific Organisations (IFCC)

**NMI**
- National Metrological Institute

**ARML, ML**
- Accredited Reference Measurement Laboratory

**ML**
- Manufacturer's Laboratory

**Mf.**
- Manufacturer
“An inevitable precondition for the establishing of traceable results to calibrators and control materials is the specificity of the measurement procedures applied. **Results of measurement cannot be traceable when the procedure applied partially detects components which are not consistent with the definition of the measurand.**

The complete traceability chain is valid only for those measurable quantities that can have a value expressed in SI units. When primary or secondary calibrators are not available, the traceability chain for many measurands in laboratory medicine ends at a lower level, e.g. at the manufacturer's standing measurement procedure.“

*Note – the term ‘selectivity’ is now preferred.*
3. The crucial distinction between two types of analyte

Type 1
Well-defined, single chemical entities with determined values traceable to SI units, and internationally recognized reference procedure-defined measurands.

Type 2
Less well-defined entities or heterogeneous mixtures of precursors / isoforms / fragments with or without biological activity, that are not SI-traceable and/or no internationally-recognized reference measurement procedures exist that are applicable to patient samples.
Roger Ekins taught us that …

‘Analytical’ assays

estimate a **defined** analyte in systems which give results in **method-independent** units of **amount** of the analyte

Applicable to Type 1 analytes - we **can** truly measure these

‘Comparative assays’

estimate **undefined** 'analyte' in systems which give results in **method-dependent** units of **effect** of the 'analyte' **in that system**

Applicable to Type 2 analytes - we **cannot** truly measure these

Only about 20% of the quantities we ‘measure’ in Laboratory Medicine are Type 1
4. JCTLM – Joint Committee for Traceability in Laboratory Medicine

**Sponsoring Organizations**

- Intergovernmental Treaty Organization for Measurement Standards
- International NGO for Professionals in Laboratory Medicine
- International NGO for Accreditation Bodies

Bureau International des Poids et Mesures
JCTLM Executive Committee

Chairperson:
- Dr Gary L. Myers (IFCC)

Executive Secretary:
- Dr Robert I. Wielgosz (BIPM)

Members:
- Dr Graham Beattie (IFCC)
- Dr Graham Jones (ILAC)
- Dr Willie E. May (CIPM)
- Dr James W. McLaren (CIPM)
- Dr Martin J.T. Milton (BIPM)
- Ms Reginia Robertson (ILAC)
- Prof. Dr Lothar Stekmann (IFCC)

JCTLM Executive Committee meetings are also attended by:
- JCTLM-DBWG Chair and Vice-Chairs
- JCTLM-TEPWG Chair

This document is particularly recommended!
JCTLM database: Laboratory medicine and in vitro diagnostics

**JCTLM Database**
- Search Form
- General information
- List of reference materials no longer listed in the JCTLM Database
- JCTLM Database Leaflet
- Contact us

**Analyte keyword search for reference materials, measurement methods/procedures and services**

Type an analyte name in part or full, e.g. cholesterol

Refine search by analyte category
- All

Refine search by matrix category
- All

Please select your requirement:
- Higher-order reference materials
- Reference measurement methods/procedures
- Reference measurement services

Reset  Search

**Download all entries for a specific analyte or matrix category as PDF**

Please select your requirement:
- Higher-order reference materials
- Reference measurement methods/procedures
- Reference measurement services

Select an analyte category

Select a matrix category
LIST I

published initially on 01 April 2004

Certified Reference Materials and Reference Measurement Procedures for well-defined chemical entities or internationally recognized reference method-defined measurands, such as enzymes. Reference Materials included in this category are those that are traceable to the SI units. [Electrolytes, Drugs, Metabolites and Substrates, Non-Peptide Hormones, Enzymes and some Proteins]

approximately 123 Reference Measurement Procedure entries for 75 different health status markers

approximately 211 Reference Material entries for 128 measurands

http://www.bipm.org/en/committees/jc/jctlm/jctlm-db/
JCTLM LIST II

Reference Materials that are value-assigned using an internationally agreed upon protocol e.g., reference materials for Blood Typing, Coagulation Factors, Microbial Serology, Nucleic Acids, and some Proteins. The values of the measurands in the reference materials on this List are not SI-traceable and/or no internationally-recognized reference measurement procedures exist.

Initially published in January, 2005, now includes

- 21 CRMs for Coagulation Factors
- 7 CRMs for Proteins
- 3 CRMs for Blood Groupings
- 2 CRMs for Enzymes
I’d also like to mention this EQA service for reference laboratories operating reference methods registered with JCTLM …
IFCC RELA

http://www.dgkl-rfb.de:81/
Traceability is a key requirement of ISO 15189
5.3.1.4 Equipment **calibration** and **metrological traceability**

The laboratory shall have a documented procedure for the calibration of equipment that directly or indirectly affects examination results. This procedure includes:

a) taking into account conditions of use and the manufacturer’s instructions;

b) recording the **metrological traceability** of the **calibration standard** and the **traceable calibration** of the item of equipment;

c) verifying the required **measurement accuracy** and the functioning of the measuring system at defined intervals;

d) recording the **calibration** status and date of **recalibration**;

e) ensuring that, where **calibration** gives rise to a set of **correction factors**, the previous **calibration factors** are correctly updated;

f) safeguards to prevent adjustments or tampering that might invalidate examination results.
Metrological traceability shall be to a reference material or reference procedure of the higher metrological order available. NOTE Documentation of calibration traceability to a higher order reference material or reference procedure may be provided by an examination system manufacturer. Such documentation is acceptable as long as the manufacturer’s examination system and calibration procedures are used without modification. Where this is not possible or relevant, other means for providing confidence in the results shall be applied, including but not limited to the following:

- use of certified reference materials;
- examination or calibration by another procedure;
- mutual consent standards or methods which are clearly established, specified, characterized and mutually agreed upon by all parties concerned.
Traceability in laboratory medicine is governed by ISO 17511:2003
ISO 17511:2003  In vitro diagnostic medical devices —
Measurement of quantities in biological samples —
Metrological traceability of values assigned to
calibrators and control materials

Depending on the possibility of metrological traceability to SI and on the availability of various metrological levels of measurement procedures and calibrators, the following five typical upper ends of the metrological traceability chain may be identified.

a) Quantities for which results of measurements are metrologically traceable to SI.

A primary reference measurement procedure and one or more (certified) primary reference materials (used as calibrators) are available. These levels exist for approximately 25 to 30 types of quantity having well defined components, e.g. some electrolytes, metabolites, steroid hormones, and some thyroid hormones. These types of quantity cover a large proportion of the routine results provided by medical laboratories.
b) Quantities for which results of measurements are not metrologically traceable to SI.

1) An international conventional reference measurement procedure (see 3.12) (which cannot be called a primary reference measurement procedure) and one or more international conventional calibration materials (see 3.11) with values assigned by that procedure are available.

2) An international conventional reference measurement procedure is available but no international conventional calibration materials. These conditions apply for about 30 types of quantity with components such as haemostatic factors.

3) One or more international conventional calibration materials (used as calibrators) with a protocol for value assignment are available, but no international conventional reference measurement procedure. These conditions apply for over 300 types of quantity, e.g., for quantities referred to World Health Organization's International Standards, such as protein hormones, some antibodies, and tumour markers.

4) Neither reference measurement procedure nor reference materials for calibration are available. The manufacturer can establish 'in-house' measurement procedure(s) and calibrator(s) to support value assignment to his product calibrator. These conditions apply for about 300 types of quantity with components such as tumour markers and antibodies.
Traceability is a requirement of the original EU IVD Directive …
IVD Directive 98/79/EC
Excerpts related to the requirement for traceability

ANNEX I: Essential Requirements

A. General requirements: The traceability of values assigned to calibrators and/or control materials must be assured through available reference measurement procedures and/or available reference materials of a higher order.

ANNEX III: EC Declaration of Conformity

3. The technical documentation ... must include in particular: adequate performance evaluation data showing the performances claimed by the manufacturer and supported by a reference measurement system (when available), with information on the reference methods, the reference materials, the known reference values, the accuracy and measurement units used;
I have always been rather concerned that both the IVDD and ISO 17511:2003 talk about the traceability of values assigned to calibrants and controls and not the end result for the patient.

We shall see if this situation has now been improved!
The ‘new’ ISO 17511

I can only share with you some proposals about the current revision, as we are bound by strict ISO confidentiality rules!

Title of proposed revision:
ISO 17511:201x. In vitro diagnostic medical devices —requirements for establishing metrological traceability of values assigned to calibrators, trueness control materials and human samples.

Justification
ISO17511:2003 and ISO 18153:2003 have now been in place for more than 12 years, and the expert technical community has recommended to ISO/TC212/WG2 several opportunities to improve these standards. These opportunities include:

1) clarification within the ISO 17511 standard that there is an end-user expectation that metrological traceability does not end with the calibrator, and that final reported results on patient samples are also expected to be metrologically traceable to the highest order available metrological reference for a measurand;
1) improvement (for clarity) of the **descriptions of the potential approaches and models** that may be applied in establishing a calibration hierarchy, as a function of state of the art and availability of higher order references;

2) inclusion of a model calibration hierarchy that is **compatible with the implementation of a harmonization protocol** to support standardization of multiple measurement procedures for measurands without higher order reference measurement procedures and reference materials; and

3) address a recommendation that **ISO 18153 content concerning establishing metrological traceability for enzyme catalytic concentrations might instead be incorporated into a revised ISO 17511**, thereby eliminating the need for ISO to maintain two standards, and also minimize cost to end users who might otherwise need to purchase two standards instead of one.

**So that is all good!**
The EU IVDD has now been revised and strengthened to become the new IVD Regulation

REGULATION (EU) 2017/746 OF THE EUROPEAN PARLIAMENT AND OF THE COUNCIL

of 5 April 2017


(Text with EEA relevance)
The European Medical Device Regulations (MDR 2017/745) and In Vitro Diagnostic Regulations (IVDR 2017/746) entered into force as of May 26, 2017.

The Regulations’ entry into force is the last milestone before full implementation of the MDR in May 2020 and the IVDR in May 2022.

The official three-year countdown to the MDR’s date of application (full implementation)—May 26, 2020—has begun. By that date, medical device manufacturers active in Europe will have to be fully compliant with the MDR. The five-year countdown to the IVDR’s date of application (May 26, 2022) has also begun.

In the shorter term, European Notified Bodies may begin applying for designation under the MDR and IVDR starting November 26, 2017.
IVDs are now defined as:

- a reagent, reagent product, calibrator, control material, kit, instrument, apparatus, equipment, software or system, whether used alone or in combination, intended by the manufacturer to be used in vitro for the examination of specimens, including blood and tissue donations, derived from the human body, solely or principally for the purpose of providing information:
  - concerning a physiological or pathological state;
  - concerning a congenital abnormality;
  - concerning the predisposition to a medical condition or a disease;
  - to determine the safety and compatibility with potential recipients;
  - to predict treatment response or reactions;
  - to define or monitor therapeutic measures.
How the IVDR Impacts Device Classification

• The IVDR substantially changes the mechanism by which IVDs may bear the CE mark.
• A new risk-based classification scheme will replace the "general IVD" category with four new device classes: A, B, C, and D (lowest risk to highest risk, respectively).
• Classes B through D will require an assessment of the technical documentation by a Notified Body. This technical documentation must include three types of clinical evidence:
  • **Scientific Validity**: association of an analyte to a clinical condition or physiological state
  • **Analytical Performance**: ability of an IVD to correctly detect and measure the analyte (LOD, LOQ, accuracy, precision and reproducibility)
  • **Clinical Performance**: ability of the device to yield results that relate to a particular clinical condition for the intended use and in accordance with target population, and to the intended user (if applicable)
... where Traceability is mentioned in the new IVDR ...

Grey boxes refer to ‘general’ traceability – we can skip over these; blue boxes refer to metrological traceability – these are relevant!
P.1 item (4) Key elements of the existing regulatory approach, such as the supervision of notified bodies, risk classification, conformity assessment procedures, performance evaluation and performance studies, vigilance and market surveillance should be significantly reinforced, whilst provisions ensuring transparency and traceability regarding in vitro diagnostic medical devices should be introduced, to improve health and safety.

P.5 item (38) The traceability of devices by means of a Unique Device Identification system (UDI system) based on international guidance should significantly enhance the effectiveness of the post-market safety-related activities for devices, which is owing to improved incident reporting, targeted field safety corrective actions and better monitoring by competent authorities. It should also help to reduce medical errors and to fight against falsified devices. Use of the UDI system should also improve purchasing and waste disposal policies and stock-management by health institutions and other economic operators and, where possible, be compatible with other authentication systems already in place in those settings.

P.29 CHAPTER III IDENTIFICATION AND TRACEABILITY OF DEVICES, REGISTRATION OF DEVICES AND OF ECONOMIC OPERATORS, SUMMARY OF SAFETY AND CLINICAL PERFORMANCE, EUROPEAN DATABASE ON MEDICAL DEVICES

Article 22 Identification within the supply chain 1. Distributors and importers shall cooperate with manufacturers or authorised representatives to achieve an appropriate level of traceability of devices.
**P.30 Unique Device Identification system**  1. The Unique Device Identification system (‘UDI system’) described in Part C of Annex VI shall allow the identification and facilitate the **traceability** of devices, other than devices for performance studies, and shall consist of the following:

**P.33 under Summary of safety & performance:**  2. The summary of safety and performance shall include at least the following aspects:
   (f) the **metrological traceability of assigned values**;

**P.81 Article 111 Evaluation**  By 27 May 2027, the Commission shall assess the application of this Regulation and produce an evaluation report on the progress towards achievement of the objectives contained herein including an assessment of the resources required to implement this Regulation. Special attention shall be given to the **traceability** of devices through the storage, pursuant to Article 24, of the UDI by economic operators, health institutions and health professionals. The evaluation shall also include a review on the functioning of Article 4.

**P.86 CHAPTER II REQUIREMENTS REGARDING PERFORMANCE, DESIGN AND MANUFACTURE**  
9.3. Where the performance of devices depends on the use of calibrators and/or control materials, the **metrological traceability of values assigned to calibrators and/or control materials** shall be assured through suitable reference measurement procedures and/or suitable reference materials of a higher metrological order. Where available, **metrological traceability of values assigned to calibrators and control materials** shall be assured to certified reference materials or reference measurement procedures.
CHAPTER III REQUIREMENTS REGARDING INFORMATION SUPPLIED WITH THE DEVICE. P.95 (u) the metrological traceability of values assigned to calibrators and control materials, including identification of applied reference materials and/or reference measurement procedures of higher order and information regarding maximum (self-allowed) batch to batch variation provided with relevant figures and units of measure;

ANNEX II TECHNICAL DOCUMENTATION 1. DEVICE DESCRIPTION AND SPECIFICATION, INCLUDING VARIANTS AND ACCESSORIES (b) the Basic UDI-DI as referred to in Part C of Annex VI assigned by the manufacturer to the device in question, as soon as identification of this device becomes based on a UDI system, or otherwise a clear identification by means of product code, catalogue number or other unambiguous reference allowing traceability;

6. PRODUCT VERIFICATION AND VALIDATION The documentation shall contain the results and critical analyses of all verifications and validation tests and/or studies undertaken to demonstrate conformity of the device with the requirements of this Regulation and in particular the applicable general safety and performance requirements. P.100 6.1.2.4. Metrological traceability of calibrator and control material values

ANNEX IV EU DECLARATION OF CONFORMITY
4. Product and trade name, product code, catalogue number or other unambiguous reference allowing identification and traceability of the device covered by the EU declaration of conformity, such as a photograph, where appropriate, as well as its intended purpose. Except for the product or trade name, the information allowing identification and traceability may be provided by the Basic UDI-DI referred to in point 3;
**PART C THE UDI SYSTEM**

P. 107 A shipping container is a container in relation to which *traceability* is controlled by a process specific to logistics systems.

P.108 3. The UDI 3.9 3.9. A new UDI-DI shall be required whenever there is a change that could lead to misidentification of the device and/or ambiguity in its *traceability*. In particular, any change of one of the following UDI database data elements shall require a new UDI-DI:

**PART A PERFORMANCE EVALUATION AND PERFORMANCE STUDIES**

P146 1.1. Performance evaluation plan - identification of certified reference materials or reference measurement procedures to allow for *metrological traceability*;

P.149 2.3.2. Clinical performance study plan: (e) identification and description of the device, its intended purpose, the analyte or analytes or marker or markers, the *metrological traceability*, and the manufacturer;

*So not so good!*
Comments

• So, **very disappointingly**, the IVDR does **not** say that metrological traceability extends to the final patient’s result!

• This is such a **wasted opportunity** and the IVDR will now **not** match the revised ISO 17511

• Can we speculate as to why? **Any ideas?**

• Can we do anything about this? **Any ideas?**

• **What will be the consequences?**
Finally, the importance of relationships in improving the outcomes for patients ...
Relationships

Governments

Regulators / Notified Bodies

International bodies

National Metrology Institutes

ISO standards

Reference Laboratories

CE marking

IVD Manufacturers

ISO standards

EQA providers

ISO standards

Clinical Laboratories

Clinicians

ISO standards

Patients

Accrediting Bodies

ISO standards

Key relationships
Thank you for your attention!

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