

Establishment of an Accredited Reference Measurement Laboratory

Francesco Dati, PhD

IVD-Consulting

Marburg / Germany

E-mail: f.dati@t-online.de

Quality of Analytical Systems



Reference Measurement Systems

Items of such systems are:

- **National / international regulations and guidelines**
- **Reference laboratories with proven expertise and capability of measurement**
- **Reference measurement procedures, internationally agreed**
- **Reference materials**
- **External quality control schemes**

Standardization of diagnostic assays

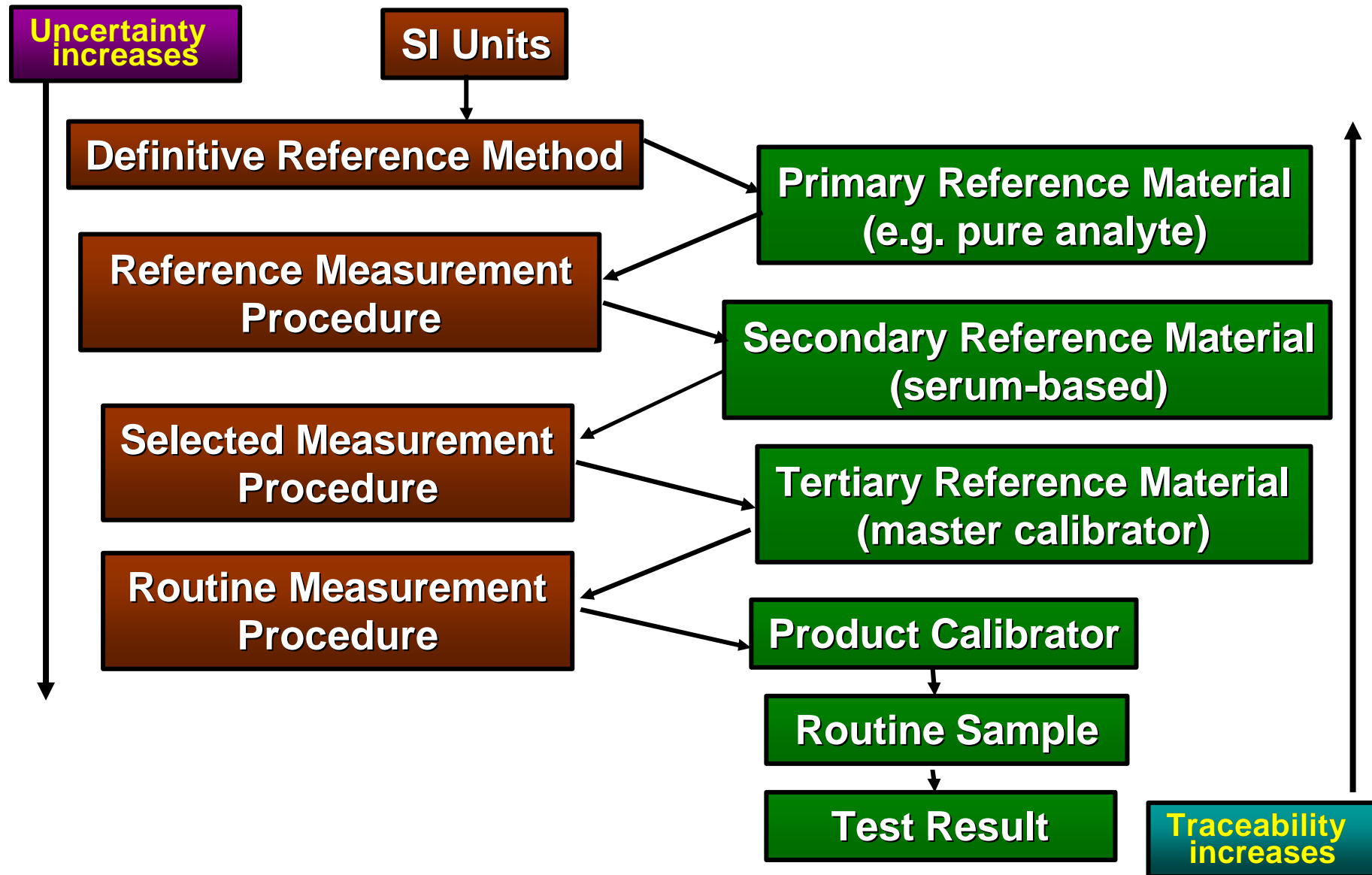
The role of the ***reference measurement system*** is to ensure that a numerical value assigned to the reference material is:

- ✍ **Traceable through the defined reference method**
- ✍ **Associated with a specified uncertainty**
- ✍ **Commutable with clinical values**

IVD Directive: Traceability of IVDs

- ✍ **The manufacturer has to provide documentary evidence of the traceability of the results of their measurements to national or international standards of measurement.**
- ✍ **Where this is not possible, the manufacturer has to provide satisfactory evidence of the correlation of results with the values of other reference materials**
 - a. **by exhaustive evaluation of the measurement process or**
 - b. **by correlation with the values of known and accepted national and/or international certified reference materials**
- ✍ **Such work can be performed either in the manufacturer's laboratories or with the help of external laboratories**

Reference Measurement System



ISO prEN DIS 15195
**“Requirements for Reference Measurement
Laboratories in Laboratory Medicine”**

The International Standard ISO 15195 on
“Requirements for Reference Measurement
Laboratories in Laboratory Medicine” refers to
the specific aspects of calibration laboratories
in the field of laboratory medicine where such
“Calibration Laboratories” are usually
denoted as “Reference Measurement Laboratories”.

Reference Measurement Laboratories

1

Obtaining traceability of measured results necessitates a calibration hierarchy of alternating measurement procedures and calibrators. And the proper traceability can be guaranteed by calibration laboratories, i.e. by the so-called ***“Reference Measurement Laboratories”***.

Reference measurement laboratories must operate at a higher metrological level than routine laboratories.

The metrological level of the results provided by reference measurement laboratories should be appropriate to enable routine laboratories to fulfil medical requirements.

Reference measurement laboratories

2

As analytical centers of competence the reference measurement laboratories perform measurements with the greatest competence and are considered expert institutions for quantifying certain well-defined analytes, using the best, internationally agreed-on measurement procedure.

They are highly specialized laboratories attached to or subcontracted by national metrology institutes, quality assessment / proficiency testing organisations, academic centres, or manufacturers of in vitro diagnostics.

Reference measurement laboratories

3

The main responsibility of reference measurement laboratories is to assign target values to Reference Materials, using the best analytical method available.

In addition, they establish for routine methods the extent of associated analytical bias in comparison with primary methods, with established Reference Methods, or if no reference method has been developed, with designated comparison methods.

Thus, these laboratories establish through a chain of comparisons the traceability of routine methods and their respective biases.

Reference Measurement Laboratories

Further tasks of reference measurement laboratories may include:

- ✍ **Assistance in investigation of new or existing measurement procedures with regard to their trueness**
- ✍ **Providing accurate (true and precise) assigned values with stated uncertainty to materials for calibration, internal quality control, and external quality assessment**
- ✍ **Acting as consultants to government, industry, and organisations conducting external quality assessment schemes as well as to specialized individual laboratories**

Competence of Calibration Laboratories

- The general requirements for the competence of calibration laboratories are laid down in the international standard ISO / IEC 17025 which relates to testing and calibration laboratories.

In accordance with this standard at present laboratory accreditation is granted by national accrediting bodies.

- **ISO/IEC 17025 covers several technical competence requirements that are not covered by ISO 9001/9002.**

Some independent laboratories and laboratories that form part of a larger organization have also obtained certification of the laboratory's quality management system on the basis of ISO 9000 series.

Competence of Calibration Laboratories

The requirements for recognition and operation are set out in ISO/IEC Guide 58 “Calibration and testing laboratory accreditation systems – General requirements for operation and recognition.”

The certificates of calibration laboratories are mutually recognized by those European countries that are organized in the “European co-operation for Accreditation (EA).”

A further organisation that could be involved in this international system of mutual recognition of reference measurement/calibration laboratories is the “International Laboratory Accreditation Co-operation (ILAC).”

Organisation and management of a reference measurement laboratory

- The laboratory should be organized and operated so that its independence of judgement and its integrity should not be influenced by commercial, financial, or other conflicts of interest.
- The laboratory management should specify the responsibility, authority, and interrelation of all personnel who manage, perform, review, and approve work affecting the quality of reference measurements.
- The management of the laboratory should designate a quality manager and nominate a deputy to serve in his/her absence.

Organisation and management of a reference measurement laboratory

- The laboratory should establish and maintain a quality management system documented in a quality manual.
- This should describe the objectives, the quality policies, and quality control programmes which enable the laboratory to assure the quality of its reference measurement results with the stated level of uncertainty of measurement according to the Guide to the expression of uncertainty [GUM, 1993].
- The contents of the quality manual should be available to and implemented by the personnel of the laboratory as appropriate.

Organisation and management of a reference measurement laboratory

- **The management of a reference measurement laboratory is responsible for defining and providing a documented list of general and specified skills and training requirements for the laboratory personnel.**
- **The personnel has to have appropriate theoretical background and adequate practical experience in the relevant field of reference measurement technology.**
- **The director and any deputy director of a reference measurement laboratory needs to have relevant academic education, training, and adequate experience.**

Organisation and management of a reference measurement laboratory

- ✍ **The laboratory staff shall include well-trained personnel knowledgeable**
 - **in the policies and practices of the laboratory,**
 - **in the technical equipment,**
 - **in materials necessary to provide metrological traceability and statements of uncertainty, and**
 - **in all relevant calibration and quality control procedures.**

- ✍ **The personnel of the laboratory will be assessed by the accrediting body or national metrology institute in terms of their education, training, experience, and ability to perform measurements.**

Organisation and management of a reference measurement laboratory

- All equipment used in the reference measurement procedure shall be regularly inspected and maintained by authorized personnel.
- A program for calibration and verification of the equipment including the relevant environmental conditions shall be established.
- Equipment operation manuals shall be maintained current and readily available.
- Each item shall be uniquely identified.

***Quality requirements for target value assignment
by reference measurement laboratories***

Organization structure	Clear defined responsibilities, skilled technicians, clear defined work procedure
Measuring instruments	Instructions and maintenance
Pipetting system	Calibration of pipettes (analytical balance)
Sample treatment	Instructions for handling lyophilized/frozen samples
Internal QC system	Use of QC charts
External QC system	QC using blind control
Protocols	Electronic system available
Storage	Adequate storage capacity, accurate control of storage temperature

Hierarchy of Laboratories

- 1. National Metrology Institutes**
- 2. Networks of Reference Laboratories**
- 3. Accredited Reference Laboratories
(universities, hospitals, manufacturers)**
- 4. Manufacturer's Standardization
Laboratories**
- 5. Routine Laboratories**

Definition: terms accreditation and certification

Certification Procedure whereby a third party (independent party) gives written notification that a product, process or service meets established requirements.

Accreditation Procedure whereby an authorized body gives formal recognition that an organization or person is authorized to carry out certain tasks.

Laboratory accreditation: Formal recognition that a test or calibration laboratory is authorized to carry out certain tests or calibrations.

Definition: terms accreditation and certification

Certification of a management system means giving an explanation that the system works according certain requirements.

In the accreditation procedures not only the system will be examined but also the competence of the organisation and the personnel will be judged.

Accreditation of the quality management system of a laboratory on the basis of ISO 17025

A reference laboratory tests IVD products and issues a certificate or test report when the tested product is found to meet the requirements.

A calibration laboratory is concerned with calibration of measuring instruments or reference materials.

A calibration laboratory also issues a certificate after calibration.

Networks of Reference Measurement Laboratories

- **The Reference Measurement Laboratories should collaborate in international networks which are the global centers of excellence for the correct measurement of a given quantity**
- **The networks should be open for the participation of analytical laboratories from the IVD industry**
- **Establishing of the reference procedures within a network of reference measurement laboratories according to stringent metrological principles**
- **Selection of commutable reference materials and certification of the materials by a network of reference measurement laboratories**

Reference Measurement Laboratories and Traceability

Essential elements of Traceability:

Competence:

the laboratories or bodies performing one or more steps in the traceability chain must supply evidence for their technical competence (e.g. by demonstrating that they are accredited)

- ***Transfer protocols & documentation;*** each step in the chain must be performed according to documented and generally acknowledged procedures / transfer protocols; the results must equally be documented

Traceability of Standards and Calibrators

Transfer Protocols

- a) **Calibration hierarchy**
 - **Primary calibrator**
 - **Secondary calibrator**
 - **Manufacturer's working calibrator**
 - **Manufacturer's product calibrator**
- b) **Rationale for selection of reference materials, and their stability and commutability**
- c) **Rationale for selection of measurement procedures including equipment**
- d) **Appropriate statistical methods**
- e) **Evaluation of matrix effects and any modifications of the analyte.**