JCTLM

- The International Committee of Weights and Mesures (**CIPM**),
- the International Federation for Clinical Chemistry and Laboratory Medicine (**IFCC**), and
- the International Laboratory Accreditation Cooperation (**ILAC**)
- agree to co-operate to establish a Joint Committee for Traceability in Laboratory Medicine, with the acronym **JCTLM**

JCTLM WHY?

- The European Directive 98/79/EC on *in vitro* diagnostic medical devices (IVD MD) requires that "the traceability of values assigned to calibrators and control materials for *in vitro* diagnostic devices must be assured through available reference measurement procedures and/or reference materials of higher order".
- The definition of "higher order" was left undefined.
- There are, however two ISO Standards (ISO/FDIS 15193 and 15194) that describe the essential requirements for higher order reference materials and methods.

JCTLM HOW?

- Under a consensus regimen, find solutions that are *fair* to:
  - science
  - metrology
  - medical applications
  - manufacturers of IVDs

Objective:

- To Harmonize results.
  - More and more people are crossing borders and changing geographic areas during their life
  - These people may be treated for certain disorders while they are in different locations and different test procedures are used to provide decision making data.
  - As our understanding of the measurand and procedures mature, large clinical studies are used to establish decision levels. These are used by physicians without regard to the methodology used in his facility

JCTLM

international and intergovernmental organizations
    measurements in laboratory medicine, metrology, health;
principal producers of IVD reference materials;
the IVD industry associations from
    Europe, Japan, USA;
regulatory bodies from
    Europe, Japan, USA;
standards writing bodies;
accreditation and quality assessment organizations.

JCTLM - Structure

- **JCTLM – Executive Board**
- Chair: J. Thijssen (IFCC), secretary R. Wielgosz (BIPM)

  Priority setting

  Approval of WG's results

- **JCTLM Working Groups: Task oriented**
  - **1. <u>Reference Materials and Reference Methods</u>**

    Chair: W.May (NIST) and H. Schimmel (IRMM)
    Compilation of existing data

  - **2. <u>Reference Laboratories - Networks</u>**

    Chair: L. Siekmann (IFCC) and L. Thienpont (IFCC)

    Guidelines for reference laboratories

    Identification of networks

JCTLM

- The global JCTLM will support comparability and equivalence of measurement results in Laboratory Medicine, through *world-wide* accepted traceability efforts following the principles of metrology.

- The JCTLM will support free trade of IVD products globally.

- The JCTLM will support IVD industry in registration and licensing the CE label for their products conforming with the EU directive.

JCTLM

- Aim to promote concept of traceability
- Close links between Ref. labs and NMI's
- Traceability to SI or beyond if needed
- Identifying and prioritizing measurands of importance requiring traceability
- Disseminating relevant information
- Providing scientific and organizational expertise for application in IVD industry

What the Manufacturer Expects

- Consistency – Within lot and between lots of reference materials the same traceable results are obtained.
  - The decision levels and expected values are based on the consistency of the reference material
  - The ability for the laboratory to provide consistent results over time is based on the consistency of the reference material
  - Note the goal is consistency of measurement over time and space

What the Manufacturer Expects

- Clarity – Instructions for use that define the conditions and tasks needed to provide traceable results
  - Clear scope of application – Intended use
  - Are the preparation instructions clear
  - Can the material be prepared/diluted in matrices similar to patient samples
- The ability to obtain the material over extended periods of time
- Recognition of the limitations of the material

What the Manufacturer Expects

- Units and measurement systems that are readily reproduced to within acceptable uncertainties.
  - Clear definition of the measurand
  - Uncertainty estimates based on technical grounds
  - When Materials change lots, the values should overlap or notification of why they do not.

What the Manufacturer Expects

- Materials that are demonstrated to meet their intended use.
  - Material value assignment is appropriate and reflects the “content” of the measurand
  - It “acts like” patient samples enough to improve or maintain the harmonization of results – or it is intended to be used as a reference material for reference methods.

What the Manufacturer Expects

When all work is done and the calibrator / method is traceable to the higher order material, the results are closer to other systems using higher order materials than if he had selected another process.

JCTLM - Structure

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JCTLM Working Group on Reference Materials and Reference Measurement Procedures

Charge:

- **establishing a process for identifying, and reviewing against agreed upon criteria** "higher order" Certified Reference Materials and Reference Measurement Procedures required for IVD industry compliance with the EC IVD Directive regarding in vitro diagnostic medical devices.

- **publishing a List** of "higher order" Certified Reference Materials and Reference Measurement Procedures required for IVD industry compliance with the EC IVD Directive regarding in vitro diagnostic medical devices.

- *Co-Chairs:* *Willie E. May (NIST)*
  Heinz Schimmel (EU IRMM)

Joint Committee for Traceability in Laboratory Medicine

Review Teams for Highest Priority Analyte Areas

Worldwide representation from Lab Accreditation Organizations, NMIs, Professional Societies , and IVD Industry

- **Electrolytes**
- **Metabolites and Substrates**
- **Nucleic Acids**
- **Hormones**
- **Enzymes**
- **Proteins**
- **Drugs**
- **Coagulation Factors**

Initial JCTLM Priority Analyte Categories I

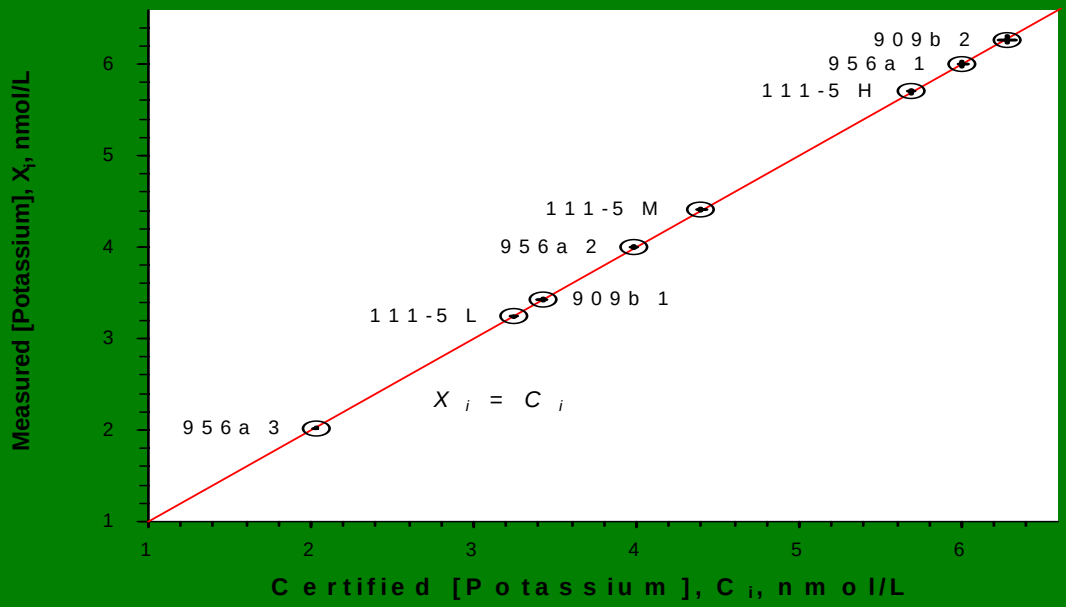
Analyte Category	Review Team Leaders
(With representative examples)	
Coagulation Factors	**Elaine Gray,** NIBSC
WHO 2nd International Standard for Antithrombin Plasma, Human	
WHO 1st International Standard for Beta Thromboglobulin Human purified	
Drugs [therapeutic and "of abuse"]	**Andre Henrion**, PTB
Digoxin/ Digitoxin *Theophylline*	
Cocaine *THC-COOH*	
Electrolytes	**Richard Miller**, Dade Behring
Calcium *Potassium* *Sodium*	
Enzymes	**Mauro Panteghini**, Azienda Ospedaliera "Spedali Civili"
AMYLASE *CK* *GGT*	

JCTLM Highest Priority Analyte Categories II

Analyte Category *(With representative examples)*	Review Team Chair
Metabolites and Substrates *Cholesterol Creatinine Glucose*	**Michael Welch**, NIST
Nucleic Acids *Hepatitis A virus RNA, Hepatitis B virus DNA*	**Helen Parkes,** LGC
Non-Peptide Hormones *Cortisol Estradiol-17ß Thyroxine*	**Heinz Schimmel**, IRMM
Proteins *Albumin Troponin-I PSA*	**David Sogin**, Abbott Laboratories

Example 1: Potassium

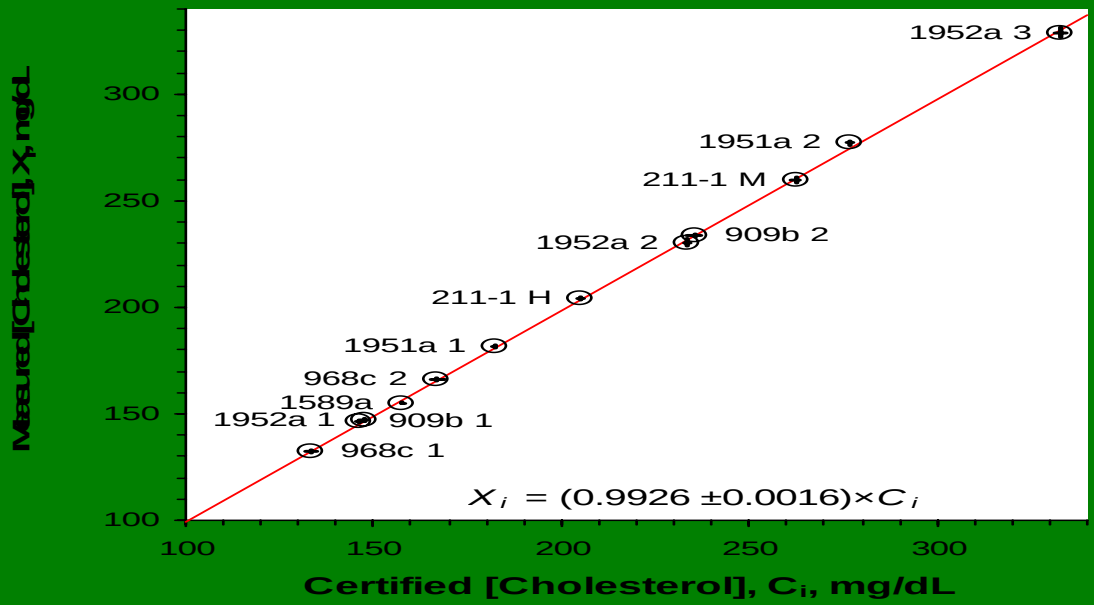
Scattergram Display



The horizontal axis reports the certified values, C_i; the vertical reports the average measured values, X_i. Each level of each CRM is displayed as approximate 95% uncertainty intervals along both axes. The intersection of these intervals is bounded by an open circle to aid visual inspection. The line denotes the identify function: $X_i = C_i$. This model was chosen after finding that the intercept of the linear model was not significantly different from zero and the slope was not significaty different from unity: $X_i = (0.003 \pm 0.013) + (0.9993 \pm 0.0028) \times C_i$.

Example 2: Cholesterol

Scattergram Display



The horizontal axis reports the certified values, C_i; the vertical reports the average measured values, X_i. Each level of each CRM is displayed as approximate 95% uncertainty intervals along both axes. The intersection of these intervals is bounded by an open circle to aid visual inspection. The line denotes the best linear model for the relationship between the measured values and the certified values: $X_i = (0.9926 \pm 0.0016) \times C_i$. This proportional model was chosen after finding that the intercept of the linear model was not significantly different from zero: $X_i = (0.92 \pm 1.27) + (0.9885 \pm 0.0059) \times C_i$.

WG-I Recommendations

[based on discussions during JCTLM Executive Meeting]

- **Publish List of Category I Reference Materials and Reference Laboratory Procedures, with descriptive Preamble, immediately [*Electrolytes, Enzymes, Drugs, Metabolites and Substrates, Non-Peptide Hormones, some Proteins*]**
- **Draft separate Preamble and publish List of Category II Reference Materials during the last quarter of 2004 after further discussions among the Working Group [*e.g. WHO materials for Coagulation Factors, Nucleic Acids, some Proteins*]**
- **Proceed with open call for new nominations in original 8 plus the 5 new categories**
- **Complete WG-I Quality Manual and present to JCTLM Executive for Adoption by August 1, 2004**

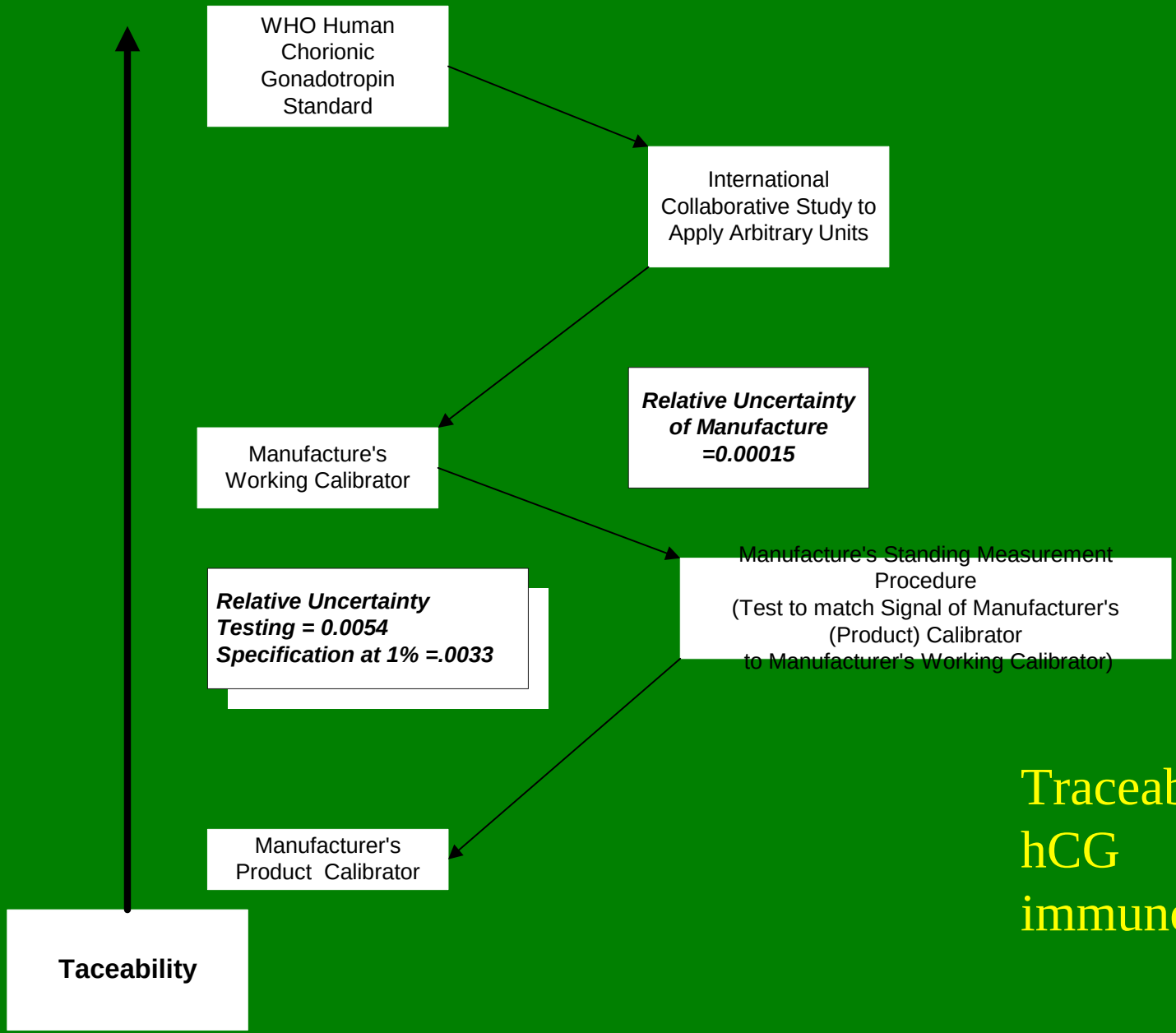
Activities of Implementation Protocols Team:

- proposing a realistic schedule for the IVD industry to change from their use of existing reference materials and methods to the “higher order” JCTLM-endorsed standards;
- proposing various means for effectively communicating the availability of the listings of these higher order standards to the industry and any changes thereof;
- establishing appropriate mechanisms by which new candidate reference materials and methods can be reviewed for inclusion in the JCTLM database and for deletion of those no longer compliant or available;
- providing a forum for continued communication among all IVD stakeholders regarding availability of standards, commutability of materials, etc.

Metrological Traceability and Its Implementation; a Report

This document provides guidance to manufacturers for establishing and reporting metrological traceability.

- An NCCLS report for global application.
- 3 december 2004



Traceability for hCG immunoassay

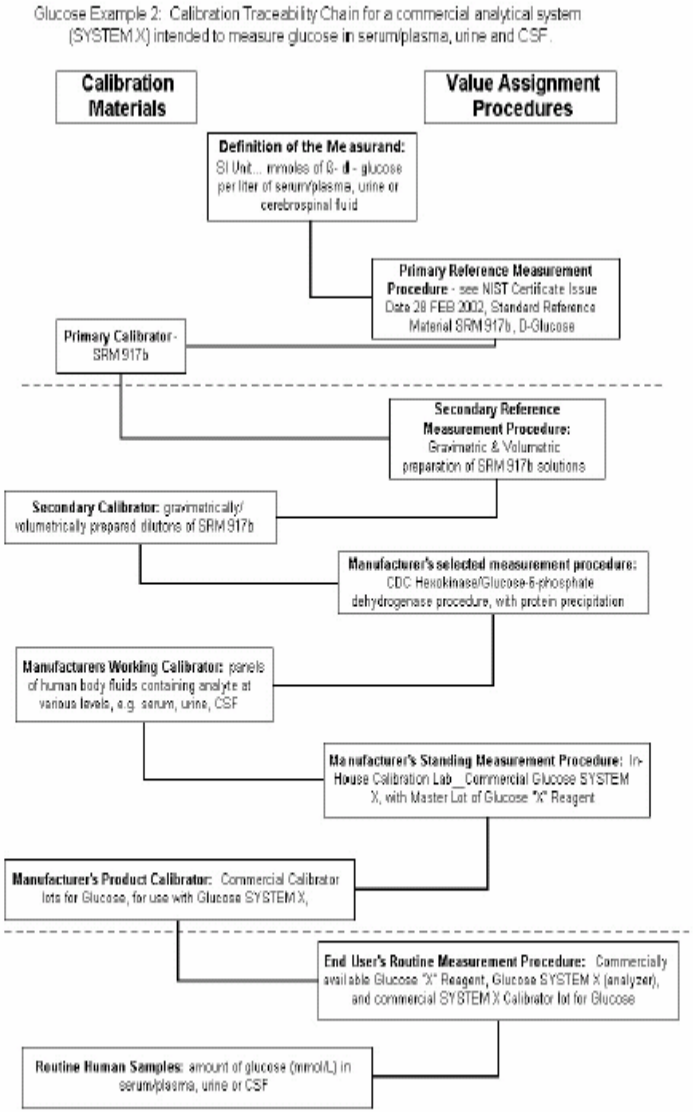


Figure 1. Traceability Chain for values assigned to calibrators, commercial SYSTEM X Calibrator for Glucose.

NCCLS report

Example 2

glucose

Metrological principles applied to Global Measurement Standards for in vitro Biological Devices

WHO consultation June 2004

WHO IS for Coagulation Factors

Summary:

- Use: measurement of coagulation activity
- Traceability: IU traceable to fresh human plasma
- Continuity: comparison to previous standard & fresh normal plasma pool
- Uncertainty: like vs like preparation for replacement standard
  (approach to minimize the level of uncertainty)

WHO IS for Hormones & other protein measurement standards

Summary:

- Use: diagnosis of diseases/monitoring of therapy
- Traceability: examples discussed
  - » TSH: traceable to the current IS
  - » hCG: measurement to SI Unit
- Uncertainty:
  - » TSH: no uncertainty
  - » hCG: uncertainty values

General Conclusions

- WHO IS: Approach for heterogenous large measurands
- Inherent variability of
    - Measurand (not necessarily defined)
    - Test procedures
- Uncertainty:
    - 1st WHO Standard – arbitrary unitage
    - Replacement IS redefines unitage
    - Multi-method collaborative study
        - » Value assignment
- Traceability path not uniform for all standards
- Commutability: in design of collaborative studies

Impact of regulatory oversight

Infectious markers & other high risk IVDs

WHO priority

Impact on Blood Safety

Hormones & other measurement Standards IFCC (NGO)

Global Measurement Standards for IVDs

Coag. Factors & Thromboplastins ISTH (NGO)

HbA1c: IFCC reference system

- **Comparability of results in medical practice**
  - Decrease costs of unnecessary tests
  - Advantage for patient
- **By**
  - Defining the measurand
  - Develop
    - Specific reference method
    - Pure compound (reference material)
  - Demonstrate decrease in variation in practice

HbA1c: IFCC reference system

- Long way to **acceptance** by other organisations
- Very extensive studies on **relations** with other **methods** (discussions with manufacturers)
- Very extensive discussions with **medical doctors** in the field of diabetes
  - EASD, ADA, JAD etc
- Consensus that IFCC-method can be used as **anchor** for all glycated hemoglobin measurements

Problems facing JCTLM

- Completely based on work by volunteers
  - From IFCC, BIPM, NMIs
- Cholesterol example NIST
- HbA1c example by
  - IFCC, one manufacturer and IRMM
- Support from manufacturers impossible
  - No profit for them, no EU-organ involved