JCTLM
Accurate results for patient care

Traceability and the IVD Industry: The Manufacturer's Role

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Global harmonization: “The World is Flat”- Thomas Friedman

CDs 

Fast Food 

Cars 

PCs

English Language

Travel 

Internet 

Fashion

Movies 

Music

Television

Mobile Phones

SI System 

Business 

Money 

But in the Clinical Laboratory field traceability and standardization is still ‘work in progress’: e.g. SI vs. ‘conventional units’; total error vs. uncertainty; lack of reference materials and methods; commutability etc.

Metrology, IVD manufacturers and the clinical laboratory

"I often say that when you can measure what your are speaking about, and express it in numbers, you know something about it; but when you cannot measure it, when you cannot express it in numbers, your knowledge is of a meagre and unsatisfactory kind."

Lord Kelvin (1824 – 1907)

"If you can't measure it, you can't manage it."

Jim Westgard, Ph.D., Clinical Chemist

International drivers for traceability

In-vitro diagnostics directive (IVDD) 98/79/EC applies to Europe but has global implications

- Requires manufacturers to establish metrological traceability of kit calibrators and trueness controls, and provide calibrator uncertainty of measurement. However, no guidance for establishing traceability/uncertainty

IVD Directive to be replaced by IVD Regulation – presentation to follow

ISO 17511:2003 Metrological traceability of values assigned to calibrators and control materials

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

ISO 17511 under review – presentation to follow

Partial list of traceability stakeholders

AACC	CLIA	FDA	IVDD	NIBSC
EFLM	DANAK	AACB	JCTLM*	NIST
BIPM	DGKL	IFCC	NATA	NMIs
BSI	EC4	ILAC	CLSI	RiliBÄK
CAP	ECCLS	JRC	NEQAS	SWEDAC
CDC	EDMA	ISO	NFKK	WHO
RCPA	NKDEP	NGSP	CSCC	ACB

Challenges and opportunities for medical directors in pathology and laboratory medicine

Hernandez JS, et al. Am J Clin Path 2010;133:8-13.

"…, lack of standardization across vendors and practices impedes integration of laboratories and often presents problems for physicians who must interpret results generated by different laboratories."

"Many physicians do not realize that many tests performed by one method cannot be reliably compared with the same tests performed on another platform… This lack of comparability presents problems for physicians who must consider testing location when interpreting results. It also creates barriers to sharing laboratory results across health care systems and can have adverse consequences for patients."

Real impact will be when EMRs (electronic medical records)/EHRs (electronic health records) are used to capture a patient's complete medical history, including all lab test results.

Traceability challenges for manufacturers

Expectation of consistent high quality (Six Sigma) laboratory service-implied quality guarantee for test results whenever and wherever they're reported

Ultimate lab product is medical information (diagnosis and treatment) as exemplified by claim that up to 70% of medical decisions are made on the basis of lab results

Healthcare consumers (physicians/patients) expect (take for granted) lab test results are high quality (accurate results from *all* labs at *all* times)

Manufacturers' goal (ethical obligation) is to provide products that meet these assumptions and expectations

Reality: Meeting this goal is not easy for manufacturers! Even though traceability success should result in a commercial advantage for a manufacturer, it's hard to prove.

Industry's traceability obligations

1. Comply with regulatory requirements (e.g., IVDD, CE mark, FDA, etc.) and professional society guidelines (e.g., AACC, NACB, IFCC, EFLM, JCTLM, etc.).
2. Provide metrological traceability/uncertainty information for calibrators as per ISO 17511 (unbroken chain from highest metrological order reference material/method to kit calibrators).
3. Strive for comparability of patient test results (results from different methods/labs/countries are equivalent and fit for purpose for clinical diagnosis/management).
4. Continuously maintain traceability and standardization or harmonization (e.g., through accuracy based EQA/PT programs).
5. Educate and train customers about traceability and assay standardization for optimal patient care (e.g., JCTLM WG-TEP).

This is a 'tough ask'

Paradigm shift for IVD manufacturers

- Manufacturers traditionally differentiate themselves from the competition on the basis of greater linearity, lower LoD, better precision, faster TAT, etc.
- Producing comparable results through traceability/ standardization has not been a priority (clear from EQA/PT peer group data; accuracy based EQA/PT relatively new)
- After IVDD, manufacturers provide traceability/uncertainty information, re-standardize assays, address commutability, etc., working with stakeholders and each other to achieve standardization, but this is a new activity and a challenge!

Traceability information provided by manufacturers

DIAGNOSTICS

Clinical Chemistry,
Immunoassay Traceability,
Uncertainty of Measurement

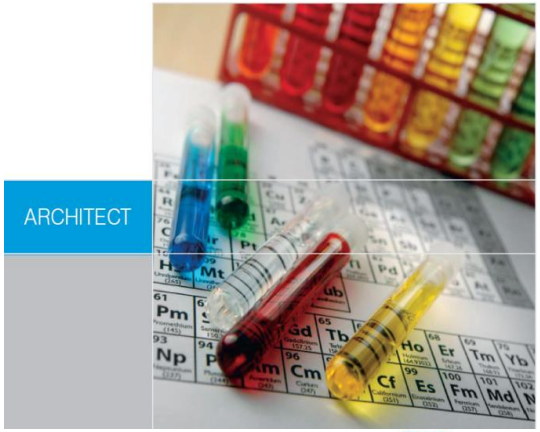
ARCHITECT

DIAGNOSTICS

Clinical Chemistry and
Immunoassay Traceability
and Measurement
Uncertainty Monograph

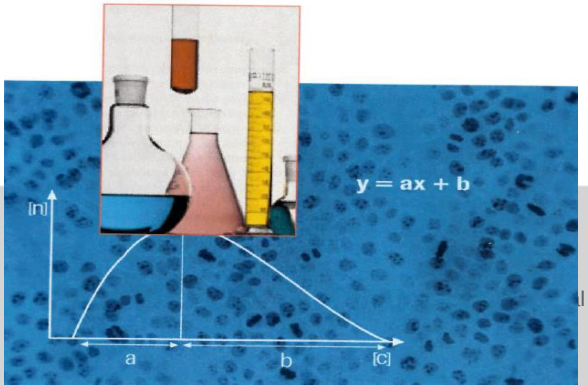
ARCHITECT

TRACEABILITY AND UNCERTAINTY
OF MEASUREMENT



Roche Diagnostics

Controls and Calibrators in Clinical Chemistry



Procedures of Standardization of Clinical Chemistry and Immuno Assays from Roche Diagnostics

Roche

cobas
Life needs answers

Manufacturer calibrator traceability/uncertainty Information

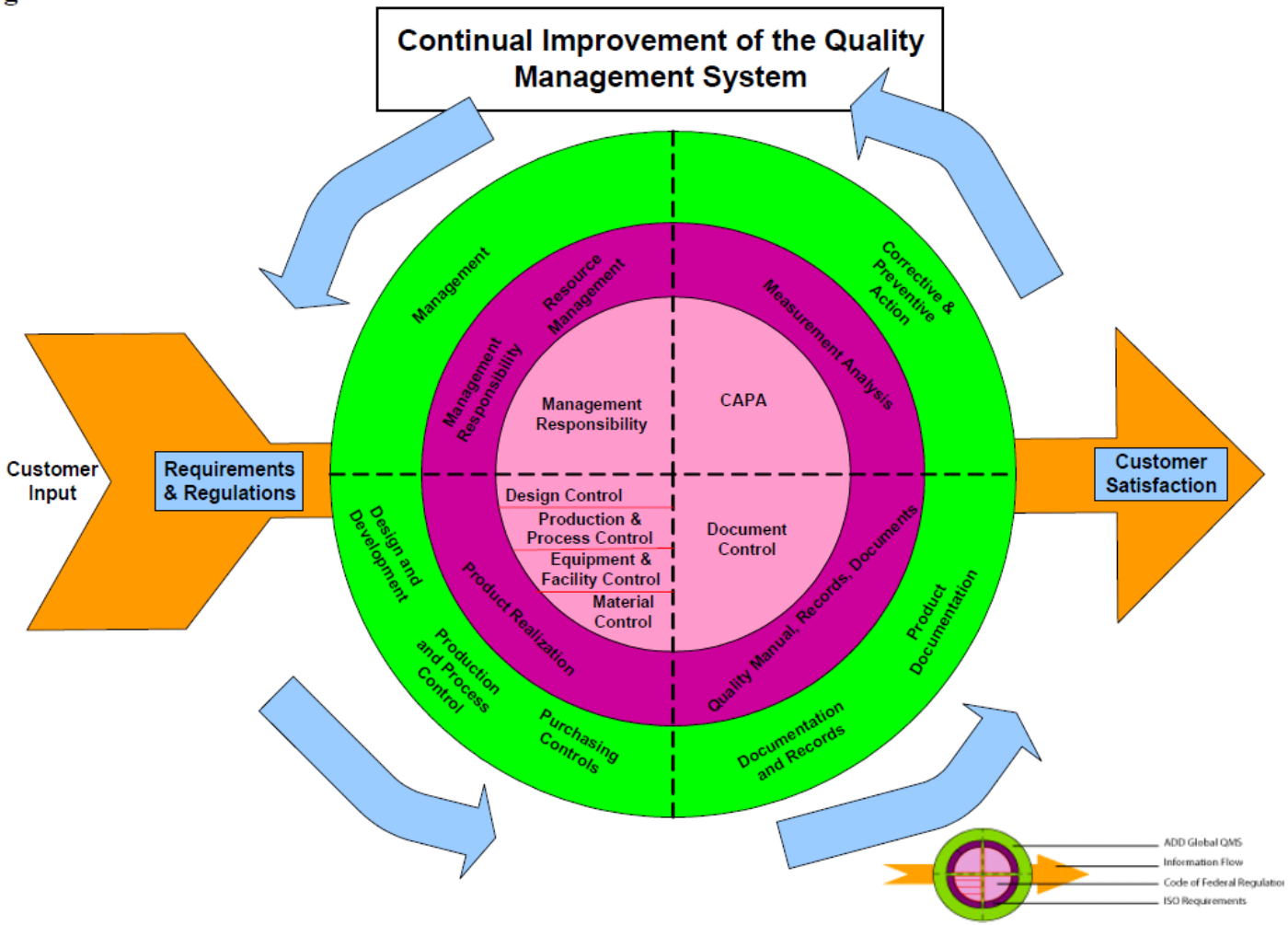
ASSAY NAME	ASSAY LIST NUMBER	CALIBRATOR LIST NUMBER – NAME	CONVEN-TIONAL UNITS (SI)	CALIBRATOR LEVEL	NOMINAL VALUE (SI)	UNCERTAINTY (SI) K = 2	REFERENCE MATERIAL (STANDARD-IZATION)	REFERENCE METHOD
A-1-AGP Serum/Plasma	6L34	6K45 – Proteins Standard	mg/dL (g/L)	1 2 3 4 5	18 (0.18) 45 (0.45) 90 (0.90) 135 (1.35) 180 (1.80)	0.966 (0.010) 2.415 (0.024) 4.830 (0.048) 7.245 (0.072) 9.660 (0.097)	ERM-DA470/ IFCC	Immunoturbi-dimetric
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	Immunoturbi-dimetric
Acetaminophen Serum/Plasma	2K99	2K99 – Acetaminophen Calibrator	µg/mL (µmol/L)	1	151 (999.62)	2.013 (13.328)	Acetaminophen Reference Stan-dard (98–100% purity)	Gravimetric
Albumin BCG Serum/Plasma	7D53	1E65 – Multiconstituent Calibrator	g/dL (g/L)	1 2	1.75 (17.5) 5.20 (52.0)	0.026 (0.258) 0.077 (0.767)	ERM-DA470	Visible spectrometry
Albumin BCP Serum/Plasma	7D54	1E65 – Multiconstituent Calibrator	g/dL (g/L)	1 2	1.75 (17.5) 5.20 (52.0)	0.030 (0.297) 0.088 (0.884)	ERM-DA470	Visible spectrometry

ASSAY NAME	ASSAY LIST NUMBER	ASSAY SHORT NAME	METHODOLOGY	REFERENCE METHOD	TRACEABILITY
Acid Phosphatase Serum	9D87	ACP	Alpha-naphthylphosphate	Original Procedure, Hillman G. (1971)[1]	Molar extinction factor
Alanine Aminotransferase Serum/Plasma	7D56	ALT	NADH without pyridoxal phosphate	NADH molar extinction factor	Molar extinction factor
Alanine Aminotrans-ferase Activated Serum/Plasma	8L92	A-ALT	NADH with pyridoxal phosphate	IFCC Reference Procedure (2002)[2]	IFCC

Note: Commutability not described; may be more critical than uncertainty.

One manufacturer's quality system manual

Diagram 1



A lot of moving parts and traceability is only one of them.

Measurement uncertainty or total error?

- Uncertainty is routine in metrology, new concept in the clinical laboratory
- ISO 15189:2012 "The laboratory shall determine the uncertainty of its measurements, where relevant and possible. Uncertainty components which are of importance shall be taken into account."
- Multiple methods to estimate MU (GUM- ISO Guide Uncertainty; BIPM Guide; Eurachem/CITAC Guide to Uncertainty; AACB Uncertainty of Measurement; CAP guideline; manufacturers' protocols), etc. (bottom up and top down;include pre- and post-analytical factors?)
- Unclear if uncertainty is useful for clinical purposes, e.g., patient result for ALT in SI units with uncertainty
  S-Alanine aminotransferase; cat. c. = 1.15 +/- 0.23 μkat/L
- "If you torture data sufficiently, it will confess to almost anything"
  Fred Menger, Chemistry Professor, Emory University

Westgard JO. Managing quality vs. measuring uncertainty in the medical laboratory. CCLM 2010;48:31-40.

"Having trained in analytical chemistry, I encountered the clash of metrological principles with production laboratory practices when I became a clinical chemist. I still remember my first experience in a medical laboratory and the realization that only a single measurement was involved in generating a test result, rather than the multiple measurements that were typical of most classical analytical laboratories."

"Horwitz put it more succinctly in a later paper: 'The absurd and budget-busting approach (for analytical chemistry) arose from metrological chemists taking over in entirety the concepts developed by metrologists for physical processes measured with 5 – 9 significant figures (gravitational constant, speed of light, etc.) and applying them to analytical chemistry measurements with 2 or 3 significant figures.'"

Oosterhuis WP, Theodorsson E. Total error vs. measurement uncertainty: revolution or evolution? Clin Chem Lab Med 2016;54:235-239.

"The 'total error' theory originated by Jim Westgard and co-workers has a dominating influence on the theory and practice of clinical chemistry but is not accepted in other fields of metrology. The generally accepted uncertainty theory, however, suffers from complex mathematics and conceived impracticability in clinical chemistry. The pros and cons of the total error theory need to be debated, making way for methods that can incorporate all relevant causes of uncertainty when making medical diagnoses ... This development should preferably proceed not as a revolution but as an evolution."

"MU has been generally accepted in all fields of metrology except in clinical chemistry despite the fact that the International Federation of Clinical Chemistry and Laboratory Medicine (IFCC) is amongst the founders of uncertainty methods in chemistry."

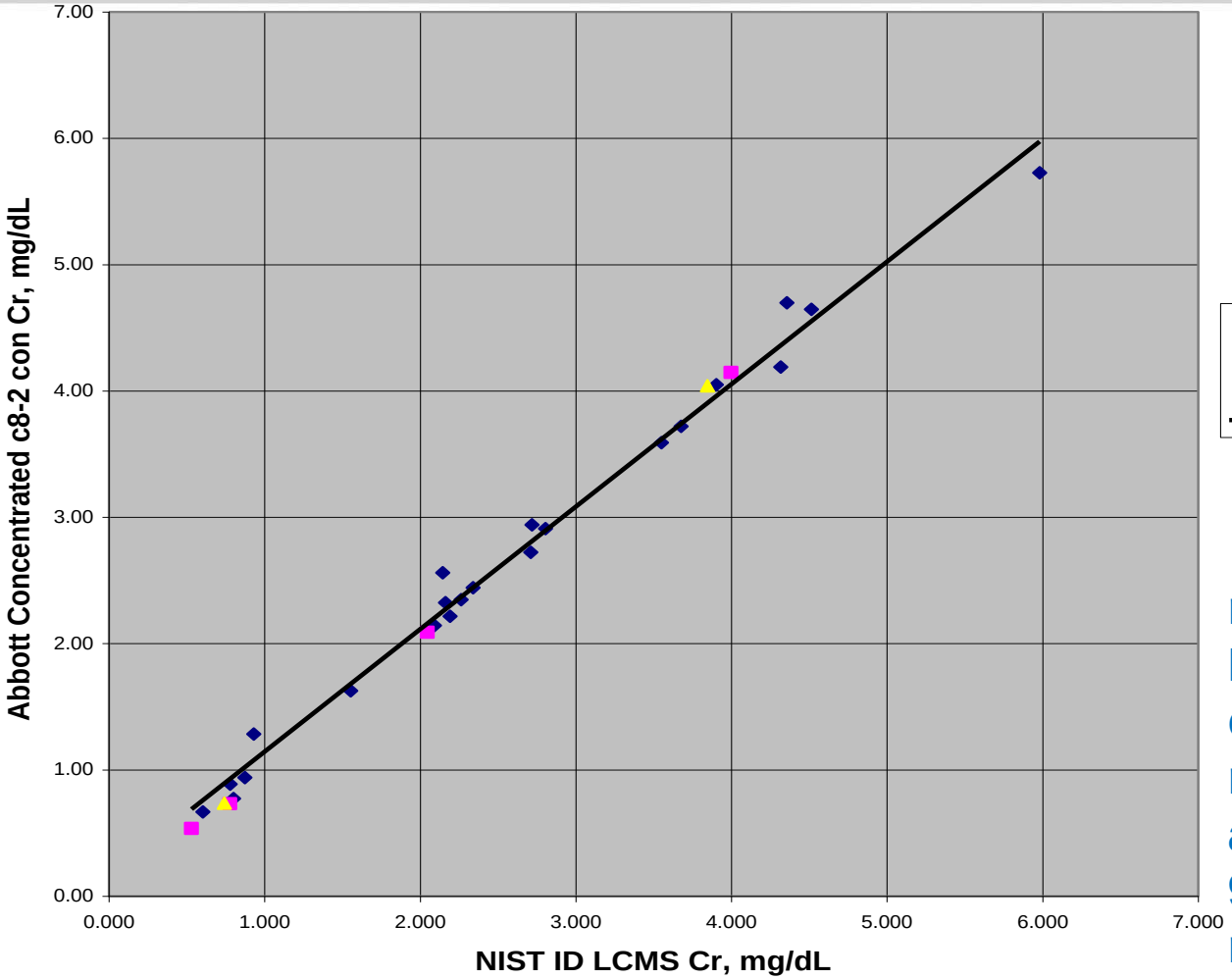
"The two main issues favoring the measurement uncertainty paradigm are that most if not all other fields of metrology are using it and that it encourages estimation of the major components of uncertainty and favors actions for their minimization."

IVD industry traceability success stories

HbA1c, two traceability schemes [NGSP (% Hb A1c) and IFCC (mmol/mol)], manufacturers now traceable to both NGSP and IFCC; results can be interconverted using the master equation; EQA/PT programs use whole blood samples with reference method target values and accuracy based grading; (total error = +/- 6% of target); bias (+/- 2%) and precision (3% CV) targets established

Creatinine: International effort involving many stakeholders resulted in re-standardization of creatinine assays from major IVD manufacturers; metrological traceability of assays is based on commutable NIST SRM 967 reference material & ID-LC/MS reference method; focused on optimal performance in reference interval concentrations to improve eGFR for kidney disease risk and monitoring

AACC/NKDEP/NIST commutability study, April – May 2006



NIST SRM 967 released to industry Feb 07 and most creatinine assays now restandardized and traceable to SRM 967 and ID MS reference method

Example of manufacturers' success in traceability with real patient impact

IFCC Scientific Division projects

The IFCC Scientific Division has a rolling programme of method standardization / harmonization projects. Many of these result in the production of reference materials and/or reference measurement procedures that are added to the JCTLM database. IVD manufacturers are full partners in these projects and often provide the resources required to achieve the outcome.

Completed	Ongoing
Haemoglobin A1c	Pancreatic lipase
Human serum proteins x12 (ERM DA-470)	Haemoglobin A2
Enzymes (ALT, CK, LDH, GGT, AMY, AST, ALP)	Carbohydrate deficient transferrin
Cystatin C	Albumin in urine
Apolipoproteins A1 and B	Pregnancy associated plasma protein A
Autoantibody tests	Insulin
Bone markers	Troponin I
Amyloid beta 1-42	Parathyroid hormone
Thyroid function tests (TSH, FT4)	Total protein

Manufacturers adapt to traceability

- "Best of all possible worlds" (best of all possible measurements) Gottfried Wilhelm Leibniz (1646 – 1716)
- "Don't let the perfect become the enemy of the good." Voltaire (1694 -1778)
- "Essentially, all models are flawed, but some are useful." E.P. Box (1919-2013)

Current dilemmas for manufacturers

1. Is clinical chemistry a sub-discipline of metrology?
2. Reporting units: SI vs. 'conventional units'
3. Inadequate reference materials and reference methods
4. Challenge of commutability and comparability
5. Total error vs measurement uncertainty
6. Many stakeholders, including new competitors

The Gordian Knot

Key publications

- Armbruster D, Donnelly J. Harmonization of clinical laboratory test results: the role of the IVD industry. eJIFCC 2016; 27: 37-47
- Armbruster D. Measurement traceability and US IVD manufacturers: the impact of Metrology. Accred Qual Assur 2009;14:393-398
- Westgard JO, Armbruster D, Westgard SA. Risk, error and uncertainty: laboratory quality management in the age of metrology. Clin Lab Med 2017; 37: Issue 1
- Armbruster D. Metrological traceability of assays and comparability of patient test results. Clin Lab Med 2017; 37: 119-135

Summary – Graham Beastall

- IVD manufacturers recognize the growing importance of TLM; the need to apply it to their methods; and report it in product IFU
- The challenges of implementing TLM are great because of unknowns and variables both now and in the future
- The new IVD Regulation and the revision of ISO 17511 are likely to increase the pressure on IVD manufacturers to deliver the highest quality, but can they at a cost the user can afford?
- IVD manufacturers currently interpret TLM as individual companies. Is there scope for an industry-wide guideline?
- Do users of IVD methods recognize the importance of TLM when selecting analytical platforms and methods?

Final thought – Graham Beastall

Traceability in laboratory medicine will seem like this to every IVD manufacturer.

Challenges are growing rather than shrinking

Is there a global way forward through collaboration?