JCTLM Members and Stakeholders Meeting
Session 2: Commutability

Commutability and Traceability: An Industry View Or 2013: The Year of Commutability

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In Vitro Diagnostics Directive (7 Dec 03)

IVDD applies to European Economic Community (CE mark), but has global implications

Requires manufacturers to establish metrological traceability of kit calibrators & provide calibrator uncertainty (linkage between traceability and uncertainty) implies commutability

Doesn't provide guidance for establishing traceability or estimating uncertainty

Traceability per ISO 17511, Metrological Traceability of Values Assigned to Calibrators and Control Materials*

- Establishes a metrology infrastructure for global assay standardization/harmonization in the clinical laboratory.
- Requires cooperation of national metrology institutes (NMIs), academia, industry, professional societies, & EQA/PT providers.

*Also ISO 15189, Medical laboratories- particular requirements for quality and competence (basis for laboratory accreditation)

Paradigm Shift for IVD Manufacturers

- Manufacturers traditionally differentiate themselves from the competition (e.g., greater dynamic range, lower LoD, better precision, smaller sample size, etc.)- **not a priority to produce comparable results, as through commutability of reference materials** (clear from review of EQA/PT peer group data)
- In era of IVDD & metrological traceability, results from different systems should be comparable. Manufacturers now provide traceability/uncertainty information, restandardize assays, **address commutability**, etc., and work with many professional organizations, including JCTLM, and each other to achieve traceability/standardization, **but this is a new approach and a new challenge**
- Manufacturers now have an integral role in educating customers about standardization/harmonization and the practice of clinical laboratory science and to ensure continued comparability of test results **(includes commutability)**

Six Pillars of International Traceability & Standardization

JCTLM established the three pillars of traceability:

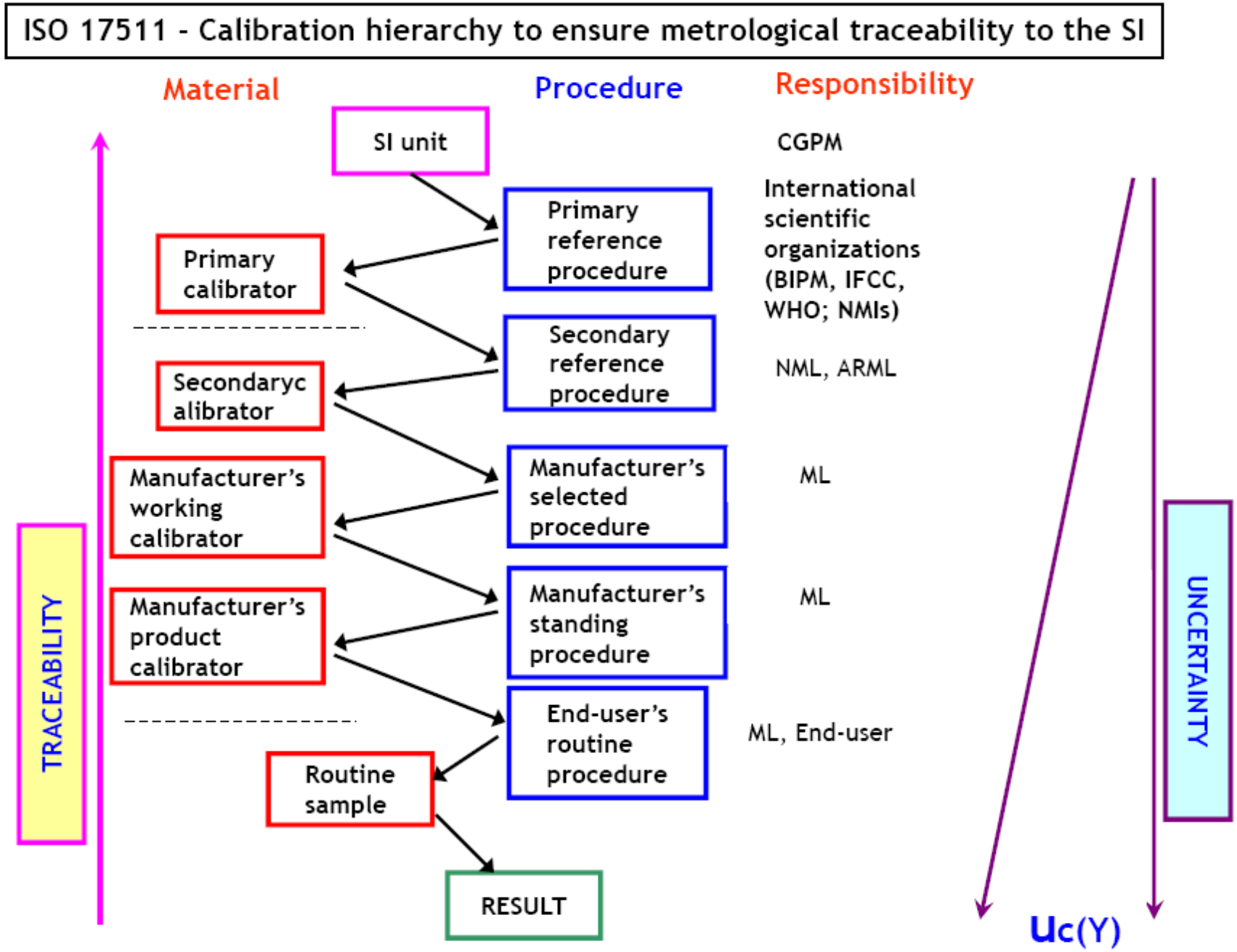
- **Reference measurement procedures (RMP)**
- **Reference materials (RM) (includes commutability)**
- **Network of Reference Measurement Laboratories**

IFCC described a fourth pillar:

- **Universal reference intervals/MDLs**

Fifth and sixth pillars:

- **Accuracy based grading EQA/PT to ensure and maintain international reference systems**
- **Total Testing Process (TTP): International standardization/harmonization of clinical laboratory practice (nomenclature/terminology/units, EBLM, etc.)**



Now recognized commutability is part of the traceability chain

Definition of Commutability

ISO 17511/15194/VIM: Property of a given reference material, demonstrated by the closeness of agreement between the relation among the measurement results for a stated quantity in this material, obtained according to two measurement procedures, and the relation obtained among the measurement results for other specified materials.

Translated from ISO-speak: a reference material and fresh patient specimens exhibit the same analytical response (regression line slope about 1.0) when tested using two different methods (preferably one being an established reference method).

Within Industry, commutability sometimes mistakenly applied to analyzers, analytical methods, reagents, etc., instead of a property of a reference material (e.g., primary or secondary RM, trueness control, calibrator, EQA/PT sample, etc.). Industry confuses "commutability" with "comparability" of test results. Use of reference materials doesn't guarantee comparable patient test results unless a commutability study is performed, ideally comparing a field method to a recognized reference method. Such studies have been uncommon and are best performed with assistance of professional societies/experts. Commutability has a very specific metrological definition and the word should be used carefully and correctly. Industry is still learning this.

Something New for the Clinical Lab

Tietz Textbook of Clinical Chemistry, 3rd Ed., 1999: no mention of uncertainty or commutability
4th Ed., 2006: uncertainty and commutability addressed, although only a definition of commutability is given (material yields the same result by two methods)
5th Ed., 2012: expanded discussion of uncertainty; same definition of commutability as in 2006.

Metrological traceability of measurement results in chemistry: Concepts and implementation. De Bievre P, et al. Pure Appl Chem 2011;83:1873-1935.

"Discussions with analytical chemists have revealed that basic concepts in metrology, including 'traceability,' are generally not an integral part of university or college curricula and are not treated in most text books of analytical chemistry."
Those unaddressed "concepts in metrology" include commutability.

"… measurement results obtained at one time must be comparable with those obtained at another time, in the same or another laboratory."

Commutability: A peculiar property of calibrationand control materials. Definition and evaluation. Cattozo G, Franzini C. Clin Chim Acta 2012:414;152-153.

"Scanning the relevant literature of the last 30 years, it appears that the concept and the terminology of commutability gave rise to remarkable enthusiasm in the community of clinical chemists worldwide. Unfortunately, both the concept and terms were often misused, and confused with other metrological properties, like analytical precision and trueness, in spite of the clear definition of the property shown above. We would like to mention here that both the concept and the terminology have been explicitly endorsed by authoritative metrological organizations."

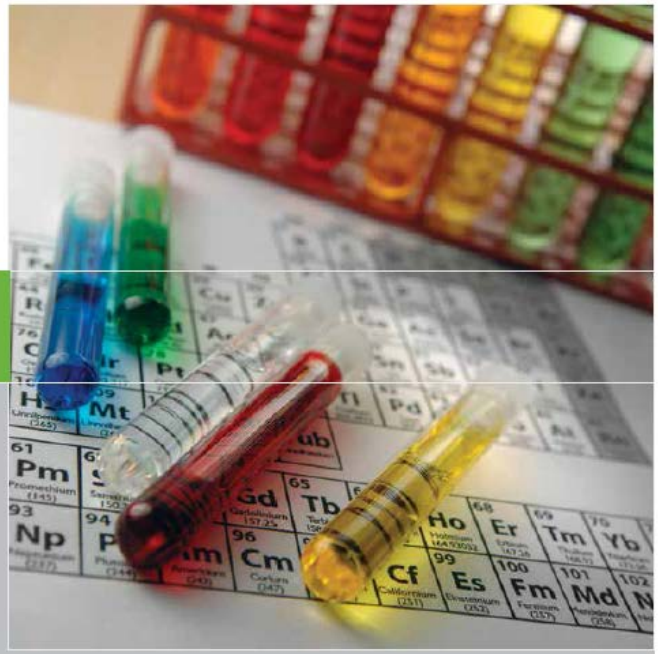
"The analytical protocol for testing the commutability (between two methods) of a stated (control) material with genuine fresh human serum is not very complicated. The two methods, the material and a number (say 20 – 100) of genuine fresh human serum samples are needed; serum samples should contain the component in concentrations spanning the range of " normal " and commonly encountered pathological values. The samples are split into two aliquots, the analytical measurements are performed with the two methods, and then appropriate statistical evaluation is applied to check if, at the chosen level of probability, the differences between the pair of values observed for the control material belongs (commutable material) or not (non-commutable material) to the population of intra-pair differences recorded for the fresh serum samples. This is the simplest, yet most valuable approach to evaluate commutabiity."

The term "commutability" must be used properly to avoid confusion!

Manufacturer's Provide Calibrator Traceability/Uncertainty Information

TRACEABILITY AND UNCERTAINTY OF MEASUREMENT

ARCHITECT



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ARCHITECT

Welcome to the ABBOTT ARCHITECT Traceability and Uncertainty of Measurement Document

This document provides information on the traceability of calibration materials used on the ABBOTT ARCHITECT Clinical Chemistry systems and the measurement of uncertainty (commonly known as uncertainty) with these instruments.

The data contained on this document has been calculated following the ISO (International Organization for Standardization) Guide to the Expression of Uncertainty in Measurement (GUM)[1] and the EURACHEM Guide for Quantitative Uncertainty in Analytical Measurement (EURACHEM/CITAC Guide)[2].

Error is the specific difference between an observed sample value and the value considered to be the true value. Uncertainty, in contrast, is an estimate of the range in which the true value of reported result may occur. Uncertainty values are estimates that describe the 95% confidence limits for the true value of a specific calibrator. Uncertainty estimates are not intended to describe a performance specification for a calibrator, but instead are a statistical description of the likelihood that the true value of the calibrator will be found in the cited range, within the stated confidence limits.

The data used to calculate estimates of uncertainty are indirect and are derived from the various steps involved in the manufacture of the calibrators. Sources of potential error are quantitated and then sequentially added in a manner consistent with GUM and the EURACHEM/CITAC Guide[1,2]. Based on the calculations, 95% of the lots of calibrators are predicted to have an actual value within the stated range. The actual target value of a calibrator may vary from lot to lot, and the uncertainty estimate may also differ slightly. The uncertainty estimates listed reflect the typical values and may be used for the calculation of the total uncertainty associated with a test result.

The total uncertainty of test results for assays depend on a variety of separate uncertainties, including the uncertainties attributable to all absorbance readings; reagent, diluent, and sample volumes; matrix effects, instrument drift, inta-individual biological variation, pre-analytical factors, etc. Total analytical uncertainty is primarily driven by the analytical imprecision of the assay system. The uncertainty estimates of calibrators typically accounts for only a small portion of the total uncertainty estimate for a test result. Additional sources of analytical uncertainty occur in each clinical laboratory, in addition to pre-analytical and post-analytical uncertainty contributed by the laboratory.

This document will be updated with additional assay information as data becomes available.

[1] Guide to the expression of uncertainty in measurement. ISO: Geneva, 1995.
[2] EURACHEM/CITAC Guide quantifying uncertainty in analytical measurement. 2nd ed. Eurachem, 2000.

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Manufacturer's Provide Calibrator Traceability/Uncertainty Information

Clinical Chemistry Traceability and Uncertainty of Measurement

Assay Name	Assay List Number	Calibrator List Number-Name	Conventional Units (SI)	Calibrator Level	Nominal Value (SI)	Uncertainty (SI) K=2	Reference Material (Standardization)	Reference Method
A-1-AGP Serum/Plasma	6L34	6K45-Proteins Standard	mg/dL (g/L)	1 2 3 4 5	18 (0.18) 45 (0.45) 90 (0.90) 135 (1.35) 180 (1.8)	0.966 (0.010) 2.415 (0.024) 4.83 (0.048) 7.245 (0.072) 9.660 (0.097)	ERM-DA470/IFCC	Immunoturbidimetric
A1-AT Serum/Plasma	6K99	6K45-Proteins Standard	mg/dL (g/L)	1 2 3 4 5	31 (0.31) 77.5 (0.78) 155 (1.55) 232.5 (2.33) 310 (3.10)	1.664 (0.017) 4.159 (0.042) 8.318 (0.083) 12.477 (0.125) 16.636 (0.166)	ERM-DA470/IFCC	Immunoturbidimetric
Acetaminophen Serum/Plasma	2K99	2K99-Acetaminophen Calibrator	µg/mL (µmol/L)	1	151 (999.62)	2.013 (13.328)	Acetaminophen Reference Standard (98-101% purity)	Gravimetric
Albumin BCG Serum/Plasma	7D53	1E65-Multiconstituent Calibrator	g/dL (g/L)	1 2	1.75 (17.50) 5.20 (52.00)	0.026 (0.258) 0.077 (0.767)	ERM-DA470	Gravimetric
Albumin BCP Serum/Plasma	7D54	1E65-Multiconstituent Calibrator	g/dL (g/L)	1 2	1.75 (17.50) 5.20 (52.00)	0.030 (0.297) 0.088 (0.884)	ERM-DA470	Gravimetric
Amikacin Serum/Plasma	6L35	6L35-Amikacin Calibrator	µg/mL (µmol/L)	2 3 4 5 6	3.00 (5.13) 10.00 (17.10) 20.00 (34.20) 35.00 (59.85) 50.00 (85.50)	0.100 (0.171) 0.333 (0.570) 0.666 (1.140) 1.167 (1.995) 1.667 (2.850)	USP grade Amikacin	Gravimetric
		5P04-TDM Multiconstituent Calibrator	µg/mL (µmol/L)	2 3 4 5 6	3.04 (5.20) 10.46 (17.89) 19.66 (33.62) 34.16 (58.41) 48.65 (83.19)	0.111 (0.190) 0.382 (0.653) 0.718 (1.228) 1.247 (2.133) 1.776 (3.038)	USP grade Amikacin	Gravimetric
Ammonia Ultra Plasma	6K89	6K89-Ammonia Ultra Calibrator	µg/dL (µmol/L)	1	500 (293.50)	10.000 (5.870)	Ultra pure Ammonium Sulfate	Gravimetric
Amphetamine/ Methamphetamine Urine	3L37	3L43-DOA MC I Calibrators 1-4	ng/mL (µmol/L)	1 2 3 4	500 (3.35) 1000.00 (6.70) 1500 (10.05) 2000.00 (13.40)	33.333 (0.223) 66.667 (0.447) 100.000 (0.670) 133.333 (0.893)	≥99% pure Methamph-etamine stock standard	Volumetric
Apolipoprotein A1 Serum/Plasma	9D92	6E54-Apo A1/Apo B Calibrator	mg/dL (g/L)	1	335 (3.35)	5.994 (0.060)	WHO/IFCC/CDC Standard SP1-01	Gravimetric
Apolipoprotein B Serum/Plasma	9D93	6E54-Apo A1/Apo B Calibrator	mg/dL (g/L)	1	265 (2.65)	6.290 (0.063)	WHO/IFCC/CDC Standard SP3-08	Immunoturbidimetric
ASO Serum	6K38	6K46-ASO Standard	IU/mL (IU/mL)	1	300.00 (300.00)	20.000 (20.000)	WHO International Standard for ASO, NIBSC code: 97/662	Immunoturbidimetric

Commutability of calibrators and/or reference materials not necessarily described!

Harmonisation of measurement procedures: how do we get it done? Gantzer ML, Miller WG. Clin Biochem Rev 2012;33:95 – 100.

"Despite the description of commutability in the early 1970s and its importance in achieving comparability of results among different procedures, the **concept is still poorly understood and appreciated.** Commutability is a property of a RM such that values measured for a RM and for the samples intended to be measured have the same relationship"
between two, or more, measurement procedures for the same measurand.

"Historically the importance of the commutability of secondary RMs has not been adequately appreciated and there are a number of secondary RMs available that have not been validated for commutability with native patient samples."

Key Components for Traceability for a Secondary Reference Material (technical items that must be considered to establish traceability of a calibrator to a higher order reference system)

- The measurand should be well-defined
- The measurement procedure should be specific for the measurand
- The calibrator should be commutable with the samples intended to be measured

Reference materials and commutability

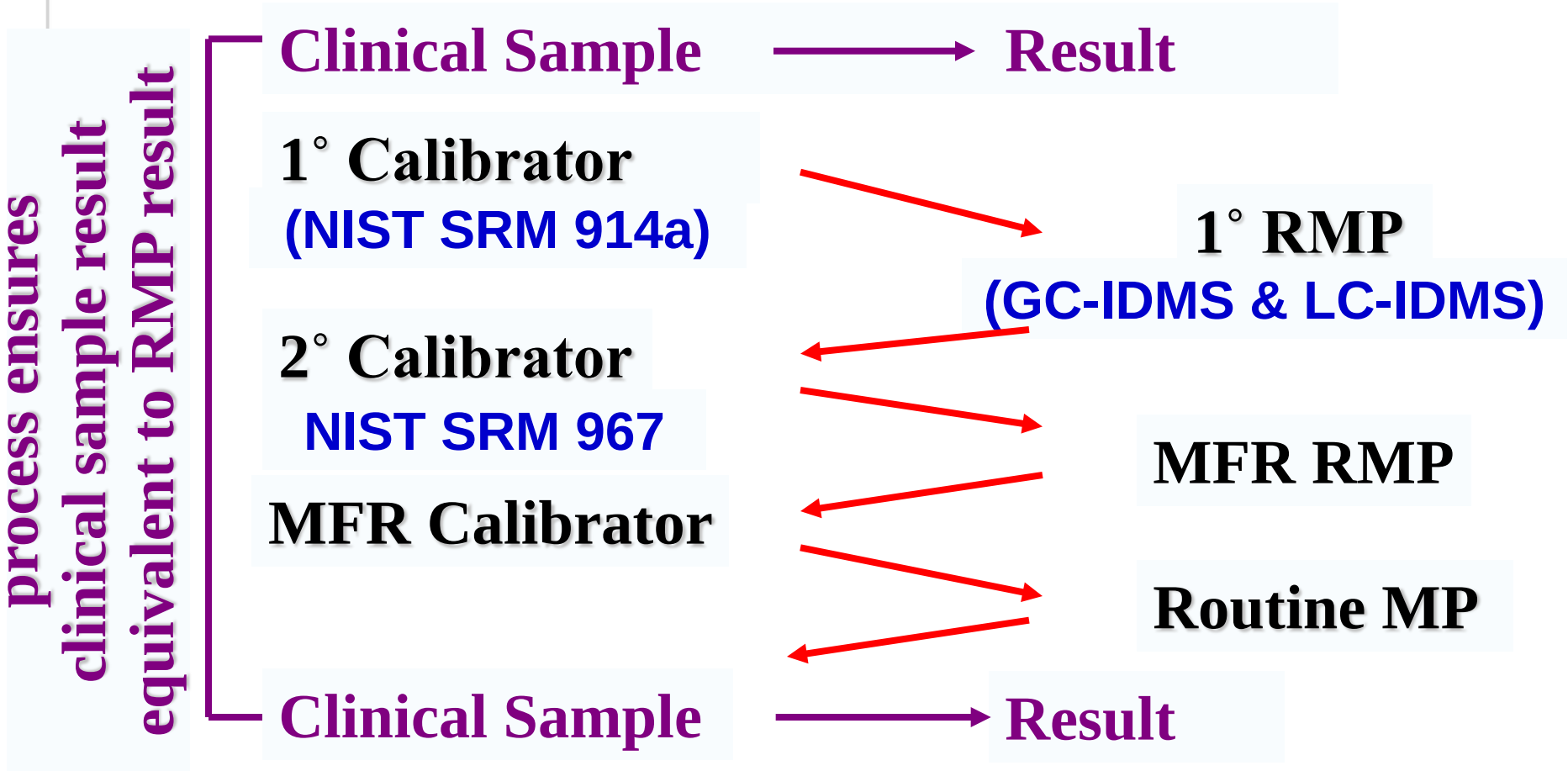
Vesper HW, Miller WG, Myers GL. Clin Biochem Rev 2007;28:139-147.

"…, RM can be considered an umbrella term for all materials used to calibrate a measurement procedure or to assess the trueness of results obtained with measurement procedures. This umbrella would include materials such as method specific calibrators, trueness controls and certified RMs (CRMs) … A variety of naming systems have been used to describe RMs to imply different levels of uncertainty such as 'primary RM', 'secondary RM' or 'higher order RM', 'lower order RM', 'primary calibrator' and 'secondary calibrator'. This imprecise nomenclature has resulted in a wide variety of terms used in the current literature and in efforts by standards organisations to clarify the terminology."

"Christenson et al. reported in a study assessing commutability of two cardiac troponin I materials among 15 measurement procedures that commutability was observed for 39% and 45% of measurement procedures, respectively. The authors concluded that the proportion of measurement procedures demonstrating commutability was too low for either of these materials to be used as a common calibrator."

"A RM would be considered commutable when a measurement procedure produces the same result for a RM as it does for an authentic patient sample that contained the same analyte concentration."

Traceability Chain for Serum Creatinine Calibrators

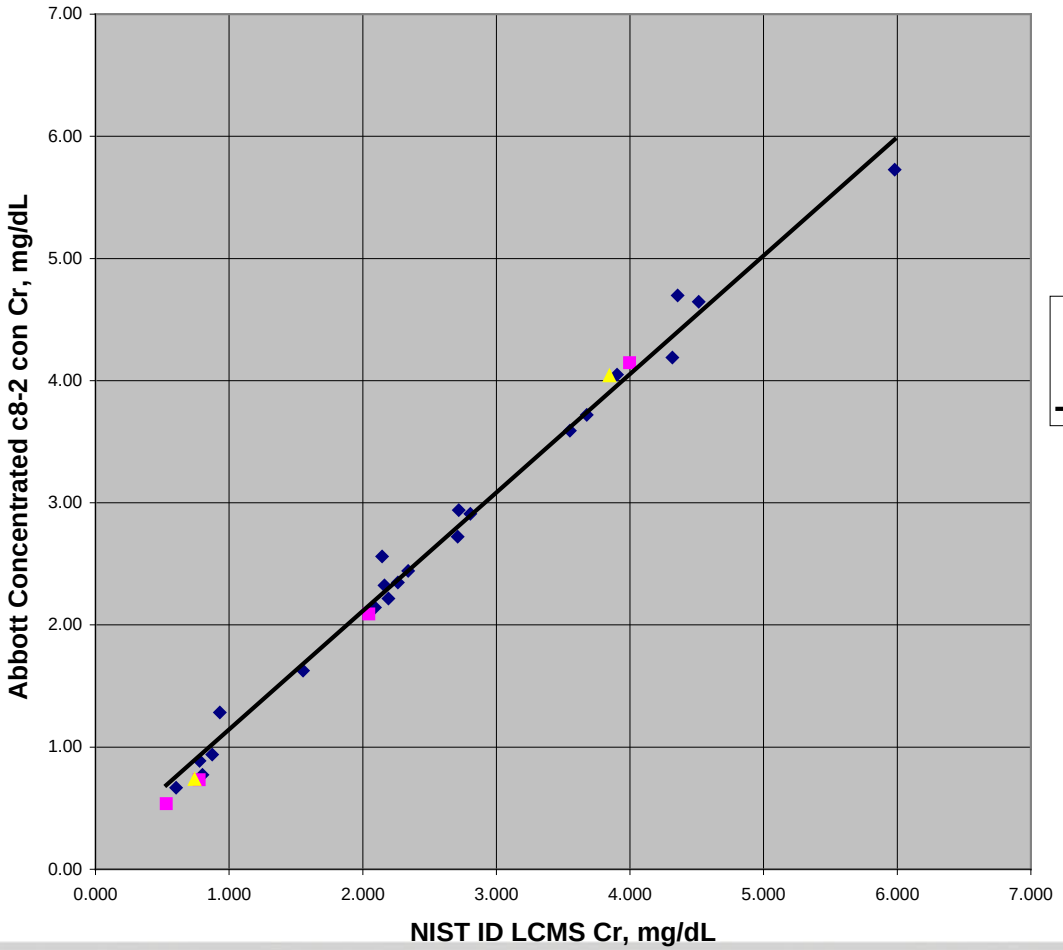


RMP = Reference Measurement Procedure
MFR = Manufacturer
MP = Measurement Procedure

NIST =National Institute of Standards and Technology
SRM = Standard Reference Material

Source: National Kidney Disease Education Program (NKDEP)

NKDEP/NIST Commutability Study
April – May 2006



NIST SRM 967 released for manufacturers' use Feb 07; most creatinine assays now restandardized

Example of CAP LN24 Report (Creatinine)

EVALUATION
ORIGINAL

LN24-B 2007 Creatinine Accuracy Calibration Verification/Linearity
Creatinine mg/dL

Your Instrument: BAYER ADV 1200/1650/2400
Your Method: RATE-BLK KIN ALK PIC

Specimen	Your Mean	NIST Values	Difference	Allowable Error	Specimens	Delta	Delta of NIST Values	Delta Ratio
LN24-01	0.800	0.794	0.8%	12.6%				
LN24-02	1.450	1.440	0.7%	6.9%	LN24-01 - 02	0.210	0.200	1.048
LN24-03	2.100	2.086	0.7%	5.0%	LN24-02 - 03	0.210	0.200	1.048
LN24-04	2.700	2.727	-1.0%	5.0%	LN24-03 - 04	0.194	0.198	0.975
LN24-05	3.300	3.378	-2.3%	5.0%	LN24-04 - 05	0.194	0.202	0.960
LN24-06	3.900	4.024	-3.1%	5.0%	LN24-05 - 06	0.194	0.200	0.968

Your Linearity Evaluation: Linear in Full Range Tested (0.800 to 3.900)
Your Calibration Verification: Verified in Full Range Tested
Your Calibration Regression Line: Slope = 0.96, Intercept = 0.07

Note: a target value is given for each sample assigned by the LC-MS/MS reference method; trueness/bias is absolute (as opposed to relative as with peer group grading). These are commutable samples.

Commutability of two JCLTM-listed secondary reference materials for two commercial lithium assays

Infusino I, Frusciante E. Clin Chim Acta 2012;414:152-153.

"… laboratories are expected to provide clinicians with accurate and comparable lithium results in order to correctly monitor the effectiveness of therapy and avoid patient's intoxication."

27 surplus patient samples, SRM 956c (NIST, frozen human serum), BCR-304 (IRMM, lyophilized human serum) tested using direct ISE (Roche Cobas Integra) and colorimetry (Abbott Architect c16000).

"Our results demonstrate that SRM 956c was not commutable between the evaluated methods. BCR-304 showed better, although not perfect, commutability and should be preferred to align lithium assays to higher-order references. According to its certified value (0.985 mmol/L±0.029 mmol/L), our results preliminarily showed a very good alignment for Abbott assay (mean BCR-304 results ± SD, 0.98 mmol/L ±0.04 mmol/L); on the contrary the Roche method showed a negative bias (−6.6%) that possibly needs some verification."

Commutability of two JCLTM-listed secondary reference materials for two commercial lithium assays.

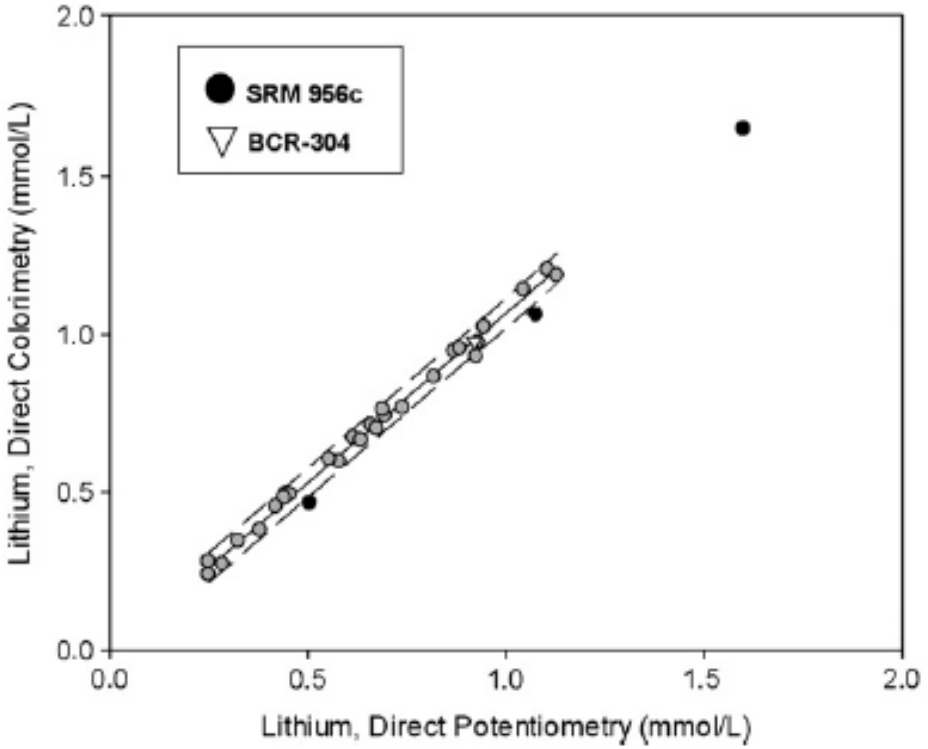


Fig. 1. Regression analysis (regression line – continuous – and 95% prediction interval – dashed lines) to evaluate commutability of IRMM BCR-304 (triangle) and NIST SRM 956c (black circles) between direct potentiometry and colorimetry assays for serum lithium. Gray circles identify native serum samples.

Why commutability matters.

Miller WG, Myers GL, Rej R. Clin Chem 2006;52:553- 554.

"When a reference material is intended to be measured by a routine clinical method, **commutability must be validated among all the methods that will use the material, including the reference measurement procedure when appropriate.** Ultimately, a reference material is used to ensure that the results for clinical samples assayed by routine measurement procedures have numerical values that are equivalent, irrespective of the clinical routine method used for the measurement.'

"A review of the **Joint Committee for Traceability in Laboratory Medicine** list of approved reference materials shows that very few have been validated for commutability with native clinical samples." **(JCTLM review team checklist now includes commutability)**

"Providers of reference and trueness control materials that are intended for calibration or routine measurement procedures … must include commutability validation as an essential requirement."

Commutability Matters

Greg Miller, CLSI Meeting, 11 Mar 13

Good laboratory medicine requires:

- **Total error of measurement small enough that result reflects a patient's biological condition**
- **Comparable results independent of where and when a test was performed and the measurement procedure used**
- **If different measurements give different results for the same patient sample, clinical practice guidelines are less useful, lab results in EHRs less useful**
- **How to achieve comparable results**
  - **Calibration of all measurement procedures is traceable to a common reference system**
  - **All measurement procedures measure the same quantity**
  - **Requires comparing results for the same samples tested using the recognized reference method and a field method(s)- commutability**

Commutability is not a universal property of reference material; must be proven with every field method.

Many secondary reference materials are not commutable and the metrological traceability chain is broken; calibration traceability doesn't ensure accuracy without commutability (makes it difficult for Industry to ensure commutability)

Commutability still matters

Miller WG, Myers GL. Clin Chem 2013:59:1291-1293.

"The International Organization for Standardization (ISO) standard 17511:2003 addresses metrological traceability of values assigned to calibrators and control materials and states that calibrators are to be **commutable at each step in a traceability chain.**"

"All providers of reference materials intended to be used either as common calibrators or to assess the agreement of results in external quality assessment/proficiency-testing programs must **take responsibility to ensure that the materials are commutable with representative clinical patient samples.**"

"The report by Zegers et al. emphasizes both the importance of validating the commutability of a reference material intended to be used as a common calibrator for routine measurement procedures and the responsibility that the reference material provider bears to evaluate commutability as part of the validation of a reference material."

The importance of commutability of reference materials used as calibrators: The example of ceruloplasmin

Zegers I, Beetham R, Keller T, et al. Clin Chem 2013;59:1322-1329.

"We performed a commutability study with 30 serum samples and the reference materials ERMDA470, ERM-DA470k/IFCC, and ERM-DA472/IFCC, using 6 different methods. Data were analyzed according to the CLSI Guideline C53-A to assess whether the reference materials had the same behavior as the serum samples with respect to measurement results obtained with combinations of the methods used."

"ERM-DA470 showed marked noncommutability for certain combinations of methods. ERMDA470k/ IFCC and ERM-DA472/IFCC were commutable for more combinations of methods. The lack of commutability of ERM-DA470 for certain combinations of methods correlates with results from the UK National External Quality Assessment Service showing discrepancies between results from these methods."

"The present work … show that EQAS samples may lack commutability even when their processing is limited to pooling, addition of sodium azide, and freezing."

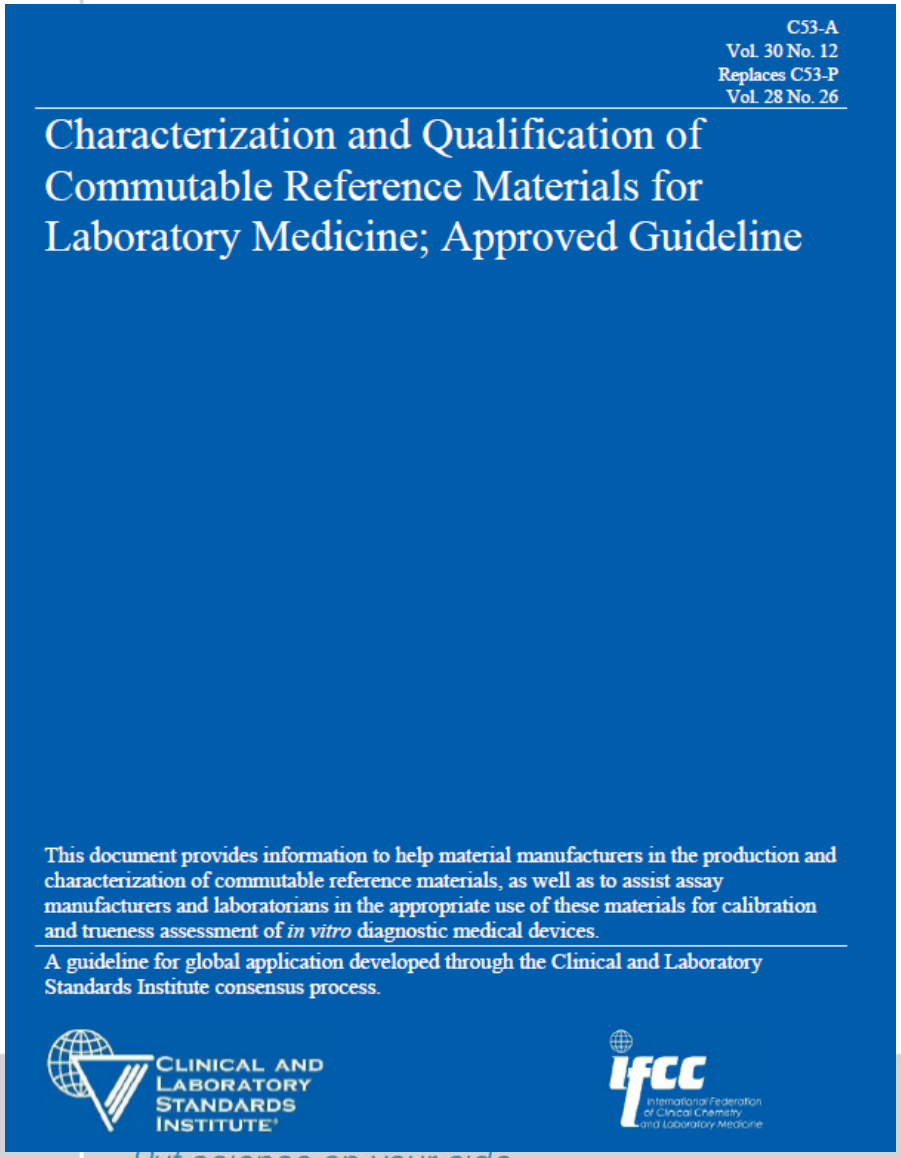
The importance of commutability of reference materials used as calibrators: The example of ceruloplasmin

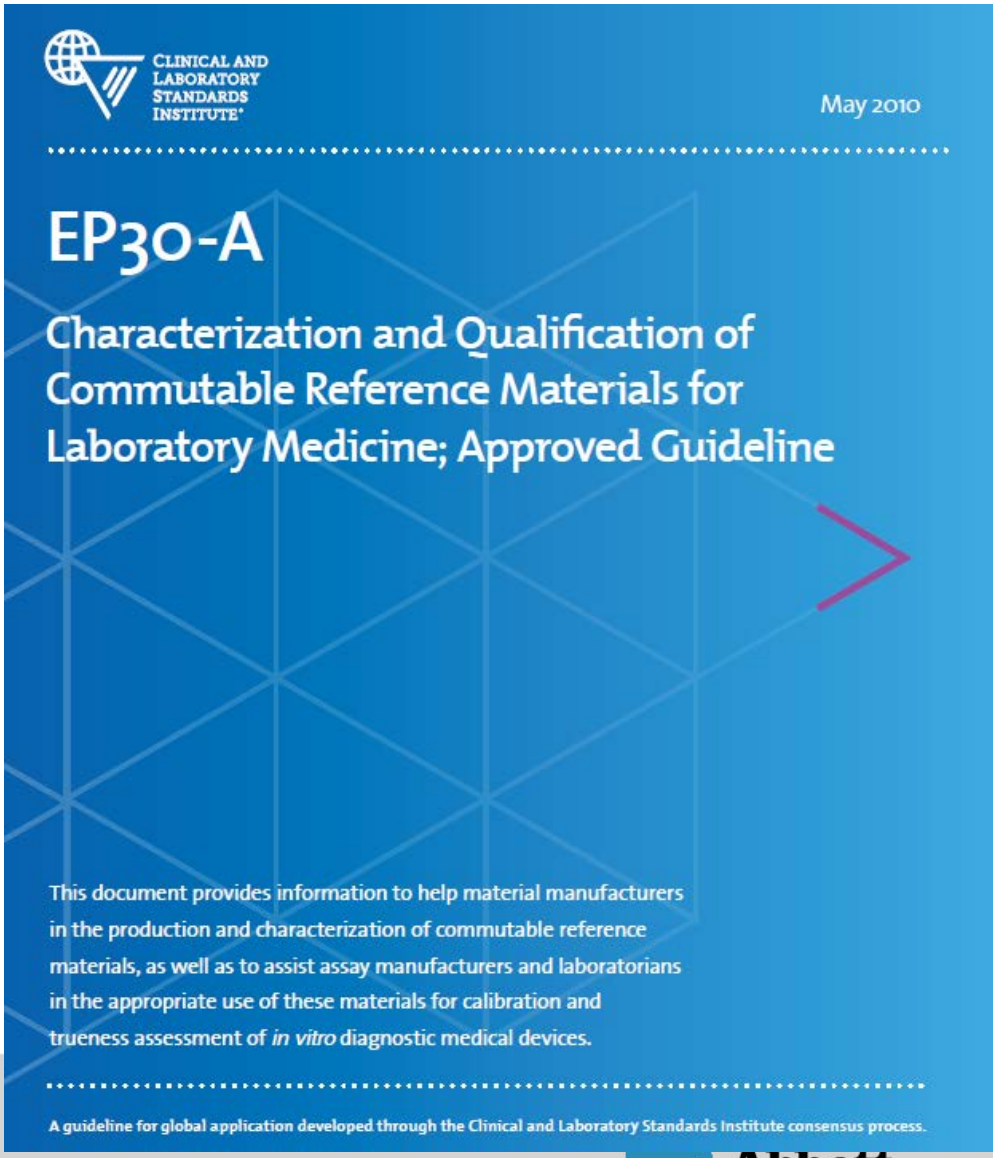
"The mean CVs for the measurement results of the serum samples obtained when using the different methods were between 1.7% and 6.1%. The Pearson correlation coefficients were 0.98 for all pair-wise method comparisons. This indicates a very good correlation of the results of different methods. In contrast the slopes for the method comparisons varied from 0.56 to 1.42 ... These values show that the measurement of the same serum sample provides very discrepant results with the different methods."

"The example of ceruloplasmin clearly shows that the use of a common calibrant that is not commutable will not result in full equivalence of results obtained with different methods."

"Ceruloplasmin in ERM-DA470 is a fully documented example of a situation in which, due to lack of commutability, the use of a common material for calibration did not lead to harmonization."
Best a company can do is prove commutability for its method, but comparability of all test results not currently feasible.

CLSI Guideline on Commutability (C53, now EP30)





CLSI EP14, Evaluation of Matrix Effects on Commutability of Processed Samples

EP14 (Draft 2)

Evaluation of Matrix Effects on Commutability of Processed Samples; Draft Guideline—Third Edition

Draft 2
Please Review and Comment

This draft document is available for broad, thorough review in the Clinical and Laboratory Standards Institute (CLSI) consensus review process. The draft document will undergo active member vote, concurrent consensus committee and Board of Directors review, and public review for a 45-day period.

Please send your comments on scope, approach, and technical and editorial content to CLSI.

Voting and comment period ends
25 July 2013

This document provides guidance for evaluating the bias in analyte measurements that is due to the sample matrix (physiological or artificial) when two measurement procedures are compared.

A guideline for global application developed through the Clinical and Laboratory Standards Institute consensus process.

CLINICAL AND LABORATORY STANDARDS INSTITUTE®

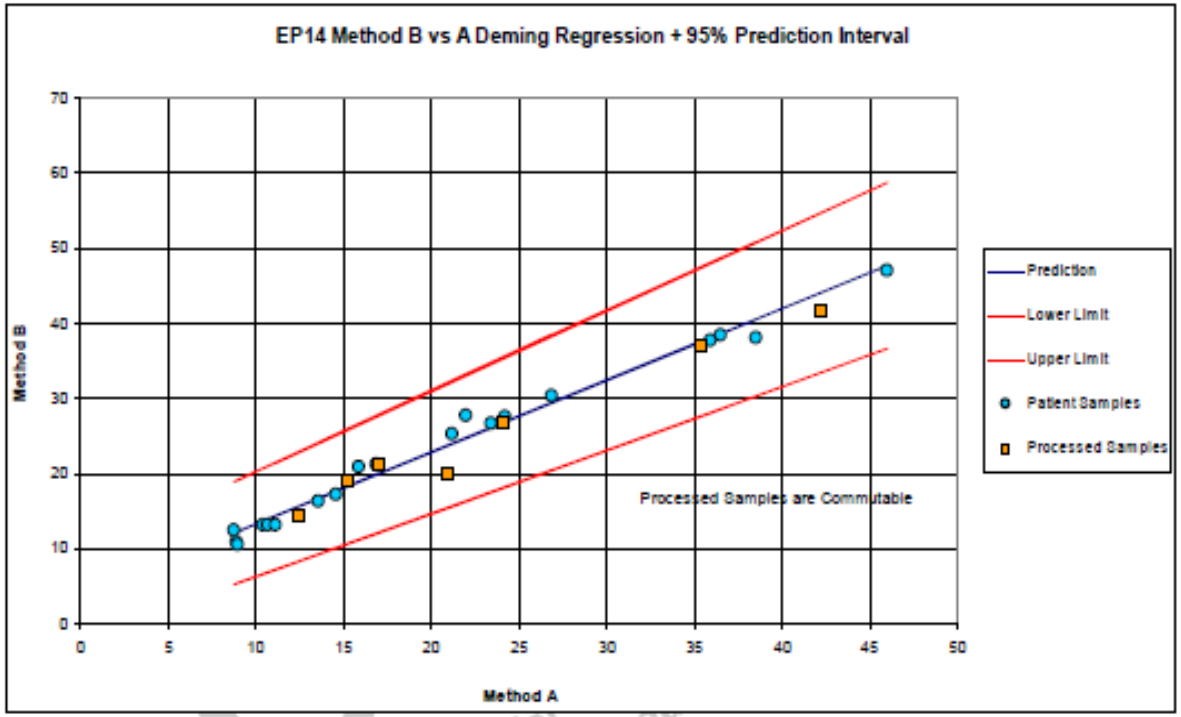
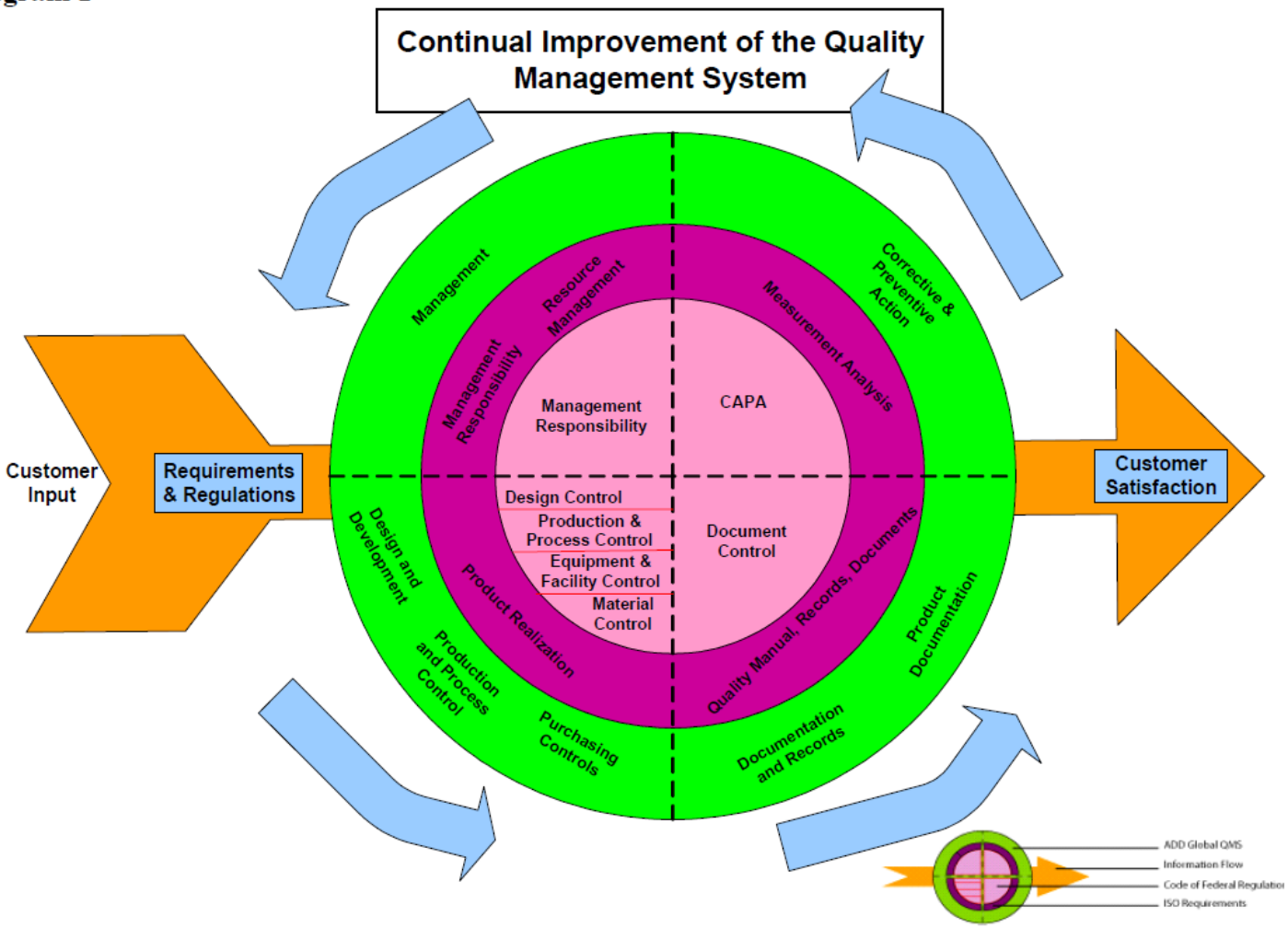


Figure 1. Use of the Deming regression protocol and 95% prediction interval to evaluate commutability between methods A and B. In this example, the processed samples are commutable.

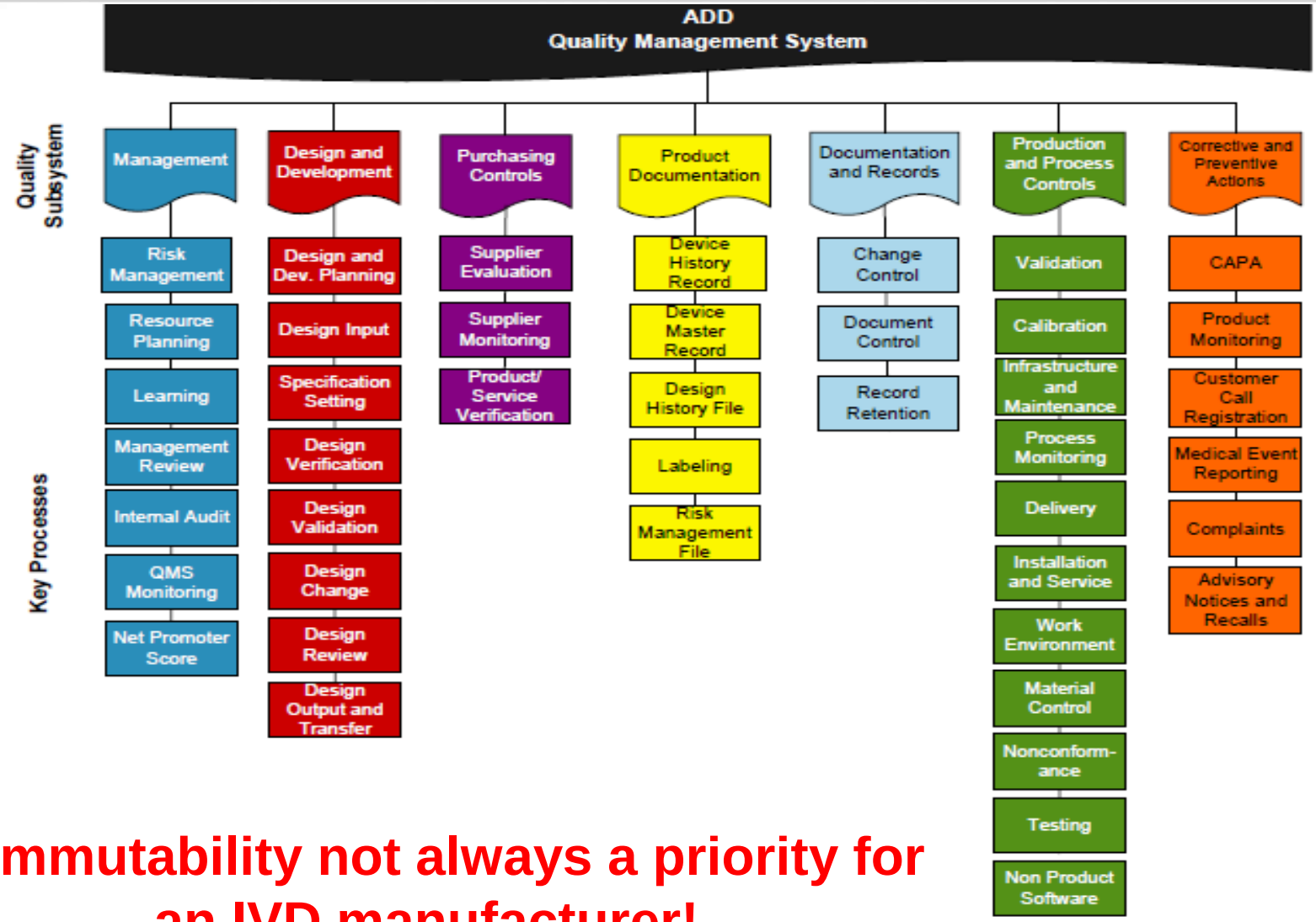
Manufacturer's Quality System Manual

Diagram 1



Commutability not always a priority for an IVD manufacturer!

Manufacturer's Quality System Manual



Commutability not always a priority for an IVD manufacturer!

Conclusion

Making commutability an integral part of IVD manufacturing is a necessity, but …
It's like turning the QE2. She's slow to answer the helm.

IVD manufacturers want to employ commutable materials but they're simply not always available, and proving commutability is a challenge.