

Activities of the Joint Committee on Traceability in Laboratory Medicine

The recently enacted European Directive 98/79/EC on *in vitro* diagnostic medical devices (IVD MD) requires, among other things, 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 the term “higher order” was left undefined in the Directive. There are, however two ISO Standards (ISO/FDIS 15193 and 15194) that describe the essential requirements for higher order reference materials and methods.

To facilitate the identification of the “higher order” Reference Measurement Procedures and Certified Reference Materials (CRMs) that are currently available, the Joint Committee on Traceability in Laboratory Medicine (JCTLM) was created at a meeting held at the International Bureau of Weights and Measures (BIPM) in early June 2002. The aim of the Joint Committee is to meet the need for a worldwide platform to promote and give guidance on internationally recognized and accepted equivalence of measurements in Laboratory Medicine and traceability to appropriate measurement standards. The JCTLM Executive, which oversees the activities of the Joint Committee, is made up of representatives from the International Bureau of Weights and Measures (BIPM), the International Federation for Clinical Chemistry and Laboratory Medicine (IFCC) and the International Laboratory Accreditation Cooperation (ILAC). Professor Joseph H.H. Thijssen, The Netherlands and representing IFCC is the current Chairman of JCTLM. The secretariat of the JCTLM is maintained by the BIPM.

The sixty people present at the meeting represented the major international and intergovernmental organizations concerned with measurements in laboratory medicine, metrology, and health; the principal producers of IVD reference materials; the IVD industry associations from Europe, Japan and the USA; regulatory bodies from Europe, Japan and the USA; standards writing bodies; and accreditation and quality assessment organizations. The JCTLM created two working groups:

- Reference Materials and Reference Procedures
- Reference Laboratory Networks

The primary function of the working groups is to provide practical support to the worldwide IVD industry in establishing metrological traceability for values assigned to calibrators and/or control materials as required by the forthcoming European Directive on *in vitro* diagnostics and by comparable regulations in other countries.

Willie E. May (NIST) and Heinz Schimmel (EU Institute for Reference Materials and Measurements) are serving as Co-Chairs of JCTLM Working Group-I: Reference Materials and Reference Procedures. JCTLM WG-I is charged with establishing a process for identifying, reviewing against agreed upon criteria, and 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.

Professor Dr. Lothar Siekmann, University of Bonn (Germany), and Professor Dr. Linda Thienpont, University of Gent (Belgium), are Co-Chairs of JCTLM Working Group-II. JCTLM Working Group-II is charged with:

- Collecting information on existing and candidate reference measurement laboratories (RMLs)
- Encouraging and facilitating the formation of networks of RMLs for different groups of measurable quantities (concerning electrolytes, substrates/metabolites, enzymes, HbA1c, low molecular hormones, etc.)
- Establishing a procedure for the approval of RMLs on the basis of their metrological level according to ISO 15195 and their performance as demonstrated in inter-laboratory comparisons linked to an NMI.

Current Activities:

In order to facilitate the review process, JCTLM WG-I agreed on eight highest priority analyte categories listed below and established Review Teams for each. To the extent possible, each Review Team had representation from IVD manufacturers, National Metrology Institutes, accreditation organizations, and professional societies from the US, Europe, and the Asia Pacific Region.

<u>Analyte Category</u> <i>(With representative examples)</i>	<u>Review Team Chair</u>
Coagulation Factors <i>WHO 2nd International Standard for Antithrombin Plasma, Human</i> <i>WHO 1st International Standard for Beta Thromboglobulin Human purified</i>	Elaine Gray, NIBSC
Drugs [therapeutic and “of abuse”] <i>Digoxin/ Digitoxin</i> <i>Theophylline</i> <i>Cocaine</i> <i>THC-COOH</i>	Andre Henrion, PTB
Electrolytes <i>Calcium</i> <i>Potassium</i> <i>Sodium</i>	Richard Miller, Dade Behring
Enzymes <i>AMYLASE</i> <i>CK</i> <i>GGT</i>	Mauro Panteghini, Azienda Ospedaliera “Spedali Civili”
Metabolites and Substrates <i>Cholesterol</i> <i>Creatinine</i> <i>Glucose</i>	Michael Welch, NIST
Nucleic Acids <i>Hepatitis A virus RNA,</i> <i>Hepatitis B virus DNA</i>	Helen Parkes, LGC
Non-Peptide Hormones <i>Cortisol</i> <i>Estradiol-17β</i> <i>Thyroxine</i>	Heinz Schimmel, IRMM
Proteins <i>Albumin</i> <i>Troponin-I</i> <i>PSA</i>	David Sogin, Abbott Laboratories

Nominations for higher order Reference Materials and Reference Measurement Procedures were solicited through a widely distributed open call where information was requested in common a format defined by templates that were provided for Reference Materials and Reference Measurement procedures.

JCTLM Working Group-I, has conducted four meetings to review nominations received for ~ 80 Reference Methods and 435 Reference Materials. The “higher order” Reference Materials and Reference Measurement Procedures identified through this review process [Reference Measurement Procedures for ~40 measurands and Reference Materials for ~100 measurands/analyte-matrix combinations] will be published in a database maintained by the BIPM. This List of “higher order” Standards will be publicly available on the BIPM, IFCC and other relevant websites by the end of March 2004. Two Lists of Higher Order Reference Materials and Reference Measurement Procedures will be published:

List I. Certified Reference Materials and Reference Measurement Procedures for well-defined chemical entities or internationally recognized reference method-defined measurands. Reference Materials and Measurement Procedures included in this category are those that provide values that are traceable to the SI units; e.g., Electrolytes, Enzymes, Drugs, Metabolites and Substrates, Non-Peptide Hormones, and some Proteins. List I will be published in April, 2004.

List II. International Conventional Reference Materials, i.e. where the measurand(s) is/are not SI traceable and/or no internationally recognized reference measurement procedure is available; e.g., WHO reference materials for Coagulation Factors, Nucleic Acids, and some Proteins. List II will be published during the last quarter of 2004.

As measurement science is advanced to the point that ListCategory II measurands can be clearly defined and/or internationally-recognized reference measurement procedures are developed, reference materials could move from ListCategory II to List Category I. Measurands that cannot be included in either Category I or Category II are not traceable to a higher metrological order. These measurands are traceable only to a manufacturer’s internal value assignment process.

Each List will be preceded by a preamble that clearly explains its contents and a brief explanation of the process used to determine which Reference Materials and Reference Measurement Procedures are included. See example below for JCTLM List I Reference Measurement Procedures and Reference Materials for cholesterol:

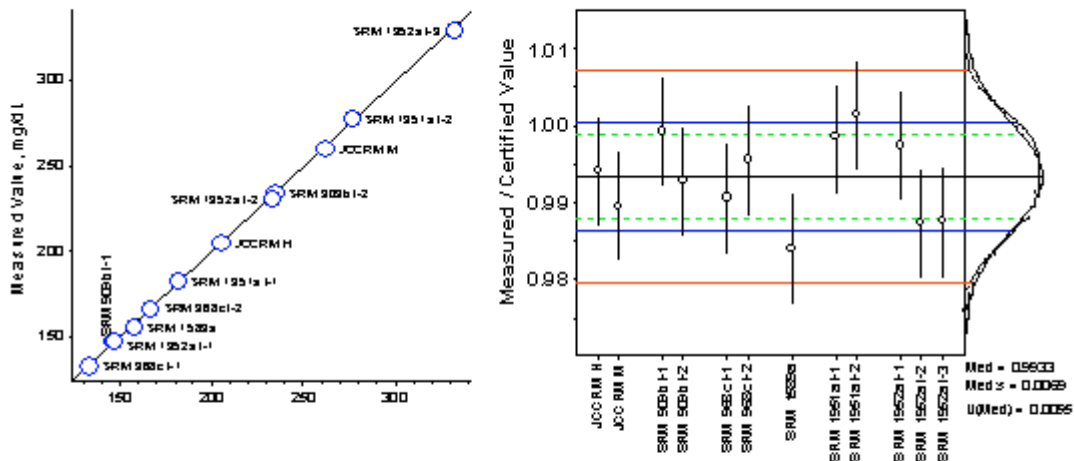
Reference Measurement Procedure					
Procedure Name and/or ID #	Analyte Name	Applicable Matrices	Measurement Principle	Reference Procedure Citation(s) or Document(s)	Reference Procedure Comparability Assessment Studies
NIST definitive method for serum cholesterol	cholesterol	lyophilized, fresh, or frozen serum	ID/GC/MS	Anal Chem 61, 1718-1723 (1989)	CCQM-K6; http://kcdb.bipm.org/appendixB/appbr esults/ccqm-k6/ccqm-k6_final_report.pdf ; Clin Chem 36, 370-375 (1990)
U. Of Ghent reference method for cholesterol	cholesterol	lyophilized, fresh, or frozen serum	ID/GC/MS	Clin Chem 39,1001-6 (1993) [=part II of Clin Chem 39,993-1000 (1993)]; Eur J Clin Chem Clin Biochem 34, 853-60 (1996); Clin Chem 42, 531-5 (1996)	EUROMET 563
DGKC definitive Method for Serum Cholesterol	cholesterol	lyophilized, fresh, or frozen human serum or plasma	ID/GC/MS	Siekmann et al., Z. anal. Chem. 279, 145-146 (1976)	PTB - National Key Comparison for Accreditation
CDCAbell-Kendall method for cholesterol	cholesterol	lyophilized, fresh or frozen human serum	Spectrophotometry	Cooper, GR, et al, Clin Chem 32: 921-929, 1986	Clin Chem 36, 370-375 (1990)

Reference Materials					
Information about Material				Contact Information	
Analyte	Matrix	Material Name and/or ID #	Estimated * Availability (months, as of Jan 2004)	- Producer - Country - Website - Email Address - Phone Number - Fax Number	Commutability Study Information and/or Citations
cholesterol	cholesterol	GBW09203b	60	NRCCRM, China Tel: 086-10-64221811 Fax: 086-10-64213149 Email: crmservice@nrccrm.com.cn	Primary calibrator for higher order reference methods
cholesterol	cholesterol	SRM 911b	21	NIST, USA http://ts.nist.gov/ts/htdocs/230/232/232.htm Email: srminfo@nist.gov Tel:(301)975-6776 Fax: (301)948-3730	Primary calibrator for higher order reference methods
cholesterol	human serum	JCCRM 211	12	HECTEF, Japan http://www.in8.co.jp/hectef/starte.htm Tel: 81-44-813-0055 Fax: 81-44-813-0224	
cholesterol	human serum (frozen)	SRM 1951b	60	NIST, USA http://ts.nist.gov/ts/htdocs/230/232/232.htm Email: srminfo@nist.gov Tel:(301)975-6776 Fax: (301)948-3730	Material prepared following NCCLS Document C37-A "Preparation and Validation of Commutable Frozen Human Serum Pools as Secondary Reference Materials for Cholesterol Measurement Procedures; Approved Guideline" Method used for certification: Anal Chem 61, 1718-1723 (1989)
cholesterol	human serum (lyophilized)	SRM 1952a	60	NIST, USA http://ts.nist.gov/ts/htdocs/230/232/232.htm Email: srminfo@nist.gov Tel:(301)975-6776 Fax: (301)948-3730	
cholesterol	human serum (lyophilized)	SRM 968c	38	NIST, USA http://ts.nist.gov/ts/htdocs/230/232/232.htm Email: srminfo@nist.gov Tel:(301)975-6776 Fax: (301)948-3730	
cholesterol	human serum (lyophilized)	SRM909b	60	NIST, USA http://ts.nist.gov/ts/htdocs/230/232/232.htm Email: srminfo@nist.gov Tel:(301)975-6776 Fax: (301)948-3730	

A laboratory-based quality assurance audit program will also be initiated to provide measurement results that demonstrate the comparability of multiple "higher order" Reference Materials for the same analyte-matrix combination (measurand) on the list as well as to verify the veracity of the review process. Results from a study for Cholesterol in Serum CRMs

where NIST measurement results are plotted vs. CRM certified values are shown below. The error bars represent 95% confidence intervals ($k=2$).

Comparison of “higher order” Cholesterol in Serum CRMs



⇒ CRM comparability independent of analyte level

The measured/certified ratios for this set of CRMs are:

- ~ normally distributed
- with a standard deviation of ~0.7%

Based on the contents of the “List” and input from the medical professional, laboratory accreditation and IVD manufacturing communities, JCTLM WG-I will also identify highest priority needs for new CRMs and Reference Measurement Procedures. NIST, IRMM and certified reference materials producers in the European Union and the Asia Pacific region are discussing approaches for sharing the work-load involved in developing and maintaining any additional measurement standards needed.

If there are questions about JCTLM Working Group-I activities in general or any particulars about the review process please contact Dr. Willie E. May (willie.may@nist.gov) or Dr. Heinz Schimmel (heinz.schimmel@irmm.jrc.be).

Future Plans: During the coming year, the JCTLM Review Teams will continue to function in the eight areas already established. New JCTLM Review Teams for Blood Gases, Blood Groupings, Microbial Serology, Non-Electrolyte Metals and Vitamins will be established in 2004. The next “open season” for nominations of Reference Materials and Reference Measurement Procedures will be February 1 - May 1, 2004. This “open season will be announced by a letter that will be distributed widely and also posted on the BIPM, IFCC and other relevant webpages in January, 2004. JCTLM WG-II is currently in the process of establishing criteria and processes for assessing the needed competencies of candidate Reference Laboratories which will include the establishment of networks for conducting “ring trials” to allow assessment of competence in the implementation of Reference Laboratory Procedures on a measurand-by-measurand basis. Data from the “ring trials” will also be used to assess the comparability different “higher order” Reference Measurement Procedures for the same measurand. The functions of the Review Teams will be expanded to include responsibility for evaluating the competence of candidate Clinical Reference

Laboratories against ISO/FDIS 15195. Nominations have been received for more than 300 laboratory-measurand combinations. A more detailed account of JCTLM WG-II activities will be provided in an upcoming issue of this newsletter and the initial list of Clinical Reference Laboratories endorsed by the JCTLM should be available by late 2004.

An Implementation Protocols Team working under the auspices of JCTLM WG-I has been established to address issues regarding the IVD Industry use of the JCTLM-endorsed Reference Materials, Reference Measurement Procedures and Reference Laboratories. Led by Dr. Craig M. Jackson, Hemosaga Diagnostics Corporation, the Team is addressing issues such as:

- 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.