4th International Scientific Meeting
Rethinking Quality Control in the Traceability Era

Are Commercial Analytical Systems Fulfilling Goals Based on Medical Relevance? The Industry's View

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Global Scientific Affairs, Abbott Diagnostics

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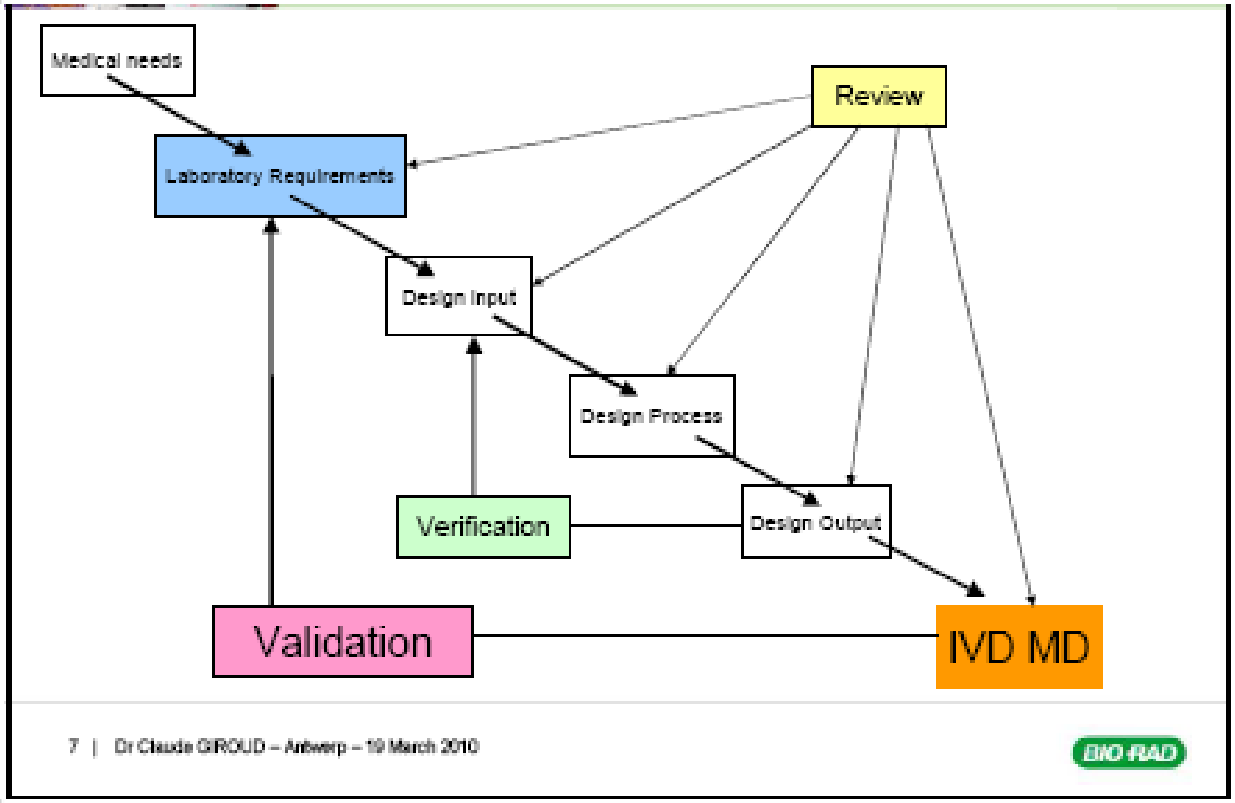
Objectives

1. Examine current clinical laboratory performance and its medical relevance.
2. Review current approaches to defining and measuring quality of analytical performance in the clinical laboratory.
3. Describe what IVD manufacturers are doing to optimize analytical performance to meet clinical goals.

Quality Specifications for IVD Manufacturers

Quality in the Spotlight Conference, Antwerp, 2010



Verification testing: build the assay right (i.e., performance meets design specifications)
Validation testing: build the right assay (i.e., assay meets laboratory requirements, including medical relevance)

Courtesy of

Courtesy of Claude Giroud, BioRad Laboratories

State of the Art in Trueness and Interlaboratory Harmonization for 10 Analytes in General Clinical Chemistry

Miller WB, Myers GL, Ashwood ER, et al. Arch Pathol Lab Med 2008;132:838-846.

Table 1. Reference Measurement Procedures

Method	Reference Method(s)*	References
Bilirubin	Jendrassik-Grof	19
Chloride	IDMS, amperometry	20
Glucose	IDMS, hexokinase	21–23
Iron	Ferrozine, ferene	24
Magnesium	Atomic absorption	25
Phosphate	Ammonium molybdate	26, 27
Potassium	IDMS, flame photometry	28
Sodium	Gravimetry, flame photometry	29
Urea nitrogen	IDMS, urease	30–32
Uric acid	IDMS, uricase	21, 22, 33, 34

* IDMS indicates isotope dilution mass spectrometry.

Table 2. Allowable Bias (%) Criteria Based on Biologic Variability for 3 Method Performance Conditions*

	CV_W†	CV_G‡	Optimal	Desirable	Minimal
Bilirubin	25.6	30.5	5.0	10.0	14.9
Chloride	1.2	1.5	0.2	0.5	0.7
Glucose	5.7	6.9	1.1	2.2	3.4
Iron	26.5	23.2	4.4	8.8	13.2
Magnesium	3.6	6.4	0.9	1.8	2.8
Phosphate	8.5	9.4	1.6	3.2	4.8
Potassium	4.8	5.6	0.9	1.8	2.8
Sodium	0.7	1.0	0.2	0.3	0.5
Urea nitrogen	12.3	18.3	2.8	5.5	8.3
Uric acid	8.6	17.2	2.4	4.8	7.2

* Calculated as [factor × SQRT(CV_W^2 + CV_G^2)] where factor is 0.125, 0.25, or 0.375 for optimal, desirable, or minimal performance conditions, respectively.[11]

† CV_W is average biologic variability as coefficient of variation (%) within an individual.[12]

‡ CV_G is average biologic variability as coefficient of variation (%) among a group of healthy individuals.[12]

State of the Art in Trueness and Interlaboratory Harmonization for 10 Analytes in General Clinical Chemistry

Context.—Harmonization and standardization of results among different clinical laboratories is necessary for clinical practice guidelines to be established.

Objective.—To evaluate the state of the art in measuring 10 routine chemistry analytes.

Design.—A specimen prepared as off-the-clot pooled sera and 4 conventionally prepared specimens were sent to participants in the College of American Pathologists Chemistry Survey. Analyte concentrations were assigned by reference measurement procedures.

Participants.—Approximately 6000 clinical laboratories.

Results.—For glucose, iron, potassium, and uric acid, more than 87.5% of peer groups meet the desirable bias goals based on biologic variability criteria. The remaining 6 analytes had less than 52% of peer groups that met the desirable bias criteria.

Conclusions.—Routine measurement procedures for some analytes had acceptable traceability to reference systems. Conventionally prepared proficiency testing specimens were not adequately commutable with a fresh frozen specimen to be used to evaluate trueness of methods compared with a reference measurement procedure.

Miller WB, Myers GL, Ashwood ER, et al. Arch Pathol Lab Med 2008;132:838-846.

Trueness assessment of glucose measurement in Korean nation-wide proficiency testing by comparison with the definitive method

Goals: TEa = ≤ 7.9%, Imprecision ≤ 3.3%, Bias ≤ 2.5%

PT sample target value assigned by ID-GC/MS (Trial 9, 2008)

40% of labs +/- 2.5% from ID GC/MS target value

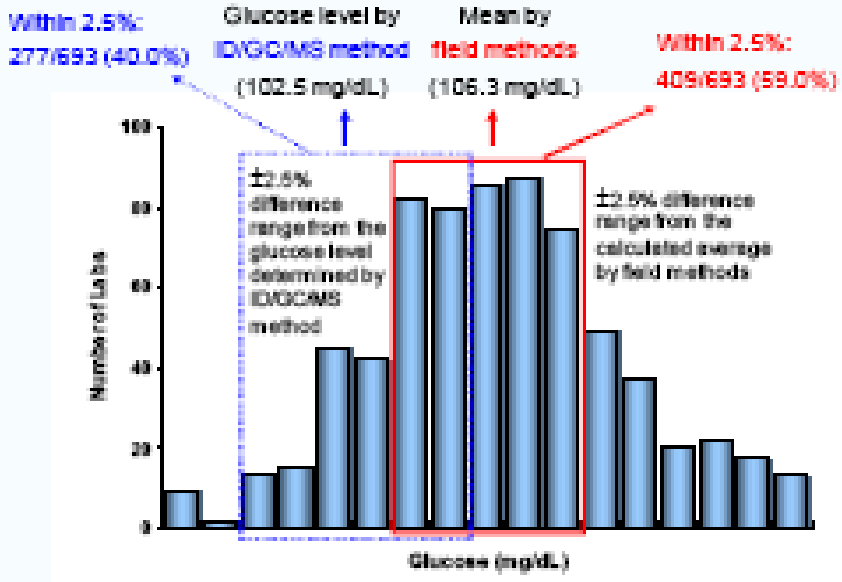


Figure 3. Distribution of glucose results reported in the proficiency testing for trial 9 in 2008. Among the 693 participants, 409 results (59.0%) were within ±2.5% difference range from the calculated average by field methods. Meanwhile, the glucose level measured by ID/GC/MS was 102.5 mg/dL, which is lower than the estimated average (106.3 mg/dL) by 3.8 mg/dL and the results from 277 (40.0%) participants were within ±2.5% difference range from the glucose level determined by ID/GC/MS. Dashed rectangle represents the ±2.5% difference range from the glucose level measured by definitive method and solid rectangle shows the ±2.5% difference range from the estimated mean by field methods.

Lee W, Chung H-J, Hannestad U, et al. APCCB Oct 2010 Poster

Challenges and Opportunities for Medical Directors in Pathology and Laboratory Medicine

"…, 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 1 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."*

"… numerous international organizations have implemented efforts to standardize and harmonize laboratory testing systems by developing reference standard materials for laboratory analytes and establishing traceability of commercial reagents to those standards, thus promoting comparability of results across different reagant sets. Through the traceability process, results generated by a test method are related, through a series of comparisons, to established standards."

*EMR (electronic medical record)

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

Why Metrological Traceability?

"A fundamental goal of of laboratory medicine is that results for patients' samples will be comparable independent of the medical laboratory that produced the results. Routine measurement procedures of acceptable analytical specifications that have calibration traceable to the same higher-order reference material or reference measurement procedure should produce numerical values for clinical samples that are comparable irrespective of time, place, or laboratory generating the results."

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

"Serial results from an individual are often obtained using more than one method. Results should be transferable over time and locale…Test results should be comparable over both time and geography;…"

Petersen PH, Fraser CG, Westgard JO, Larsen ML. Analytical goal-setting for monitoring patients when two analytical methods are used. Clin Chem 1992;38:2256-2260.

Expectation of quality (Six Sigma) from lab services for test results irrespective of time, location, or the laboratory generating the results; healthcare consumers (physicians/patients) expect (take for granted) that lab test results are high quality (accurate results from *all* labs at *all* times)

Comparability of Results and Reference Systems

"Foremost among the laboratory's problems is the poor comparability of analytical results that originate from different laboratories using different methods. Even today considerable differences can still be observed in the results obtained using different measurement procedures for the same analyte."

Metrological vs. "Clinical" Traceability: "… incorrect clinical decisions if patient results are true with regard to the reference system, but the decision-making criteria are only valid by using the previous calibration for the test."

Commutability: secondary reference materials (SRM) as intermediate step in traceability chain; human serum as desired matrix; if SRM is not available, only possible alternative for traceability is for IVD manufacturers to use split fresh human samples with target values from the reference method.

Traceability, reference systems and result comparability. Panteghini M. Clin Biochem Rev 2007;28;97-104.

"Unfortunately, there are no guidelines for what concerns the extent of traceability that should be reached by routine methods for clinical chemistry. In our opinion, they should adopt the concepts for deriving quality specifications, as, for example, proposed in the "Stockholm Consensus Conference"

Reference measurement systems in clinical chemistry. Thienpont LM, van Uytfanghe K, De Leenheer AP. Clin Chim Acta 2002;323:73-87.

Consensus agreement, Strategies to set global quality specifications in laboratory medicine, Stockholm. Scand J Clin Lab Invest 1999;59.

1. Evaluation of the effect of analytical performance on clinical outcomes in specific clinical settings
2. Evaluation of the effect of analytical performance on clinical decisions in general
   a. data based on components of biological variation
   b. data based on analysis of clinicians' opinions
3. Published professional recommendations
   a. from national and international expert bodies
   b. from expert local groups or individuals

4 Performance goals set by
   a. regulatory bodies (e.g., CLIA, RiliBÄK, RCPA, etc.)
   b. organizers of External Quality Assessment (EQA) schemes

5 Goals based on the current state of the art
   a. as demonstrated by data from EQA or Proficiency Testing schemes
   b. as found in current publications on methodology

Impact of Traceability on Clinical Practice

Traceability as a unique tool to improve standardization in laboratory medicine Panteghini M. Clin Biochem 2009;42;236-240.

"Standardization of laboratory measurements would ensure the interchangeability of results over time and space ..."

"The prostate-specific (PSA), … Currently, two sources of calibration are in common use for PSA. One is based on the traditional calibration scheme … used to establish the clinically relevant PSA cutoff of 4.0 ug/L. The second calibration approach provides traceability to the WHO International Reference Preparation 96/670.

Harmonizing PSA Testing: What's the Right Standard? Clinical Laboratory Strategies, 9 Jun 05, www.aacc.org/strategies

Different patient PSA results depending on assay

- **Bayer Centaur & Abbott AxSYM use WHO IRP; Beckman Coulter Access uses Tandem-R**
- ***J Urol* 2004;171:2234-38: 19% of patients candidates for biopsy by Access, but not by Centaur (based on 4.0 ng/mL cutoff); differences in calibration change test results with potential for misdiagnosis and adverse patient impact**

Baseline PSA as a predictor of prostate cancer- speficic mortality over the past 2 decades. Tang P, Sun L, Uhlman M, et al. Cancer, 2010;116:4711-7.

International Reference Measurement System

The JCTLM has established the three main pillars:

Reference measurement procedures

Reference materials

Network of Reference Measurement Laboratories

IFCC has described a fourth pillar:

Universal reference intervals

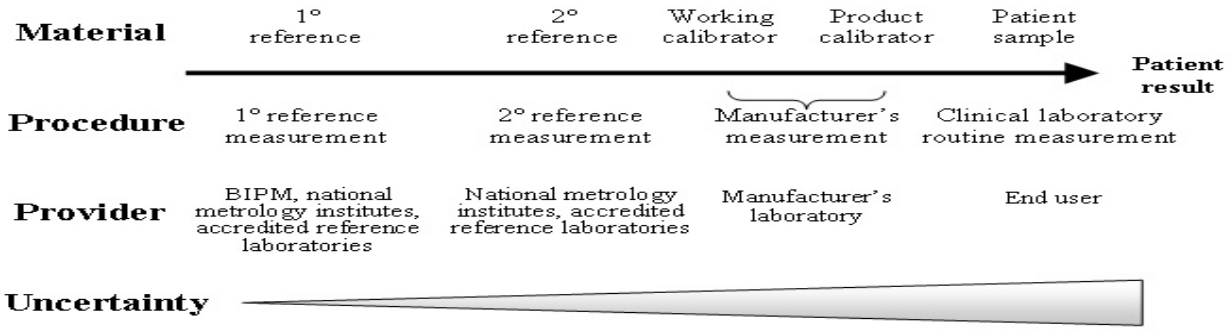
The fifth pillar:

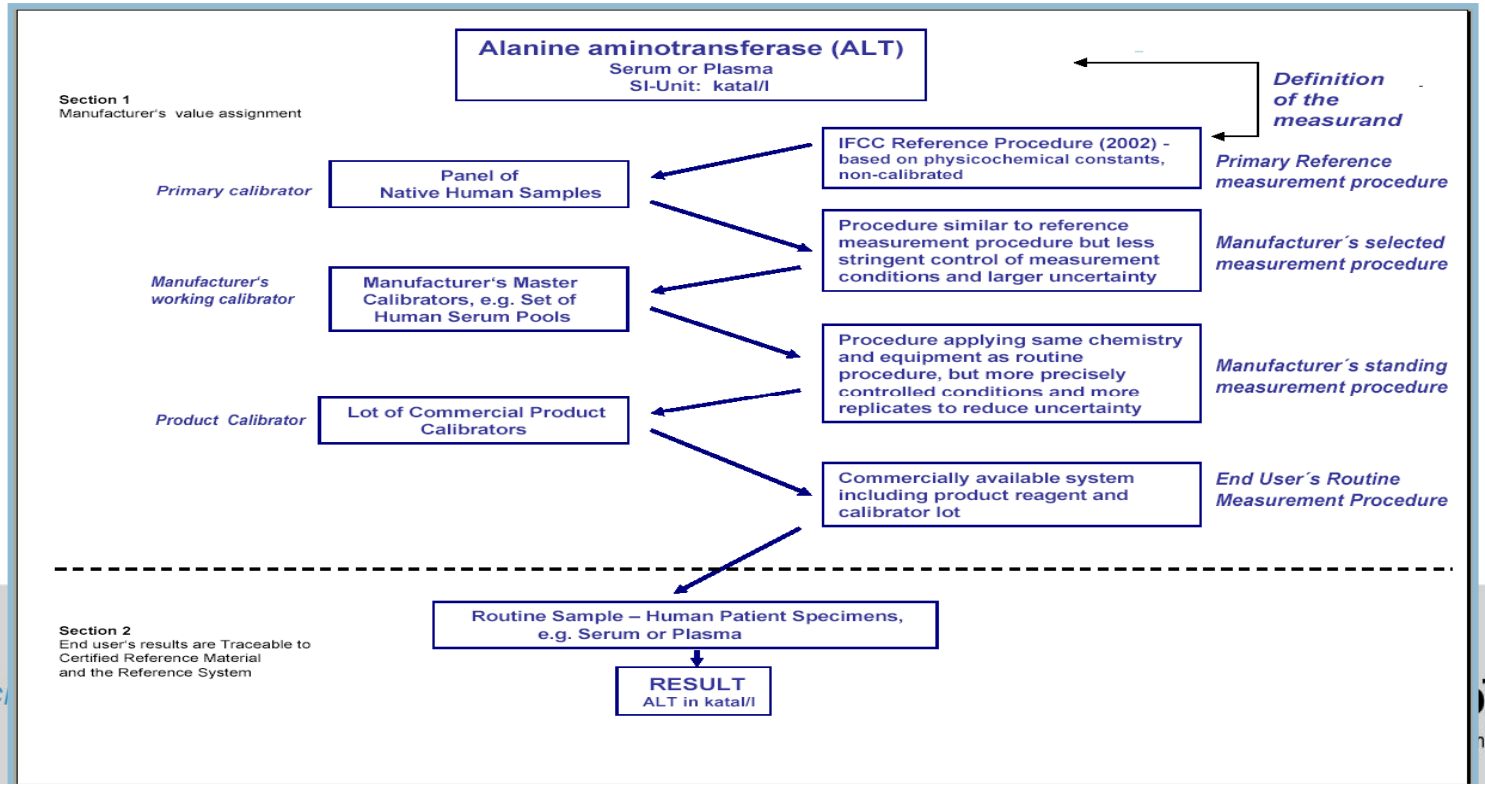
EQA/PT programs that ensure the international reference system is continually maintained

"… commutability of conventional PT specimens is not adequate to evaluate the trueness of a routine method… peer group means from conventional PT results cannot be used to harmonize results across testing platforms. … it should be noted that proficiency testing is typically used to measure a laboratory's proficiency at performing a test and not the trueness of the test method itself or its performance relative to other methods…Results from this study suggest that traditional PT materials are not suitable for field-based post marketing assessments of a method's trueness."
Miller WB, Myers GL, Ashwood ER, et al. Arch Pathol Lab Med 2008;132:838-846.

JCTLM: A global approach to promote the standardisation of clinical laboratory test results

Armbruster D. Miller RR. Clin Biochm Rev 2007:28:105-113.





Uncertainty

Uncertainty is routine in metrology, but a new concept in the clinical laboratory (not in 1999 3rd edition of *Tietz*, but discussed in 2006 4th edition)

Calculation of uncertainty is complex and there are multiple methods, e.g., BIPM Guide for Estimation of Uncertainty in Measurement (GUM); Eurachem/CITAC Guide to Uncertainty; Uncertainty of Measurement in Quantitative Medical Testing (AACB guide); ISO 25680; CLSI C51, QMP-LS, EA-4/02 (European Cooperative for Accreditation)

No one method for estimating uncertainty has been accepted (e.g., include pre- and post-analytical factors?)

"If you torture data sufficiently, it will confess to almost anything."

- Fred Menger, chemistry professor

Example: patient result for ALT in SI units with uncertainty

S-Alanine aminotransferase; cat. c. = 1.15 +/- 0.23 μkat/L

Uncertainty

2007 EDMA Position Paper Uncertainty of Measurement Results

Upon request, manufacturers should provide the laboratories with the uncertainty data associated with the calibrators and trueness control materials provided to the user. It is the responsibility of the laboratory to do the following:

- **Calculate the final measurement uncertainty of the result**
- **Decide whether and how to present that measurement uncertainty to the clinician.**

Panteghini M. Clin Chem Lab Med 2010;48:7-10.

"…, the application of GUM in clinical laboratories is not straightforward and has encountered many practical problems and objections."

"Compliance with the IVD Directive … The manufacturer also is asked to indicate the expected uncertainty of the assay calibrators …"

"The uncertainty due to random effects (i.e., assay imprecision) can be derived by appropriately designed IQC. However, caveats exist related to the use of control materials that may not adequately reflect the analytical behaviour of patient specimens (i.e., lack of commutability)."

Measurement performance goals: how they can be estimated and a view to managing them

Kallner A. Scand J Clin Lab Invest 2010;70(Suppl 242):34-39.

"The total error (TE) is a sum of bias and imprecision. It contains information on bias and it raises the question why carry it along if it is known and thus could be eliminated with an uncertainty that can be estimated."

"In view of modern thinking we should abandon the total error concept and estimate the uncertainty of measurement procedure. The main difference lies in the perception of the 'error.' In short, if the error is known, let us compensate for it."

"The concept of uncertainty requires that the measurement is compensated for any known and significant bias."

Managing quality vs. measuring uncertainty in the medical laboratory

Westgard JO. Clin Chem Lab Med 2010;48:31-40.

"Thus there exists a total error model with linear combination of bias and imprecision, an RMSD* model for combining the squares of bias and imprecision, and the detailed GUM model which involves many different components of variation, along with a host of rules and recommendations for estimating and combining variances."

"Measurement uncertainty, trueness, and traceability are new to many medical laboratories."

"The call for correction of any known biases is true to the principles of metrology, but it is a risky business in medical laboratories because there are relatively few reference methods and materials. Thus, it is difficult to know what correction is actually correct. … Bias is not as simple as a correction factor or a conversion algorithm (or a Hb A1c "master equation" for that matter)."

*root mean square measurement deviation

Managing quality vs. measuring uncertainty in the medical laboratory

Westgard JO. Clin Chem Lab Med 2010;48:31-40.

"Horwitz put it more succinctly in a later paper (39): '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."

Mary Lou Gantzer (Past President AACC, President-Elect, CLSI, Siemens); The role of Clinical and Laboratory Standards Institute (CLSI) Standards in Industry (March 2010)

Physician responses to uncertainty of measurement

- **Ignore it**
- **Overemphasize it**
- **Misinterpret it**
- **Repeat the test**
- **Criticize the laboratory**

Measurement Uncertainty (μ)

Panteghini M. Clin Chem Lab Med 2010;48:7-10.

"Recently, Guerra et al compared the uncertainty obtained with this *top-down* approach with the combined uncertainty calculated with the *bottom-up* GUM scheme for measurement of the catalytic activity of γ-glutamyltransferase. They showed very close estimates (4.1% vs. 4.3%) supporting the feasibility of the former in fulfilling the needs of the clinical laboratory, and the accreditation requirement for having reliable uncertainty data coming from IVD end users."

"A question remaining to be answered concerns the reporting (or not) of uncertainty of laboratory measurements to clinicians. Many people, including Westgard, think that the uncertainty cannot be reported with patient results, since physicians are not aware of the variation inherent in each analytical result, and rely on laboratories to not make mistakes and satisfy their expectations."

"In conclusion, 'medical laboratories should utilise the concept of total error as a practical *top-down* estimate of measurement uncertainty,' but only if traceability concepts are correctly implemented in their analytical quality control."

The Quality of Laboratory Testing Today

Westgard JO, Westgard SA. Am J Clin Pathol 2006;125:343-354.

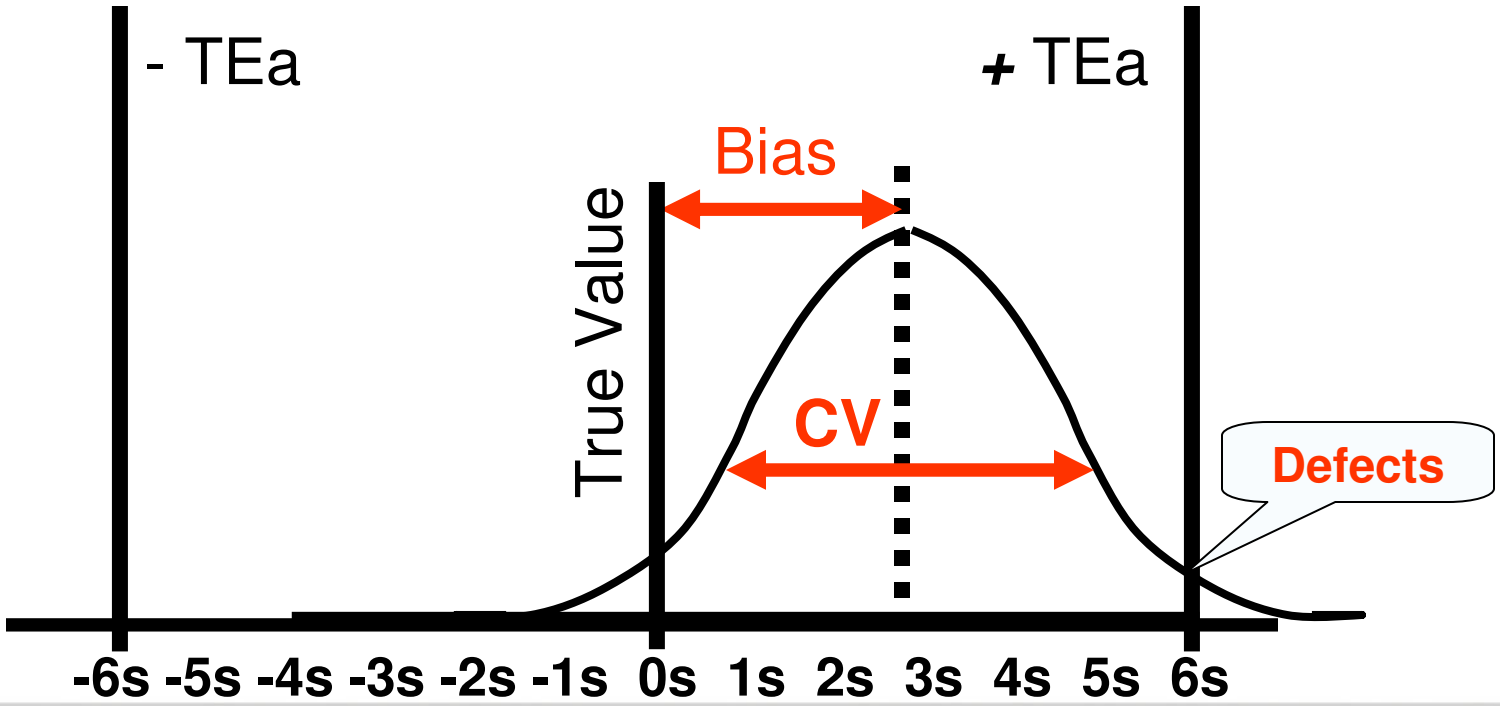
"For any measurement procedure to be eligible for EQC* procedures, it should be required to demonstrate 6 σ quality. The application of Six Sigma principles and metrics would greatly improve the proposed EQC validation process and provide a scientific basis for recommendations on the amount of QC that is needed."

"Beginning with the National Cholesterol Education Program (NCEP) guidelines in the late 1980s, desirable precision was specified as a CV of 3% or less and desirable accuracy as a bias of 3% or less. Then in 1992, CLIA defined an allowable total error of 10%. Given the combined NCEP and CLIA guidelines, the quality that would be expected would be 2.33 σ … to 3.33 σ if bias were zero."

*** EQC (equivalent quality control)**

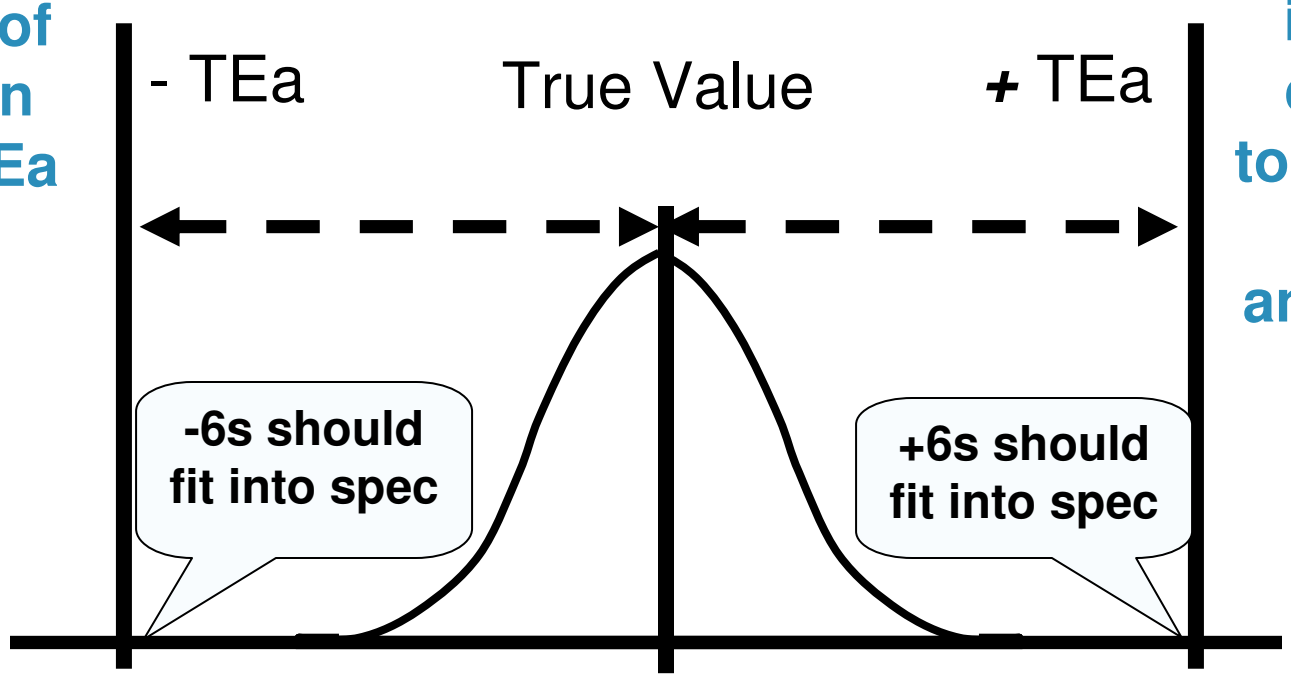
Sigma Metrics for the Clinical Laboratory

Sigma metric = (TEa – Bias)/CV (all expressed as %)



Six Sigma in the Clinical Laboraotry

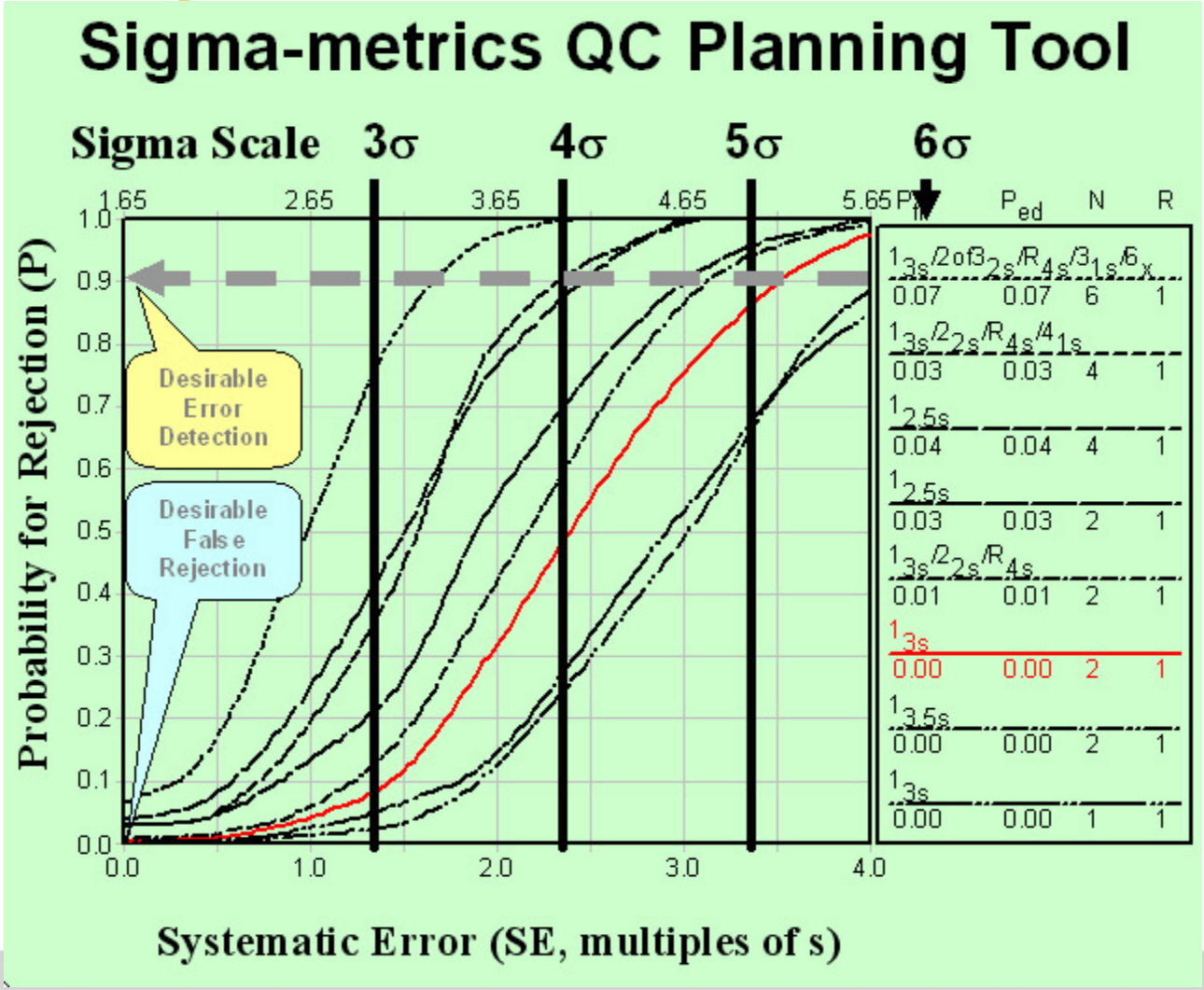
Quality goal allows six Sigmas of variation within TEa limit



Variation is small enough to allow for 6 SDs and not be out of control

Makes sense: smaller variation, higher quality of the assay

Quality Control Specifications and Six Sigma Implications: Power Curves



Proposed guidelines for the internal quality control of analytical results in the medical laboratory

"… *control* does not necessarily imply *quality*, since control by itself can only be used in monitoring of the current quality of the process, e.g., by rejection of certain errors- but it cannot improve the analytical quality properly."

"The VIM-definition of systematic error … is not sufficient for laboratory medicine. This is due to the possible sources of error which may be related either to the *calibration* … which is the same for all measured samples in a run, or to individual (but reproducible) deviations due to *non-specific reactions* or *interfering substances* in the various patient samples …"

"…, in the case that much cheaper commutable IQC* materials with reference method target values are available in the future, traceability can also be controlled internally…Genuine (non-processed) serum with traceable target values is, however, difficult to handle. It must be stored at – 80 C and mailed on dry ice, as in the Nordic protein project, so further efforts are needed to solve this.

*Internal Quality Control

Petersen PH, Ricos C, Fraser C, Thienpont L, Stockl D, et al. Eur J Clin Chem Biochem 1996;34:983-999.

One Clinical Chemist's Experience Working for an IVD Manufacturer

1999, joined Clin Chem R&D; Company strategy: identify the best performance offered by competitor's assays (e.g., precision, LoD, linearity, dynamic range) and provide assays that match or exceed

7 Dec 2003, IVDD in Europe requires traceability/uncertainty- major impact

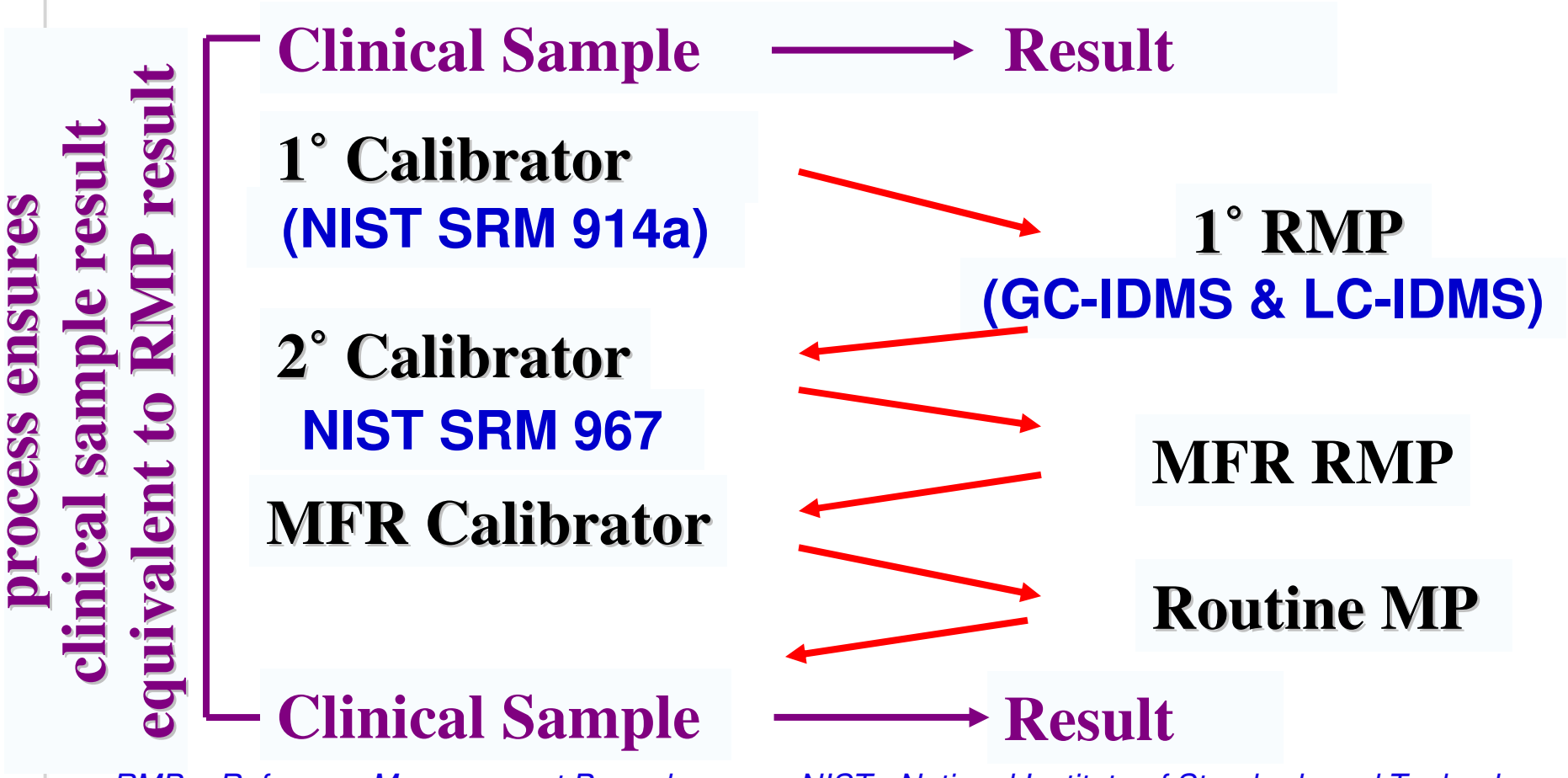
2007 – 2008, Restandardization of creatinine assays driven by medical relevance; metrological traceability with commutable SRM 967 & ID-LC/MS, optimal performance in reference interval (not high concentration) to improve eGFR; all major manufacturers participate

2010, Hb A1c, two traceability chains (NGSP and IFCC), reporting in % Hb A1c and mmol/mol, master equation to inter-convert, potential for reporting eAg; commutable PT/EQA whole blood samples with reference method target values

IVD manufacturers have traditionally sought to differentiate their products from the competitors- *not to provide equivalent performance/comparable results*

Assay standardization/harmonization to ensure comparable results over time and space is a paradigm shift for IVD manufacturers

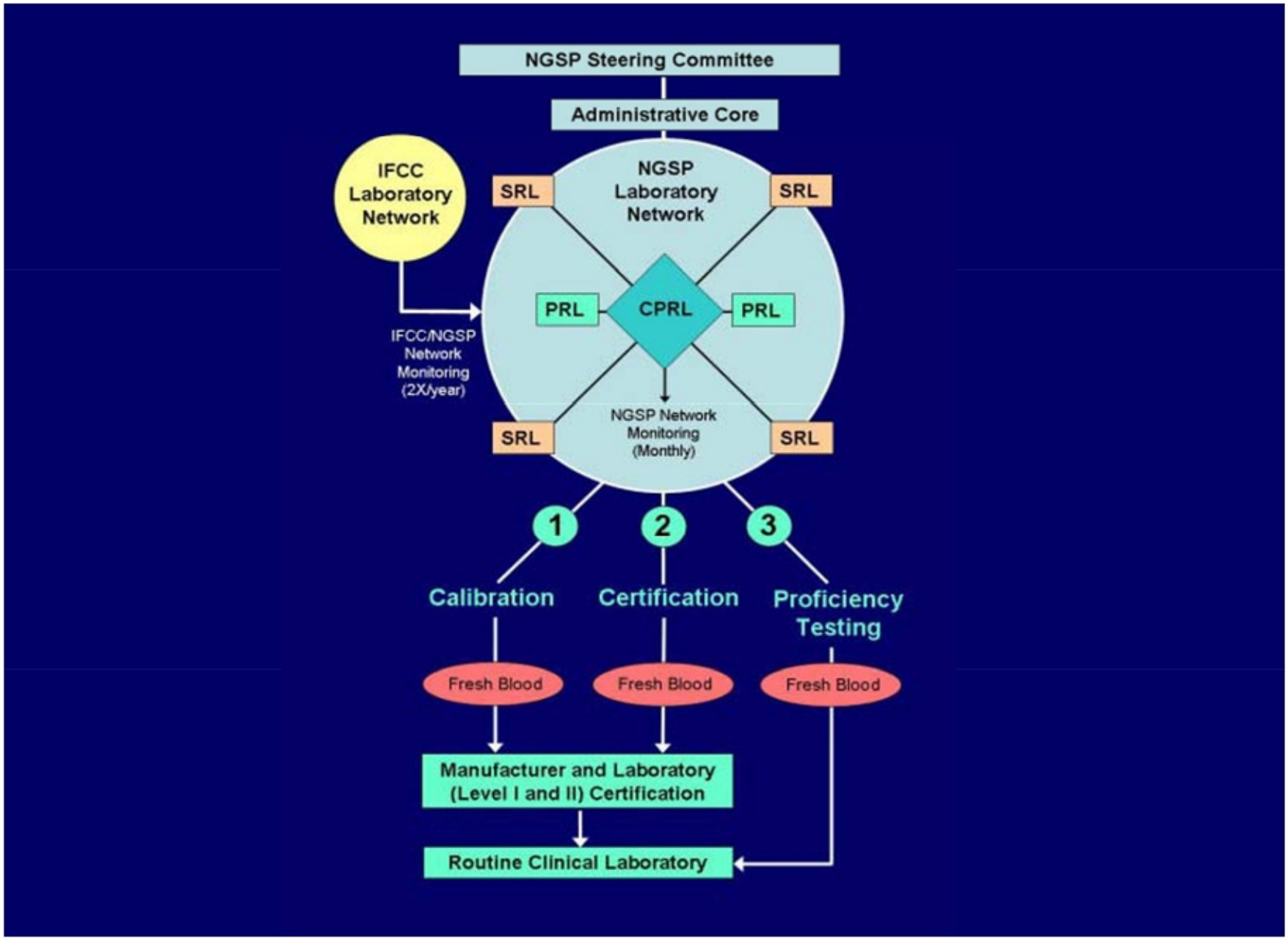
Traceability Chain for Serum Creatinine Calibrators



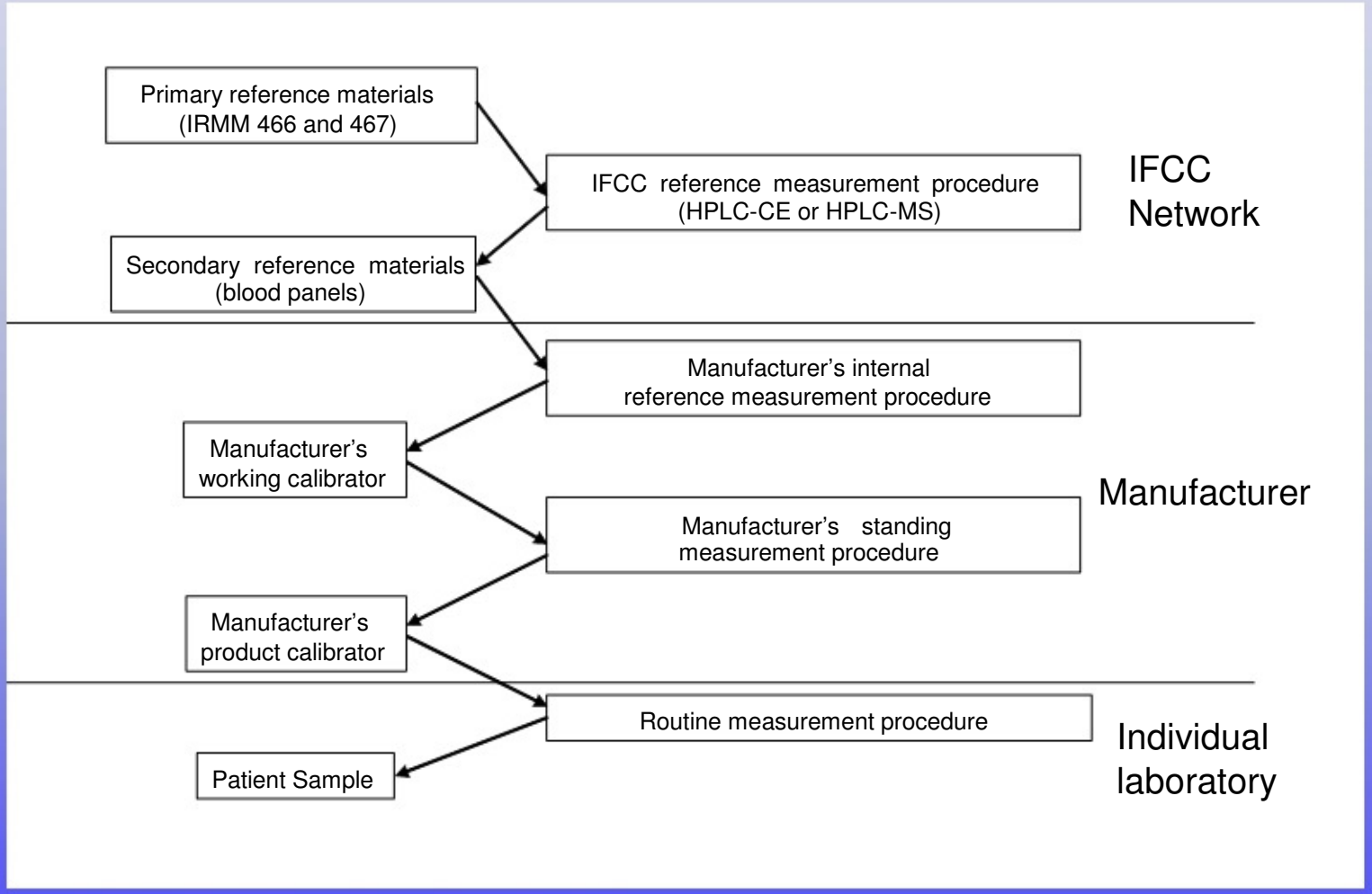
RMP = Reference Measurement Procedure
MFR = Manufacturer
MP = Measurement Procedure

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

Source: National Kidney Disease Education Program


NGSP Steering Committee
Administrative Core
IFCC Laboratory Network
IFCC/NGSP Network Monitoring (2X/year)
NGSP Laboratory Network
SRL
SRL
PRL
CPRL
PRL
NGSP Network Monitoring (Monthly)
SRL
SRL
1
2
3
Calibration
Certification
Proficiency Testing
Fresh Blood
Fresh Blood
Fresh Blood
Manufacturer and Laboratory (Level I and II) Certification
Routine Clinical Laboratory

Reference System for HbA1c (ISO 17511)



Mosca A & al, CCLM 2007;45:1077

Projected Schedule for CAP GH2 (Hb A1c) Limits

- ±12% in 2008
- ±10% in 2009
- ±8% in 2010
- ±6% in 2011
  As of Jul 10; ± 7%!

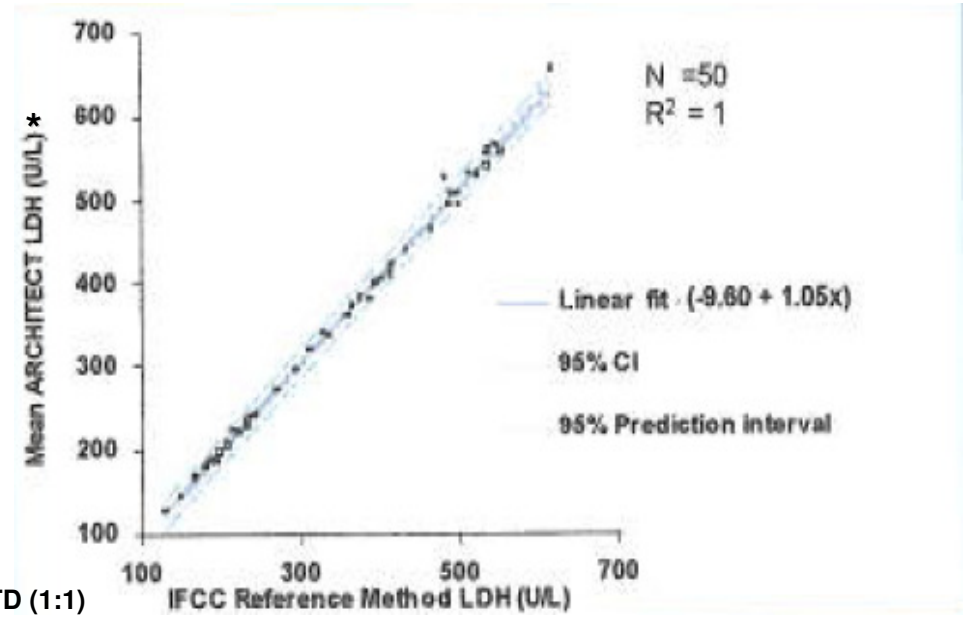
Manufacturers now attempting to understand FDA's requirement for a Diabetes diagnostic claim in addition to monitoring glycemic control

Enzyme Traceability to IFCC Reference Methods

TRACEABILITY OF THE NEW, OPTIMIZED ARCHITECT LDH ASSAY TO IFCC REFERENCE METHOD

E. Rosler[1], R. Klauke[2], C. Kasal[3], D.X. Yahalom[3], L. Lennartz[3], *M. Orth[1], G. Schumann[2]
[1]Marienhospital Stuttgart, Institut für Laboratoriumsmedizin, Stuttgart, Deutschland; [2]Medizinische Hochschule Hannover, Institut für Klinische Chemie, Hannover, Deutschland; [3]Abbott Laboratories, Abbott Diagnostics Division, Irving, Texas (USA), Wiesbaden (Germany), Deutschland

Regression analysis of the 50 samples tested with LDH IFCC primary Reference Method and the ARCHITECT LDH assay:



*** STD (1:1)**

Commutable, fresh patient samples; recognized international reference method

Rosler E, Klauke R, Kasal C, Schumann G, et al. Traceability of the New, Optimized ARCHITECT LDH Assay to IFCC Reference Method. 7th Annual Conference of the German Society for Clinical Chemistry & Laboratory Medicine, 2010, Clin Chem Lab Med 2010;49(9):A142.

Importance of Metrology to Manufacturers and the Clinical Laboratory

Metrological Traceability and Its Implementation; A Report. CLSI X5-R*
*** will become CLSI C29; CLSI & IFCC**

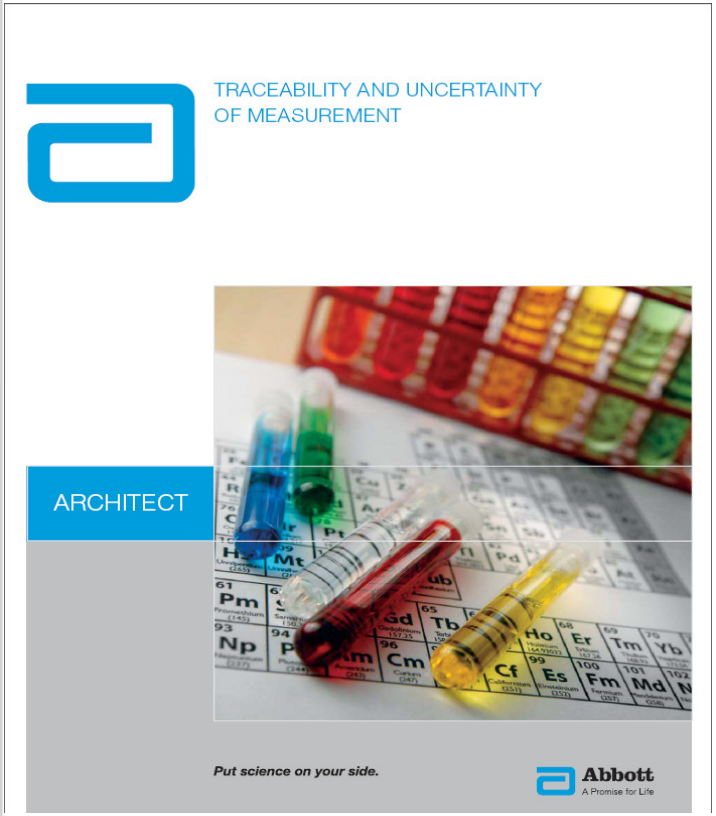
Verification of comparability of patient results within one health care system. CLSI C54-A

Expression of measurement uncertainty in laboratory medicine, CLSI C51-P

The Joint Committee on Traceability in Laboratory Medicine (JCTLM): A Global Approach to Promote the Standardisation of Clinical Laboratory Test Results.
Armbruster D, Miller RR. Clin Biochem Rev 2007;28:105-113.

Measurement traceability and US IVD manufacturers: the impact of Metrology.
Armbruster D. Accred Qual Assur 2009;14:393-398.

Traceability Information Provided by IVD Manufacturers



What Information Should Manufacturers Provide on Their Procedures

Bais reports on troubleshooting of a Ca assay due to calibrator reassignment; 5% bias for automated Ca vs. AAS

"… laboratories depend on manufacturers to provide accurate calibrators. If there is a significant reassignment of a calibrator, manufacturers need to provide supporting evidence …"

"… did not measure SRM 956b … in their standardization, and it would seem important that manufacturers use traceable materials wherever possible, rather than rely on in-house traceability."

"Should manufacturers take part in quality assurance schemes and make their results available for public scrutiny? Should they provide detailed information on their standardization procedures? And should they be more open generally about the way they ensure the quality of their products? To all of these questions, this author believes the answer is yes."

Bais R. Clin Chem 2006;52:1623-1624.

IVD Manufacturers' Efforts To Address Medical Relevance Of Their Products

- Providing calibrator traceability/uncertainty information to customers
- Restandardizing assays using internationally accepted reference materials/reference methods
- Improving manufacturing methods to decrease calibrator uncertainty and lot to lot variability
- Supporting professional organizations with assay harmonization/standardization activities (CLSI, JCTLM, IFCC, AACC, ISO, etc.)
- Designing assays to meet medically relevant performance targets such as precision, bias, total error goals (e.g., RiliBÄK, biological variability, RCPA, etc.)
- AACC's Improving Clinical Laboratory Testing Through Harmonization: An International Forum, 26 – 27 Oct 10, NIST

Conclusions

- Professional societies & clinicians must identify performance targets (e.g., MDLs/cutoffs), with analytical limitations in mind
- Laboratories must choose assays based on analytical quality and clinical relevance, not other factors (e.g., cost)
- IVD manufacturers & labs must continuously assess assay quality to monitor performance through EQA/PT using commutable samples with reference method target values
- IVD Manufacturers must design products (verification/validation testing) to meet clinical needs
- All parties must recognize that clinical laboratory science is a dynamic field and account for changes in analytical capability and clinical needs

Conclusions

Metrological traceability & assay standardization/ harmonization initiatives are impacting global clinical laboratory practice

IVD manufacturers are responding to the paradigm shift (e.g., creatinine, Hb A1c)

Legitimate scientific debate continues over the best approach to analytical quality/medical relevance (e.g., TEa vs. uncertainty)

IVD manufacturers will continue to work with the profession (e.g., IFCC, AACC, JCTLM, CLSI, etc.) and Regulatory agencies to produce devices whose performance meets clinical needs (pace of improvement & degree of success will vary with measurand)

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