

Dear Colleagues:

The purpose of this communication is to request nominations for reference materials and reference measurement procedures for potential inclusion in the Joint Committee on Traceability in Laboratory Medicine (JCTLM) Lists of Higher Order Reference Materials and Reference Measurement Procedures.

Background:

The aim of the JCTLM is to support world-wide comparability, reliability and equivalence of measurement results used for assessing and monitoring human health status and for facilitating national and international trade of *in vitro* diagnostic devices. The 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/or control materials must be assured through available reference measurement procedures and/or available reference materials of a higher order.” The definition of the term “higher order” was left undefined in the Directive. There are, however, two ISO Standards (15193 and 15194) that describe the essential requirements for higher order reference materials and methods.

To facilitate the identification of the “higher order” Certified Reference Materials (CRMs) and Reference Measurement Procedures 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 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 Chair of JCTLM. The secretariat of the JCTLM is maintained by the BIPM.

The JCTLM created two working groups:

- JCTLM WG-1, Reference Materials and Reference Procedures
- JCTLM WG-2, 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 IVD MD and by comparable regulations in other countries.

JCTLM WG-1 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 for use by the IVD industry to demonstrate compliance with the IVD MD. In order to facilitate the review process, JCTLM WG-1 identified the thirteen high priority analyte categories listed in Table I and established Review Teams for each. To the extent possible, each Review Team has representation from IVD manufacturers, National Metrology Institutes, accreditation organizations, and professional societies from the US, Europe, and the Asia Pacific Region.

Agreements and Results from Cycle I of this Process:

The first cycle (Cycle I) of this nomination and review process was conducted in the September 2002 to April 2004 time period. The “higher order” Reference Materials and Reference Measurement Procedures identified through the Cycle I review process [Reference Measurement Procedures for ~40 analyte-matrix combinations (measurands) and Reference Materials for ~100 measurands] will be published in a database that will be publicly available on the BIPM/JCTLM (<http://www1.bipm.org/en/committees/jc/jctlm/>), IFCC and other relevant websites in April 2004. There will be two Lists of Higher Order Reference Materials and Reference Measurement Procedures:

- List I. 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, Enzymes, Drugs, Metabolites and Substrates, Non-Peptide Hormones, some Proteins*] This List will be published in April 2004.
- List II. International Conventional Reference Materials, i.e., where the measurand(s) is/are not completely defined and/or no internationally recognized reference measurement procedure is available [e.g. WHO reference materials for Coagulation Factors, Nucleic Acids, some Proteins]. This List will be published by the last quarter of 2004.

Tables 2 and 3 provide examples for the reference measurement procedures and Certified Reference Materials for Cholesterol reference materials that are included on the First Provisional List.

Cycle II nomination and review process:

For the next cycle, additional nominations are hereby solicited for high purity substance reference materials and for human hair and body fluid-based reference materials and reference measurement procedures. For reference materials, nominations will be accepted only from the reference material producing organization. Upon request from the JCTLM, the Producer will also be expected to provide a small number of units for conducting a comparability assessment among other listed materials. (See Figures 1a and 1b)

To facilitate the nomination process, attached is an Excel file containing:

- A Template illustrated with examples for nomination of Reference Materials
- A Template illustrated with examples for nomination of Reference Measurement Procedures
- A Blank Template for use in submitting your Reference Material nominations
- A Blank Template for use in submitting your Reference Measurement Procedure nominations

Note that separate templates are used for nominating Reference Materials and for Reference Measurement Procedures. These templates are intended to solicit most of the information that

will be required for the Review Teams to make their assessments. However, the Review Teams may need to request additional information for some or all of your nominations, so please make sure to complete the "Contact Information for Additional Details" field for each nomination in the templates.

The schedule for the Cycle II nomination and review process is as follows:

- Completed Nomination Spreadsheets to be returned to wem@nist.gov by 15 May 2004.
- Information provided on spreadsheets will be sorted and provided to the Review Teams in early June 2004.
- Nominations will be reviewed by Review Teams from June to December 2004
- Approved nominations will be added to the JCTLM List of Higher Order Reference Materials and Reference Measurement Procedures in January 2005.

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

When published, each List will be preceded by a preamble that clearly explains its contents and provides a brief explanation of the process used to determine which Reference Materials and Reference Measurement Procedures are included.

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 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 in Figure 1. The error bars represent 95% confidence intervals ($k=2$).

If there are questions about JCTLM WG-1 activities in general or any particulars about the Reference Method and/or Reference Materials review process, please contact:

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Table I**Analyte Category***(With representative examples)***Review Team Chair****Blood Gases**

pO₂
pCO₂

Susan Blonshine, TechEd Consultants**Blood Groupings**

British Standard for anti-D (Rho) antibodies, human
British Minimum Potency Reference Preparation for anti-A blood grouping reagents

Sue Thorpe, NIBSC**Coagulation Factors**

WHO 2nd International Standard for Antithrombin Plasma, Human
WHO 1st International Standard for Beta Thromboglobulin Human Purified

Elaine Gray, NIBSC**Drugs [therapeutic and “of abuse”]**

Digoxin/Digitoxin
Theophylline
Cocaine
THC-COOH

Andre Henrion, PTB**Electrolytes**

Calcium
Potassium
Sodium

Richard Miller, Dade Behring**Enzymes**

Amylase
CK
GGT

**Mauro Panteghini, Azienda Ospedaliera
“Spedali Civili”****Metabolites and Substrates**

Cholesterol
Creatinine
Glucose

Michael Welch, NIST**Microbial Serology**

Hepatitis B surface antigen (HBsAg)
Antibodies to hepatitis A virus
Antibodies to toxoplasma

Morag Ferguson, NIBSC**Non-Electrolyte Metals**

Arsenic
Cadmium
Lead

Lee Yu, NIST

Non-Peptide Hormones

Cortisol
Estradiol – 17 β
Thyroxine

Heinz Schimmel, IRMM

Nucleic Acids

Hepatitis A Virus RNA
Hepatitis B Virus DNA

Helen Parkes, LGC

Proteins

Albumin
Troponin-I
PSA

David Sogin, Abbott Laboratories

Vitamins and Micronutrients

Retinol (Vitamin A)
Alpha Tocopherol (Vitamin E)
Beta Carotene
Folates

Katherine Sharpless, NIST

Table 2. Reference Measurement Procedures for Cholesterol

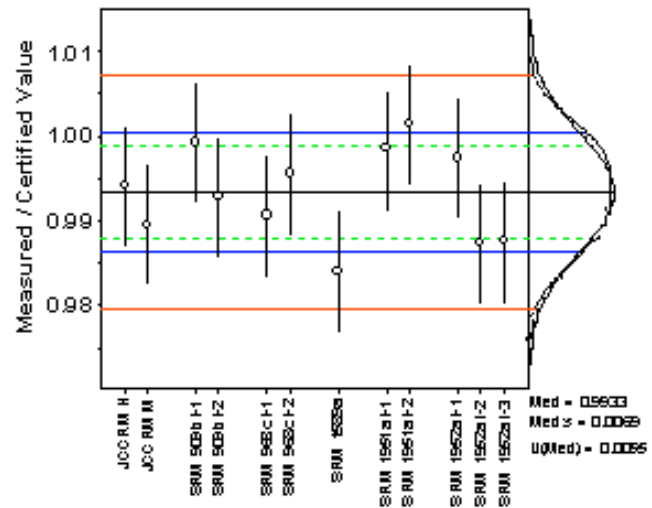
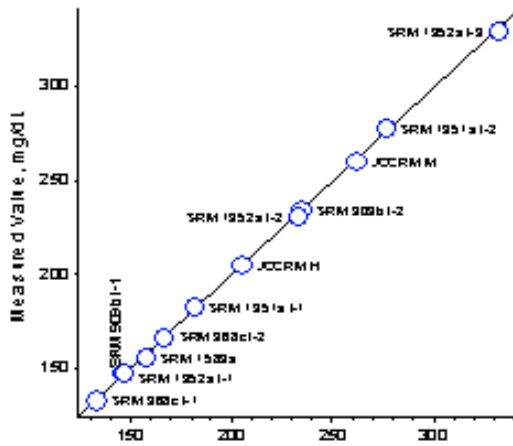
Reference Measurement Procedure					
Procedure Name and/or ID #	Analyte Name	Applicable Matrices	Measurement Principle	Reference Procedure Citation(s) or Document(s)	Reference Procedure Comparability Assessment Studies
NIST definitive method for serum cholesterol	cholesterol	lyophilized, fresh, or frozen 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	Siekman 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)

Table 3. Certified Reference Materials for Cholesterol

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	

Figure 1.

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%