IFCC EXTERNAL QUALITY ASSESSMENT SCHEME FOR REFERENCE (CALIBRATION) LABORATORIES IN LABORATORY MEDICINE

PROCEDURES

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2. Preamble

The concept of traceability provides the most important strategy to establish standardization in laboratory medicine aiming at accurate measurement results independent of the principle of measurement, the actual measurement procedure (e.g. the commercial test kit) as well as the laboratory where such clinical testing is performed. The implementation of the concept of traceability requires the availability of

- reference materials,
- reference measurement procedures, and
- reference (calibration) laboratories.

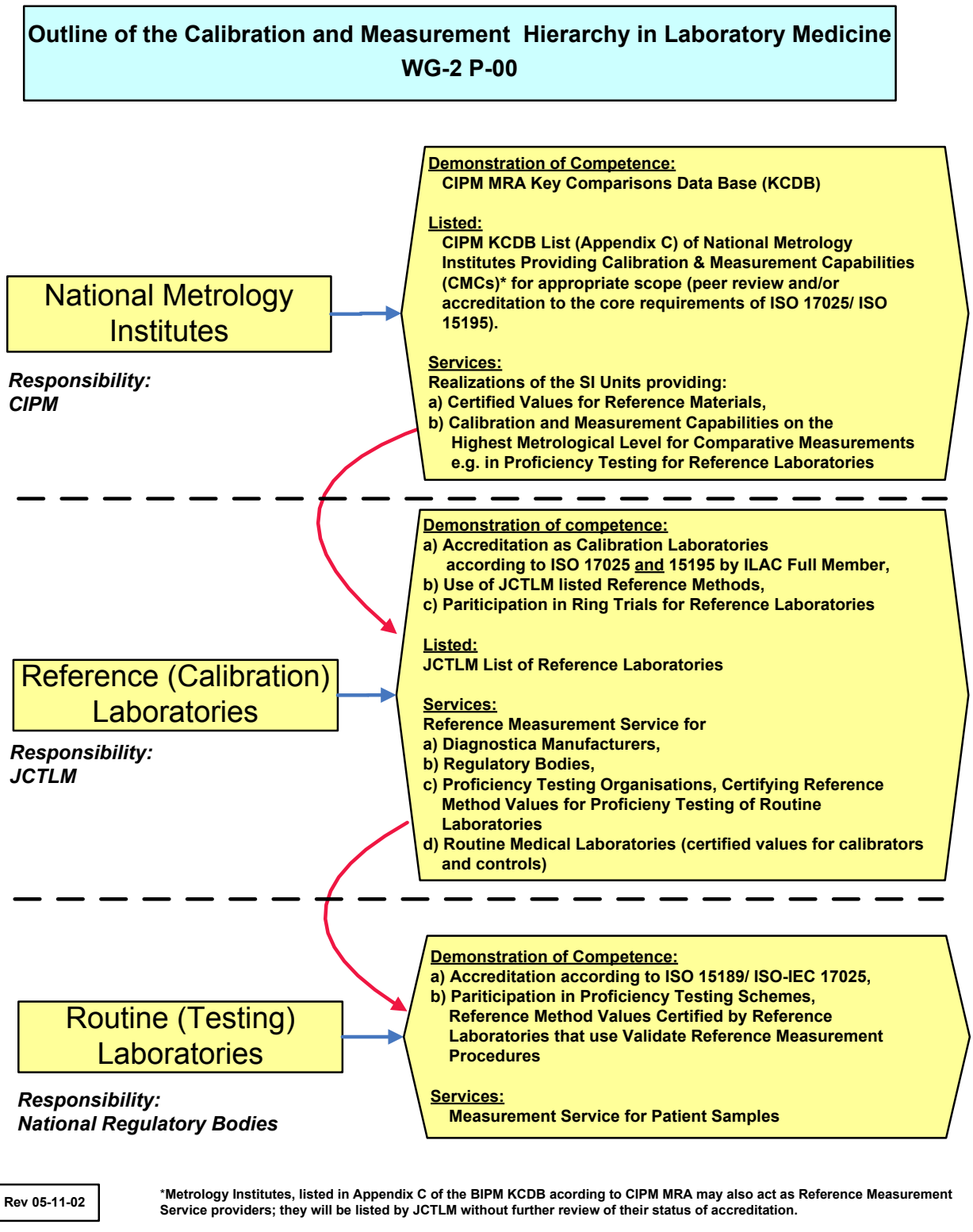
Therefore, a Joint Committee on Traceability in Laboratory Medicine (JCTLM) has been established by three organizations: The International Federation of Clinical Chemistry and Laboratory Medicine (IFCC), the International Bureau of Weights and Measures (BIPM) and the International Laboratory Accreditation Co-operation (ILAC). The objective of the JCTLM is to identify and publish lists of reference materials, reference procedures and reference laboratories.

There exists a hierarchy of laboratories which is demonstrated in Flow Chart 2-A and described in more detail in the Procedure Manual of JCTLM WG-II.
A reference measurement (calibration) laboratory applying for listing has to fulfill three different requirements (see flow chart 2-B)

- accreditation according to ISO 17025 (as calibration laboratory) and ISO 15195,
- use of a reference method accepted and listed by the JCTLM,
- participation in an External Quality Assessment Scheme (EQAS) dedicated to reference laboratories.

Since until recently, no such EQAS existed, the IFCC, in collaboration with an experienced national proficiency testing organizer, has launched a ring trial system in order to support the activities of the JCTLM.

Flow Chart 2-A



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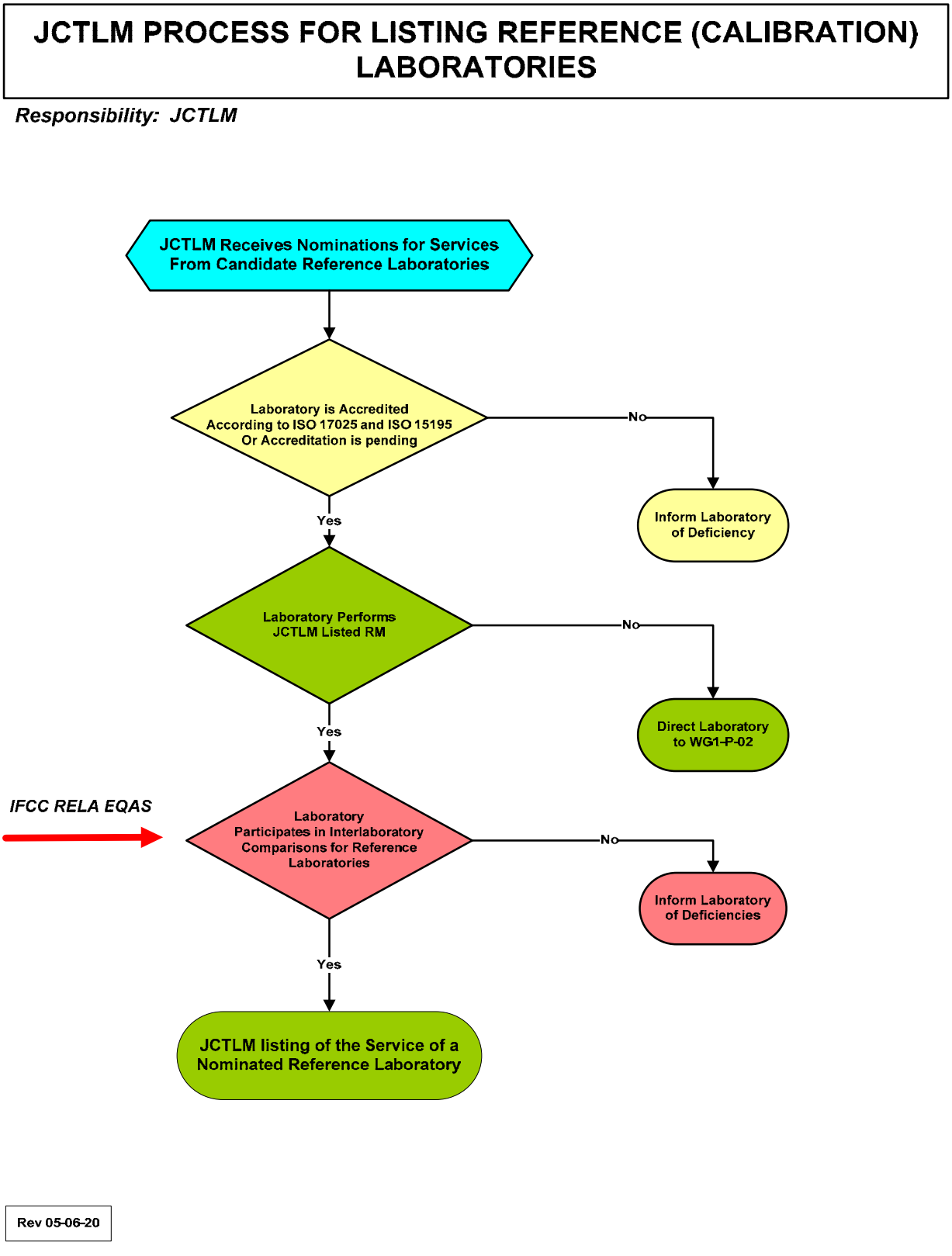
*Metrology Institutes, listed in Appendix C of the BIPM KCDB acording to CIPM MRA may also act as Reference Measurement Service providers; they will be listed by JCTLM without further review of their status of accreditation.

Flow Chart 2-B



3. Scope

The scope of the IFCC External Quality Assessment Scheme is to enable reference laboratories and candidate reference laboratories to demonstrate their competence through regular participation in ring trials.

The ring trial results may be also used to demonstrate equivalence or discordance of different reference methods.

4. Procedures for Conducting Ring Trials

4.1 **IFCC Ring Trials for Reference Laboratories** are organized on behalf of the IFCC by the Reference Institute of Bioanalysis (RfB) of the German Society of Clinical Chemistry and Laboratory Medicine (DGKL).

4.2 Ring Trials will be conducted **annually**; they will be announced on the DGKL-RfB – website (www.dgkl-rfb.de:81/index.shtml).

4.3 Ring Trials are offered for several groups of **measurands**:
Metabolites & Substrates,
Electrolytes,
Enzymes,
Proteins,
Hormones,
Glycyated hemoglobin
etc.

4.4 **Key measurands** will be selected for each group of measurands in each ring trial. This is necessary to collect statistically sound information from the ring trials.

Example:
The EQAS organization will offer ring trials for all five enzyme activity measurements according to the IFCC 37 °C reference procedures. Due to the considerable workload, not all laboratories will participate for all measurands. At the worst, Lab.A will analyze ALT, Lab.B AST, Lab.C GGT, Lab.D CK and Lab.E LDH. Because of the limited number of participating laboratories it will then be difficult to collect a statistically relevant number of results for each of the measurands necessary to demonstrate comparability of results from different laboratories. Therefore, the EQAS organizer will select one key measurand from each group of measurands for every ring trial occasion. It is recommended to provide results for this key measurand. Participation for all other measurands is voluntary. The selected key measurand for each group of measurands will change from one ring trial to the next.

4.5 It is generally expected that laboratories apply **reference measurement procedures according to ISO 15193 and as listed in JCTLM list 1**. However, **candidate laboratories** which are investigating a new analytical principle for establishing a reference procedure are also invited to validate their procedures by participation in the ring trials. **Results from laboratories that obviously perform routine procedures will be excluded from the evaluations**.

4.6 **Registration forms** for participation may be obtained from the DGKL-RfB website (www.dgkl-rfb.de:81/index.shtml) or are available on request from the organizers (info@dgkl-rfb.de)
Registration forms contain, in addition to the laboratory coordinates, the list of measurands. Key measurands are expressively labeled. A ring trial participant may select and register for any measurand listed on the registration form.

4.7 For each measurand, **two samples** with different concentrations/activities will be distributed to the participants.

4.8 It is expected that the results be established in the manner the participating laboratory usually employs when providing reference measurements for a customer. Therefore, an **appropriate number of vials** will be sent to the participants in order to enable repeat measurements necessary for the calculation of uncertainty.

4.9 **A dead-line** for reporting results will be set at six months after distribution of samples.

4.10 Participants are requested to report **information on their results** (mean values and expanded uncertainties) as well as the **reference method** applied.

4.11 Participants will receive the **individual results** for each registered measurand in comparison to the **overall results** of all participating laboratories for that particular measurand in a tabulated form as well as a **Youden diagram**.
In addition, 'limits of equivalence' are displayed in the Youden diagram. These limits are not be considered as a "grading" system. They are of no regulatory impact but may be used for educational means to improve laboratory performance.
The 'limits of equivalence' are set to one quarter of acceptable performance limits for testing (routine) laboratories (see Appendix 1).
Results of at least five reference laboratories using a JCTLM listed procedure must be available so that the median and the limits can be calculated on a statistcally firm basis.

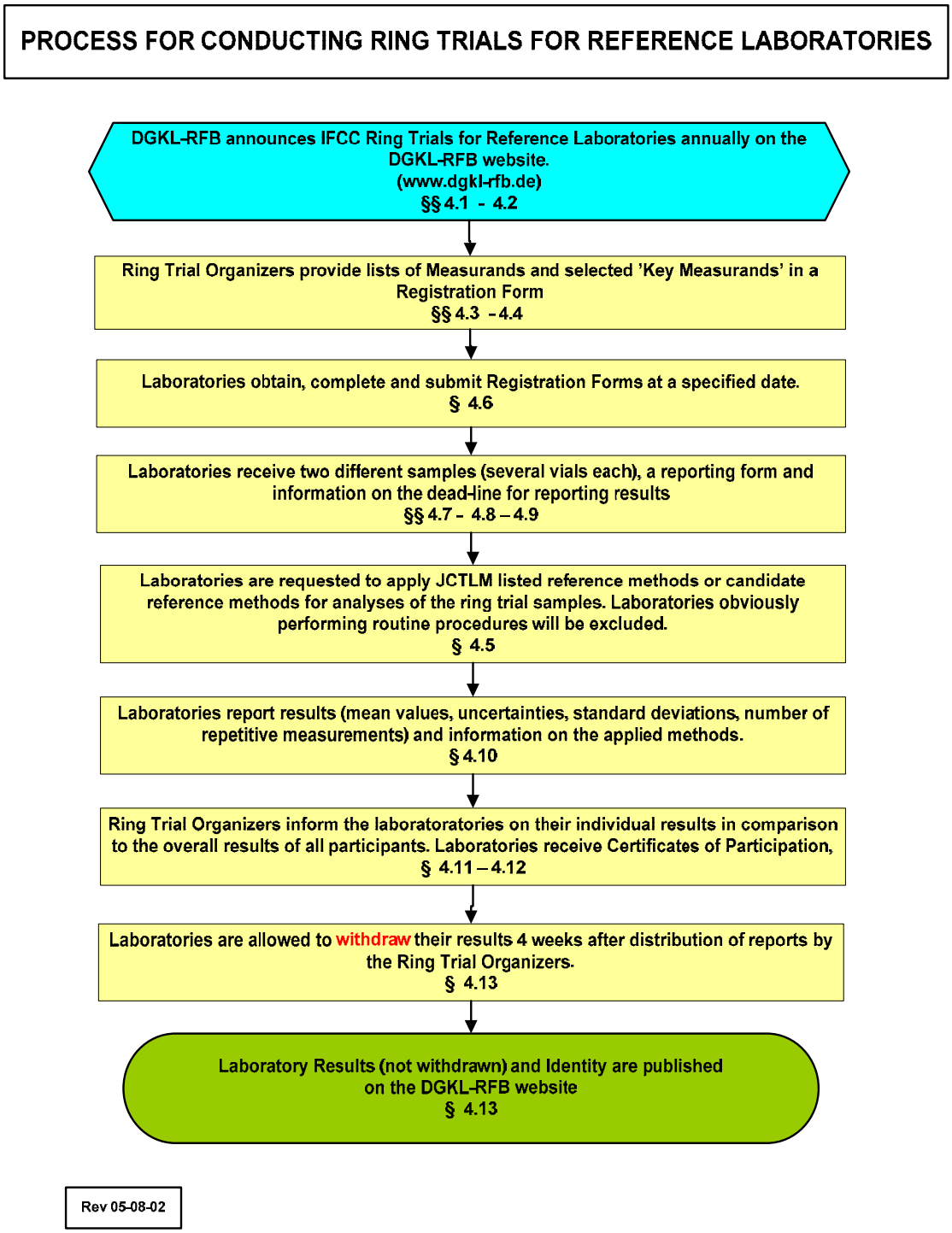
4.12 Participants will also receive a **certificate of participation** indicating the measurands for which results were reported.

4.13 Participants may **withdraw** their results four weeks after the first report has been distributed to the individual laboratories. Thereafter, **all results (not withdrawn) including information on the identity of the laboratories** will be made publicly available on the DGKL-RfB (www.dgkl-rfb.de:81/index.shtml) website.

4.14 **Participants are charged with a fee in order to cover the expenses** for transport

and materials. A small amount is necessary for administrative services (computing and secretarial work). The costs are calculated on a non-profit basis.

Flow Chart 4



5. Related documents

5.1. BIPM. The International System of Units (SI), 7th Edition. Paris, France (1998). Website: http://www1.bipm.org/en/si/si_brochure/

5.2. BIPM/IEC/IFCC/ISO/IUPAC/IUPAP/OIML. International vocabulary of basic and general terms in metrology, 2nd Edition. ISO, Geneva, Switzerland (1993).

5.3. Directive 98/79/EC of the European Parliament and of the Council of 27 October 1998 on in vitro diagnostic medical devices.
Website: http://www.fxtrans.com/medical/IVD98-79-EC.pdf

5.4. ISO 17025, General requirements for the competence of testing and calibration laboratories, ISO, Geneva, Switzerland (Date)

5.5. ISO 15195, Laboratory medicine - Requirements for reference measurement laboratories, ISO, Geneva, Switzerland (2003)

5.6. ISO 15193. In vitro diagnostic systems – Measurement of quantities in samples of biological origin – Presentation of reference measurement procedures. ISO, Geneva, Switzerland (2002).

5.7. ISO 15194. In vitro diagnostic systems – Measurement of quantities in samples of biological origin – Description of reference materials. ISO, Geneva, Switzerland (2002).

5.8. ISO 17511. In vitro diagnostic medical devices -- Measurement of quantities in biological samples -- Metrological traceability of values assigned to calibrators and control materials. ISO, Geneva, Switzerland (2003).

5.9. ISO 18153. In vitro diagnostic medical devices -- Measurement of quantities in biological samples -- Metrological traceability of values for catalytic concentration of enzymes assigned calibrators and control materials. ISO, Geneva, Switzerland (2003).

5.10. Joint Committee for Traceability in Laboratory Medicine, PREAMBLE (2004). Website: http://www.bipm.org

5.11. Joint Committee for Traceability in Laboratory Medicine, Working Group II, Procedure Manual, Website: http://www.bipm.org

6. Acronyms

BIPM ..... International Bureau of Weights and Measures, website: http://www.bipm.org

CIPM……...International Committee for Weights and Measures

C-TLM……IFCC Committee on Traceability in Laboratory Medicine

IFCC ..... International Federation of Clinical Chemistry and Laboratory Medicine, website: http://www.ifcc.org

ILAC ..... International Laboratory Accreditation Cooperation

ISO ..... International Standardization Organization

IVD..... *In Vitro* Diagnostic

IVDD..... IVDD Directive (Directive 98/79/EC of the European Parliament and of the Council of 27 October 1998 on *in vitro* diagnostic medical devices)

JCTLM ..... Joint Committee for Traceability in Laboratory Medicine.

JCTLM WG1 ..... Working Group 1 of the JCTLM, is responsible for Reference Materials and Reference Measurement Procedures

JCTLM WG2 ..... Working Group 2 of the JCTLM, is responsible for Reference Laboratory Networks

RM ……..Reference Method

7. Definitions

Analyte ..... component indicated in the name of a measurable quantity. (ISO 18153, 3.1, 2002)

Commutability..... Commutability of a material - ability of a material to yield the same numerical relationships between results of measurements by a given set of measurement procedures, purporting to measure the same quantity, as those between the expectations of the relationships obtained when the same procedures are applied to other relevant types of material (ISO 15194, 3.5)

Comparability..... A measure of the equivalence of values of the same quantity assigned to two or more CRMs that are used for calibrating or validating a specified measurement process. CRM comparability can be estimated from the extent of overlap between certified (expectation with uncertainty) and measured values (expectation with uncertainty), using a specified process under repeatability conditions. Comparability among CRMs with any given measurement process does not assure commutability of any CRM across different measurement processes.

JCTLM List I..... The list of CRMs and RMPs evaluated by JCTLM WG1 and maintained by the JCTLM Secretariat, website: (http://www.bipm.org/en/committees/jc/jctlm/jctlm-db/

Certified reference materials and reference measurement procedures for well-defined chemical entities with determined values traceable to SI units, and internationally recognized reference procedure-defined measurands; e.g. enzymes are placed in List I.

JCTLM List II ..... The list of materials evaluated by JCTLM WG1 and maintained by the JCTLM Secretariat, website: (http://www.bipm.org/en/committees/jc/jctlm/jctlm-db/

Reference Materials that are value-assigned using an internationally agreed upon protocol; e.g., WHO 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 that are applicable to patient samples. List II also contains a group of purified substances which due to the absence of reference measurement procedures should not be directly used for calibration unless commutability is established.

Measurand ..... A "particular quantity subject to measurement" (VIM 1993, 2.6)

Procedure-defined measurand ..... A measurable quantity which is defined by a measurement process rather than a primary reference material. Examples are the catalytic concentrations of enzymes which are defined by the 'Primary IFCC Reference Measurement Procedures'

Uncertainty of measurement……Parameter, associated with the result of a measurement, that characterizes the dispersion of the values that could reasonably be attributed to the measurand [VIM:1993, 3.9, GUM:1993, B.2.18] Methods for calculation must be specified.

8. Revision History

Version number	Date of Issue/Review	Summary of change
1.0	05/20/2005	Draft Issue for IFCC C-TLM
1.1	08/02/2005	
1.2	10/01/2008	4.11 is modified ('limits of equivalence'), Appendix 1 is added

9. Appendix 1

According to the decision to the SD Executive the limits of equivalence are currently set to 25 % of the performance limits for routine laboratories prescribed by the directive for External Quality Assurance for routine laboratories in Germany (valid from April 1, 2008).
In Table 1 all limits of equivalence for measurands offered in RELA ring surveys are listed. This list has to be supplemented as soon as new measurands are introduced.

Table 1(Part 1): Measurands and the corresponding Limits of Equivalence

Group	Measurand	Limits of Equivalence [%]
Metabolites and Substrates (META)	Total Cholesterol	+/- 3.25
	Total Glycerol	+/- 4.0
	Creatinine	+/- 5.00
	Uric Acid	+/- 3.25
	Urea	+/- 5.00
	Glucose	+/- 3.75
	Total Bilirubine	+/- 5.50
Electrolytes (ELEC)	Sodium	+/- 1.25
	Potassium	+/- 2.00
	Chloride	+/- 2.00
	Calcium	+/- 2.50
	Lithium	+/- 3.00
	Magnesium	+/- 3.75
Enzymes (ENZY)	ALT	+/- 5.25
	AST	+/- 5.25
	CK	+/- 5.00
	LDH	+/- 4.50
	GGT	+/- 5.25
	Amylase	+/- 5.25
Glycated Hemoglobins (GLYC)	HbA1c	+/- 4.50
Proteins (PROT)	Total Protein	+/- 2.50

Table 1(Part 2): Measurands and the corresponding Limits of Equivalence

Group	Measurand	Limits of Equivalence [%]
Hormones (HORM)	Aldosterone	+/- 8.75*
	Cortisol	+/- 7.50
	Progesterone	+/- 8.75
	Testosterone	+/- 8.75
	Estradiol-17β	+/- 8.75
	Estriol	+/- 7.50*
	Total Thyroxine	+/- 6.00
	Total Triiodthyronine	+/- 6.00
	17-OH-Progesterone	+/- 7.50*
Therapeutic drugs (THER)	Digoxin	+/- 7.50
	Digitoxin	+/- 7.50
	Theophylline	+/- 6.00

* The measurand is not yet listed in the directive of the German Medical Association.