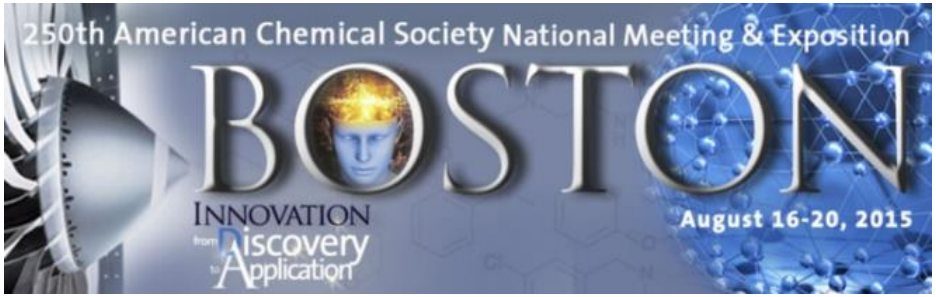

Boston, MA
August 19, 2015

Symposium: **"Chemistry and the International System of Weights and Measures"**

Session I: The Consultative Committee on Metrology in Chemistry and Biology: Who We are, What We Do, and Why You Should Care

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"CCQM Activities and Impact in Healthcare "

Willie E. May, Ph.D

NIST Director & Under Secretary of Commerce for Standards and Technology

President, CIPM Consultative Committee on Metrology in Chemistry & Biology

Vice President, International Committee on Weights and Measures

NMI's around the world *are working together to link our global measurement system to the fundamental constants of nature*

Unit		*Reference value used to define the unit*		
		in current SI	*in the new SI*	
second,	s	$\Delta\nu(^{133}Cs)_{hfs}$	$\Delta\nu(^{133}Cs)_{hfs}$	Cs hyperfine splitting
metre,	m	c	c	speed of light in vacuum
kilogram,	**kg**	$m(\mathcal{K})$	h	Planck constant
ampere,	A	μ_0	e	elementary charge
kelvin,	K	T_{TPW}	k	Boltzmann constant
mole,	**mol**	$M(^{12}C)$	NA	Avogadro constant
candela,	cd	K_{cd}	Kcd	luminous efficacy of a 540 THz source

Rigorous realization of these units has provided undeniable impact on trade, commerce, and quality of life

In addition to supporting the realization of SI units, more and more **countries are directing their NMIs to focus increasing amounts of their research and measurement services activities on:**

Quality of Life and Economic & Social Sustainability issues

- ***health***
- ***food***
- ***environment***

Since NIST's inception, in addition to maintaining the more traditional National Physical Measurement Standards, **we have also focused a significant portion of our research and measurement services activities on addressing contemporary societal needs.**

Supporting the Industrial Revolution

NIST has become:

- a key player on the Administration's Innovation Team
- the nation's go-to agency for measurements, standards, and technology

1901 → **2015**

- Advanced Communications
- Advanced Manufacturing
- Advanced Materials
- Cyber-Physical Systems
- Cybersecurity and Privacy
- Disaster Resilience
- Forensic Science
- GHG Measurements
- **Healthcare**

Healthcare reform is a major issue throughout the world

- The rising cost of healthcare and increased prevalence of chronic diseases is having a devastating affect of economic security and quality of life in all parts of the world.

- Major efforts are underway to reform healthcare and reduce spending through increased efficiency and quality, focusing on prevention of disease and creating a healthier population.

- **It is a stated goal of the Obama Administration to improve the quality of U.S. health care while lowering its cost** by computerizing all Americans' medical records. … "this will cut waste, eliminate red tape, and reduce the need to repeat expensive medical tests …. it will save lives by reducing the deadly but preventable medical errors that pervade our health care system".

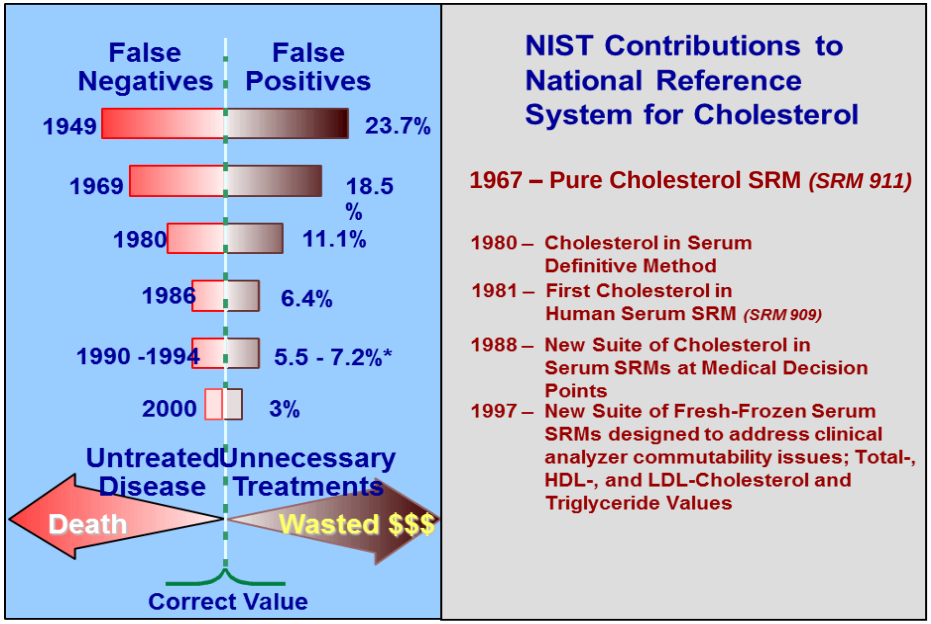
  - **Need interoperable health IT network** that is **correct, complete, secure, usable, and testable**

Measurements that are comparable over space and time are key to achieving these Global and National Goals

- **In 2015 in the U.S. alone, ~$2.9 trillion to be spent on healthcare of which 10% -15% was based on measurements**
  - **70% of healthcare decisions are based on results from clinical laboratory measurements**

- **Measurement bias affects quality of life and leads to**
  - Incorrect diagnosis and treatment
  - Impairment of patient well-being

- **Standards exists for only ~10% of the 700 diagnostic markers routinely measured**
  - Several NMIs have begun developing CRMs to address this lack of standards



NIST Contributions to National Reference System for Cholesterol

1967 – Pure Cholesterol SRM *(SRM 911)*

1980 – Cholesterol in Serum Definitive Method

1981 – First Cholesterol in Human Serum SRM *(SRM 909)*

1988 – New Suite of Cholesterol in Serum SRMs at Medical Decision Points

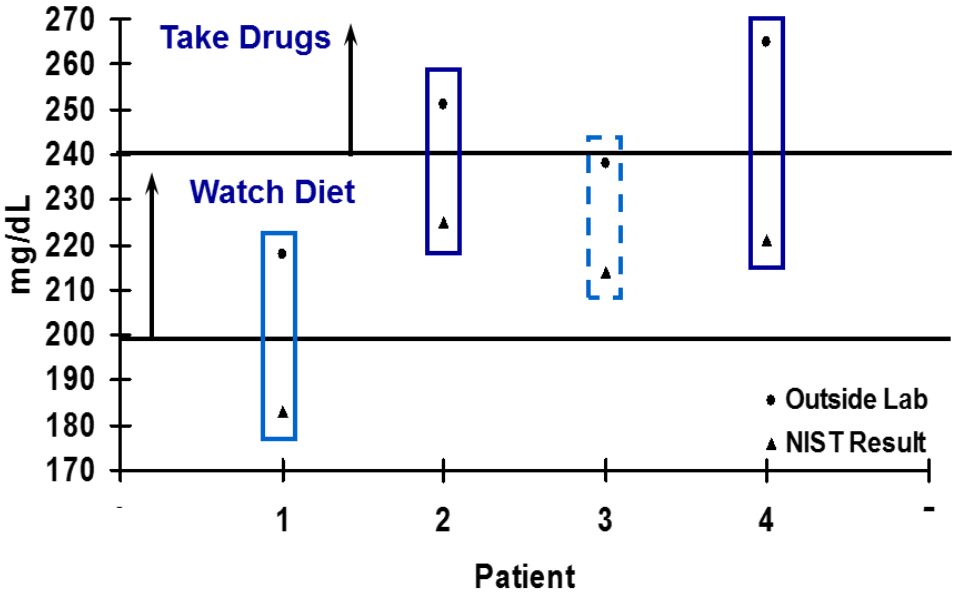
1997 – New Suite of Fresh-Frozen Serum SRMs designed to address clinical analyzer commutability issues; Total-, HDL-, and LDL-Cholesterol and Triglyceride Values

Improved Cholesterol Measurement Accuracy Saves Health Care Dollars

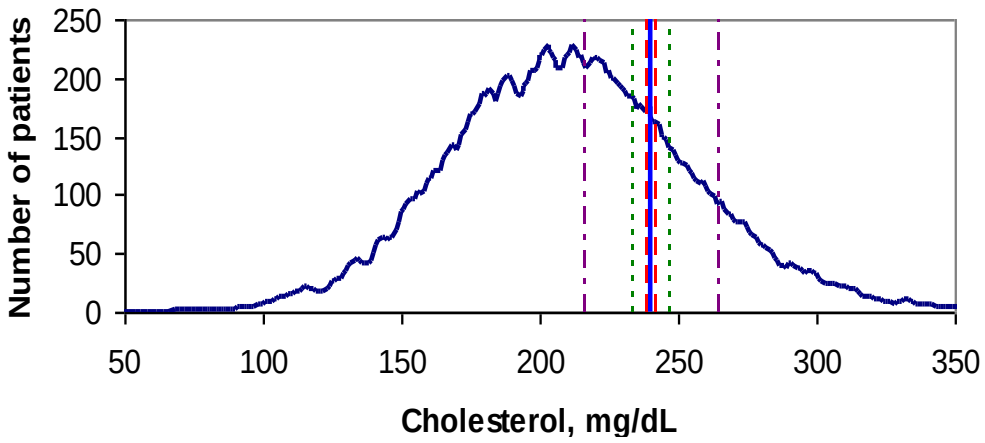
Improvement in precision since 1968 has been estimated to **save $100M/yr in treatment costs**

***Data from GAO and CAP**

NIST Cholesterol-in-Blood Experiment - Impact of Inaccurate Measurements



Bias in Cholesterol Measurements Affects Medical Decision-Making



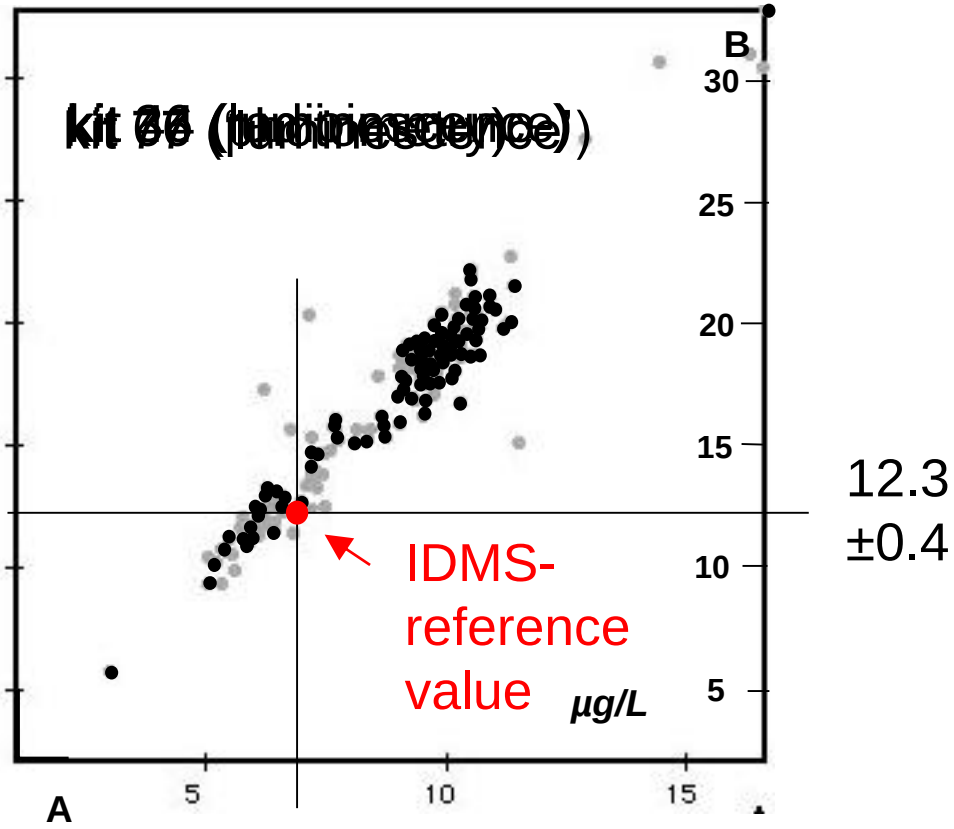
Cholesterol Frequency Distribution of >20,000 Mayo Clinic Patients

(with +1%, +3% and +10% limits around 240 mg/dL criteria point)

If measurement bias were:	Positives (>240 mg/dL) per 1000	Predicted Change in "Positives/1000"
-10% bias	120	-129
-3% bias	203	-46
-1% bias	234	-15
0% bias	249	
+1% bias	263	+14
+3% bias	300	+51
+10% bias	446	+197

Results from Analysis of "HGH" in two serum samples

- Different labs
- Different kits



12.3 ±0.4

6.8±0.5

[Data: Referenzinstitut für Bioanalytik, dgkl-rfb.de]

IDMS measurement: PTB, Arsene,C./Henrion,A.

CCQM Activities in Support of Measurements

- The CCQM is responsible for developing, improving and documenting the **degree of equivalence of national standards** (certified reference materials and reference methods) **for chemical and biological measurements.**
  - Key Comparisons among National Metrology Institutes
- Education and outreach, both among peer NMIs/DIs and the global measurement community

Working Groups are responsible for:

- **Over 5700 CMCs currently published in the KCDB**
  - **830 different analytes (3050 different analyte-matrix combinations)**
    - Number of analyte matrix combinations increasing at a rate of about 250 per year.
- **365 comparisons have been conducted over past 15 years**
- **25 additional comparisons are currently underway** Including the first 2 comparisons on Microbial Identity and Cell Counting

WGs Conduct Key Comparisons that Interrogate Measurement Competencies across a Broad Range of Critical Areas

… including the following examples:

Health
- Clinical diagnostic markers in blood

Food
- Pesticides, antibiotics hormones
- vitamins and minerals
- drinking water
- ethanol in “Adult Beverages”

Environment
- air, soil, sediments
- biological tissues
- waste water

Advanced Materials
- semiconductors, alloys, polymers

General Studies
- pH and electrolytic conductivity
- purity assessment
- calibration solutions mixtures

Forensics
- drugs, breathalyzer *(ethanol-in-air)*
- explosive residues
- DNA profiling

Commodities
- emissions trading, sulfur in fossil fuels
- natural gas
- cement

Biotechnology
- DNA quantification
- protein quantitation
- GMO

List of Completed CCQM Key Comparisons in Healthcare Area

Key Comp.	Title	Year Started
CCQM-K6 **CCQM-K6.1** *CCQM-K6.2*	**Cholesterol in serum**	**1999** **2001** *2012*
CCQM-K11 **CCQM-K11.1** *CCQM-K11.2*	**Glucose in serum**	**2001** **2005** *2112*
CCQM-K12 **CCQM-K12.1** *CCQM-K12.2*	**Creatinine in serum**	**2001** **2003** *2112*
CCQM-K14	**Calcium in Serum**	**2003**
CCQM-K55.a	**Purity assessment of high purity organic materials: (17β-Estradiol)**	**2008-2009**
CCQM-K55.c	**Purity assessment of high purity organic materials: L-valine**	**2011**
CCQM-K63.a	**Non-Peptide Hormones in Serum: Cortisol**	**2007-2008**
CCQM-K63.b	**Non-Peptide Hormones in Serum: Progesterone**	**2007-2008**
CCQM-K61	**Quantitative PCR**	**2007**
CCQM-K69	**Anabolic steroids in urine: Testosterone glucuronide**	**2008**
CCQM-K80	**Comparison of value-assignment of CRMs and PT materials: Creatinine in Serum**	**2010**
CCQM-K86	**Relative quantification of genomic DNA fragments extracted from a biological tissue**	**2010**

Completed Comparisons for pH
(spans range) and applicable to sectors in addition to Healthcare)
6 Key Comparisons (plus 3 Subsequent Linked Studies)

List of In-Progress Comparisons in Healthcare Area

Comp.	Title	Year Started
CCQM-K107	Elements and Se speciation in human serum	2012
CCQM-K115	Peptide purity determination - synthetic human C peptide (HCP)	2013
CCQM-P123	Cell quantification on solid substrate	2010
CCQM-P154	Absolute quantification of DNA	2013
CCQM-P155	Multiple cancer cell biomarker measurement	2013

List of Planned Comparisons in Healthcare Area

Comp.	Title
CCQM-K134	Relative quantification of genomic DNA fragments extracted from oil matrix (OSR)
CCQM-K135	Relative quantification of genomic DNA fragments extracted from starch matrix (rice)
CCQM-P55.2	Peptide purity determination - synthetic human C peptide (HCP)
CCQM-P137	Clinical amylase measurement
CCQM-P164	HGH quantification in serum
CCQM-P165	Quantification of CD34+ cell counts
CCQM-K139	Elements in human serum
CCQM-K55.d	Purity assessment of high purity organic materials: Folic Acid
CCQM-K78	Mass Fraction of Organic Calibration Solution: Amino acids in aqueous solution
CCQM-K109	Urea and uric acid in serum
CCQM-K132	Vitamin D in serum

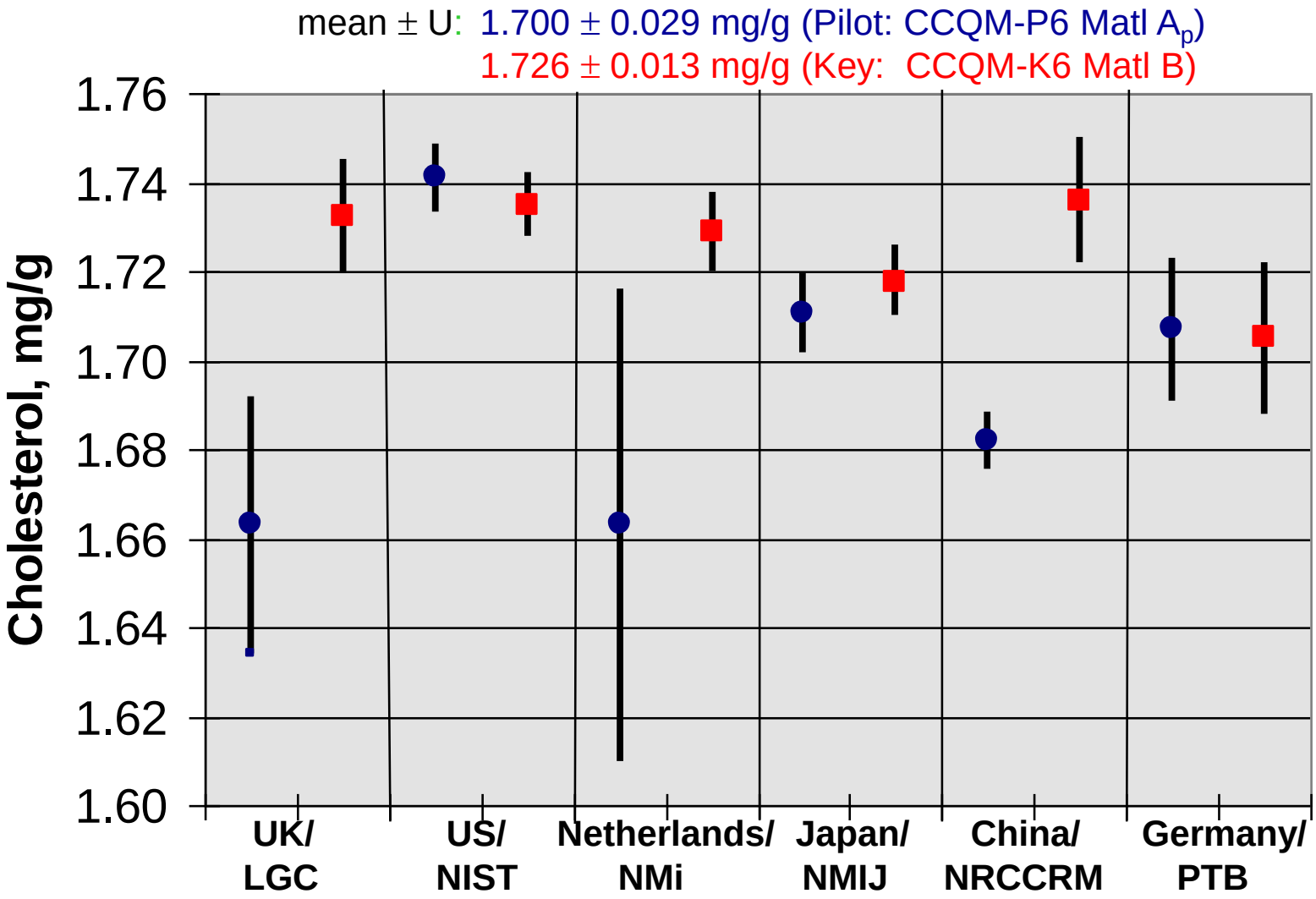
How Far Does the Light Shine?

Set of CCQM Comparisons for Well-Defined Small Molecule Health Status Markers

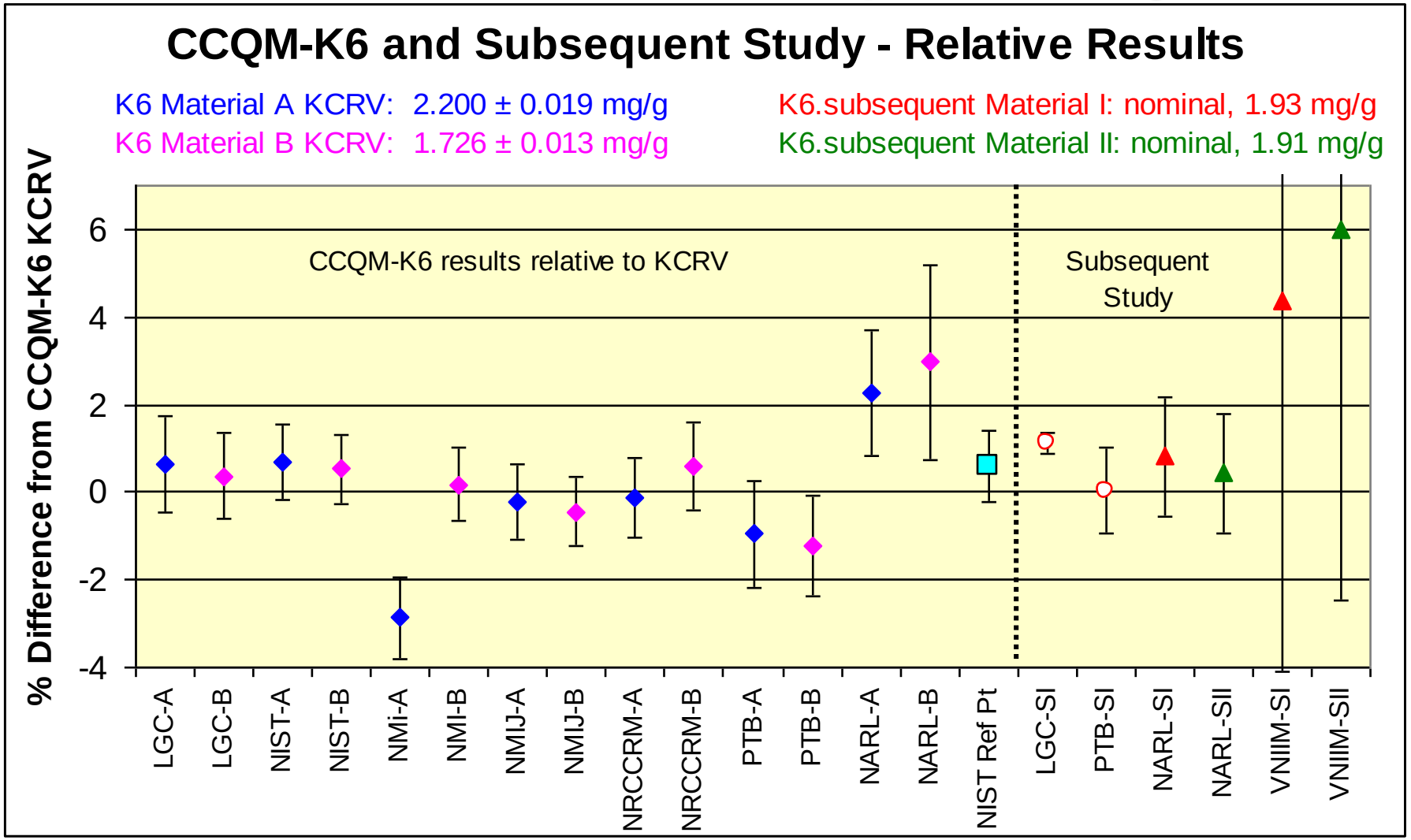
To assess the capabilities of NMIs for delivering services for **well-defined small organic analytes in serum**, the CCQM conducted Comparisons for the determinations of **serum cholesterol, glucose** and **creatinine**. They were chosen because they present very different challenges thus providing a more complete picture of the capabilities of participating NMIs.

- **Cholesterol** is lipophylic and present in serum primarily as fatty acid esters.
- **Glucose** is highly water-soluble and also associates strongly with proteins.
- **Creatinine** is very polar, present at much lower levels than cholesterol, and glucoe and its determination requires considerable care to assure separation from creatine, without interconversion between creatinine and creatine.

CCQM – Comparison of Results for Cholesterol in Serum in 1999 Pilot Study ● and in 2000 Key Comparison

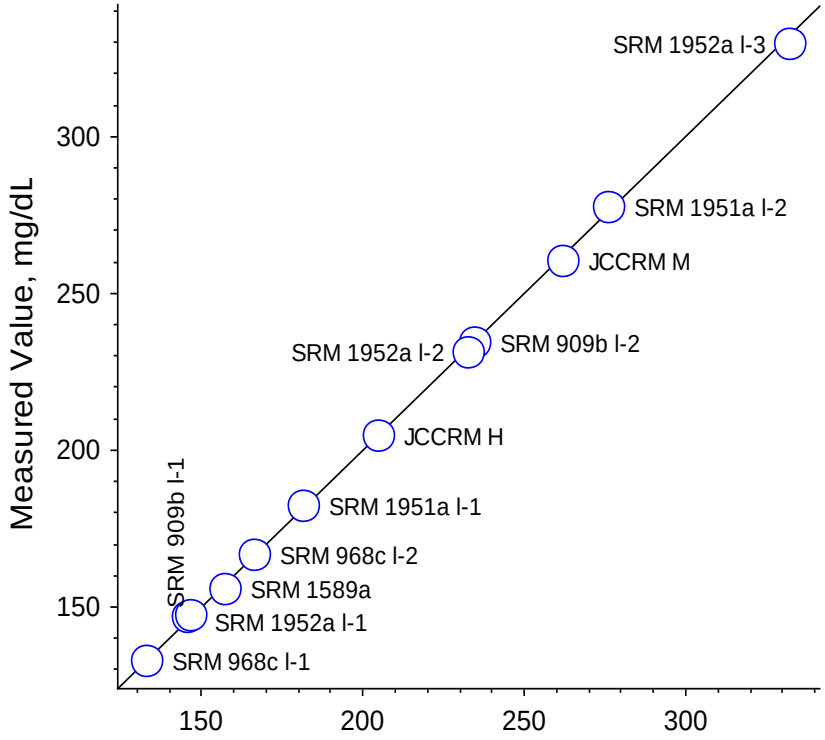


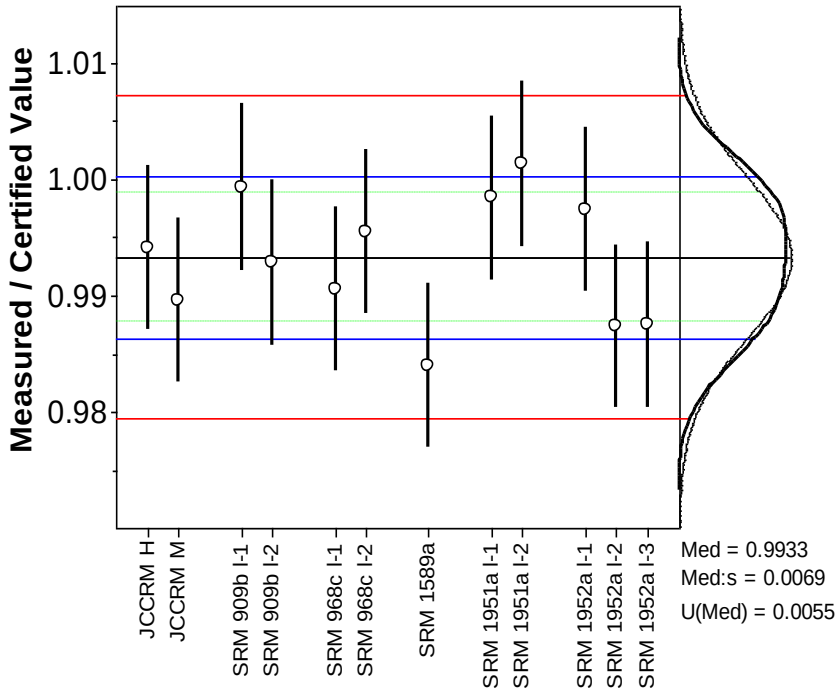
CCQM-K6 and Subsequent Study



Cholesterol in Serum: Reverse-Comparison

measurements of relevant NMI CRMs were made at NIST under repeatability conditions





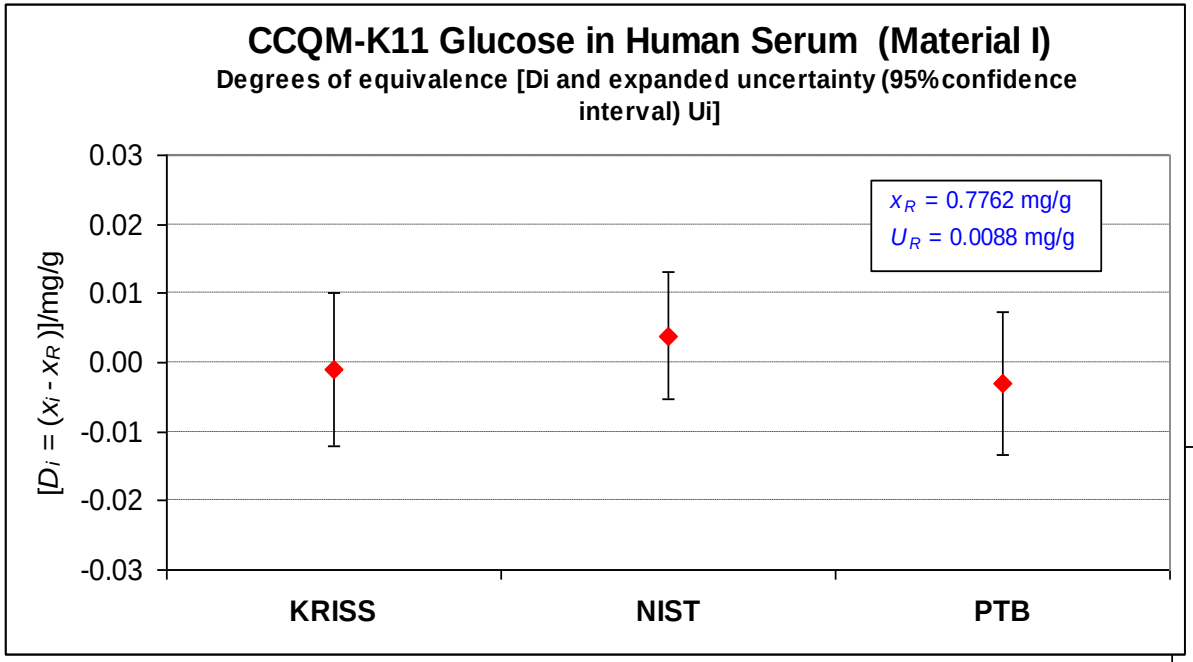
Comparability of Cholesterol in Serum CRMs between NIST/US and NMIJ/Japan

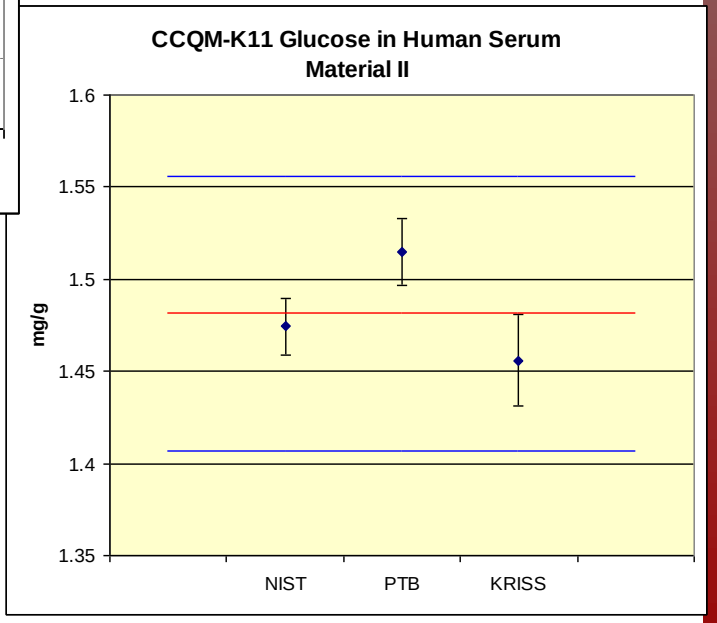
⇨

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

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

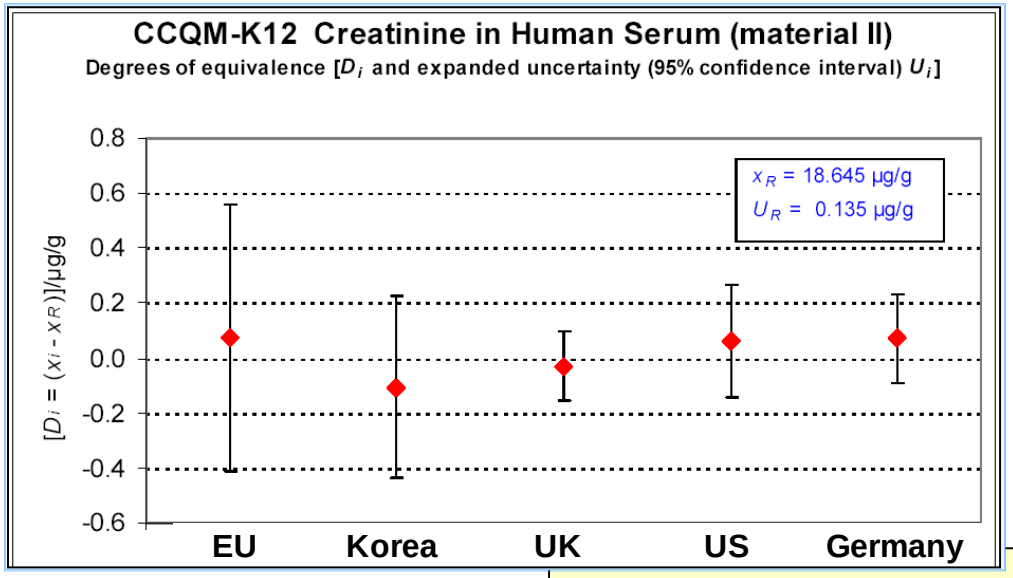
CCQM- K11 Glucose in Serum





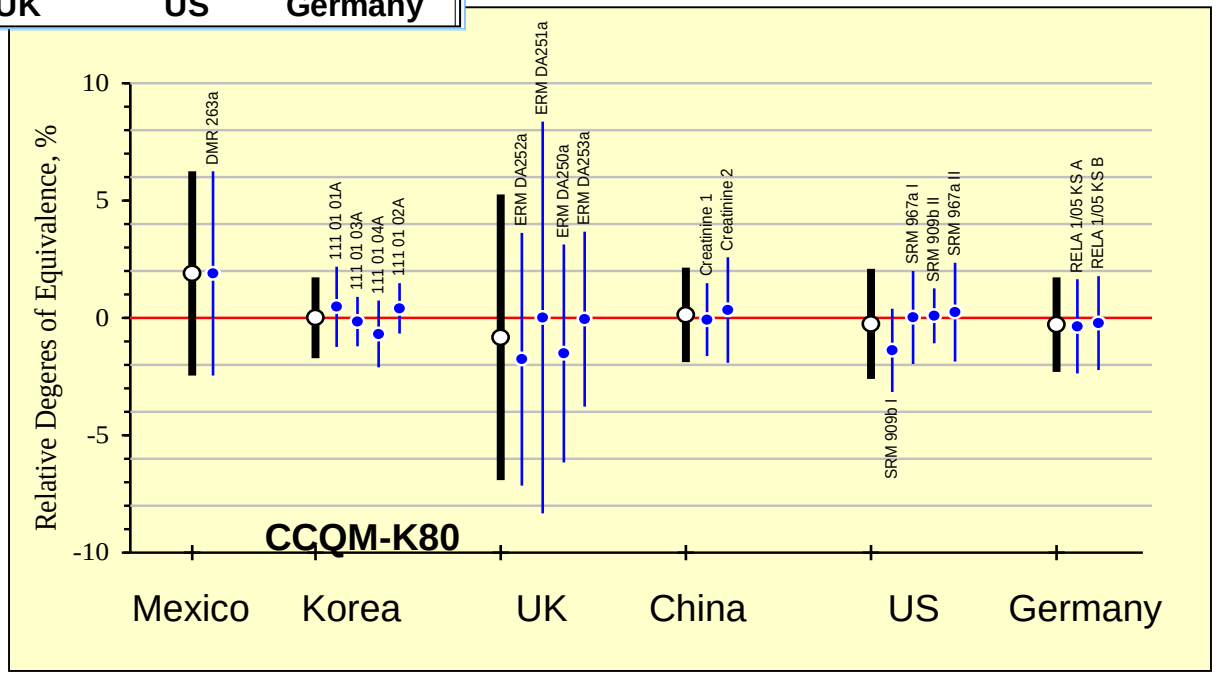
Study Period: 2000-2001

Creatinine in Human Serum



Document degree of equivalence of measurement capabilities

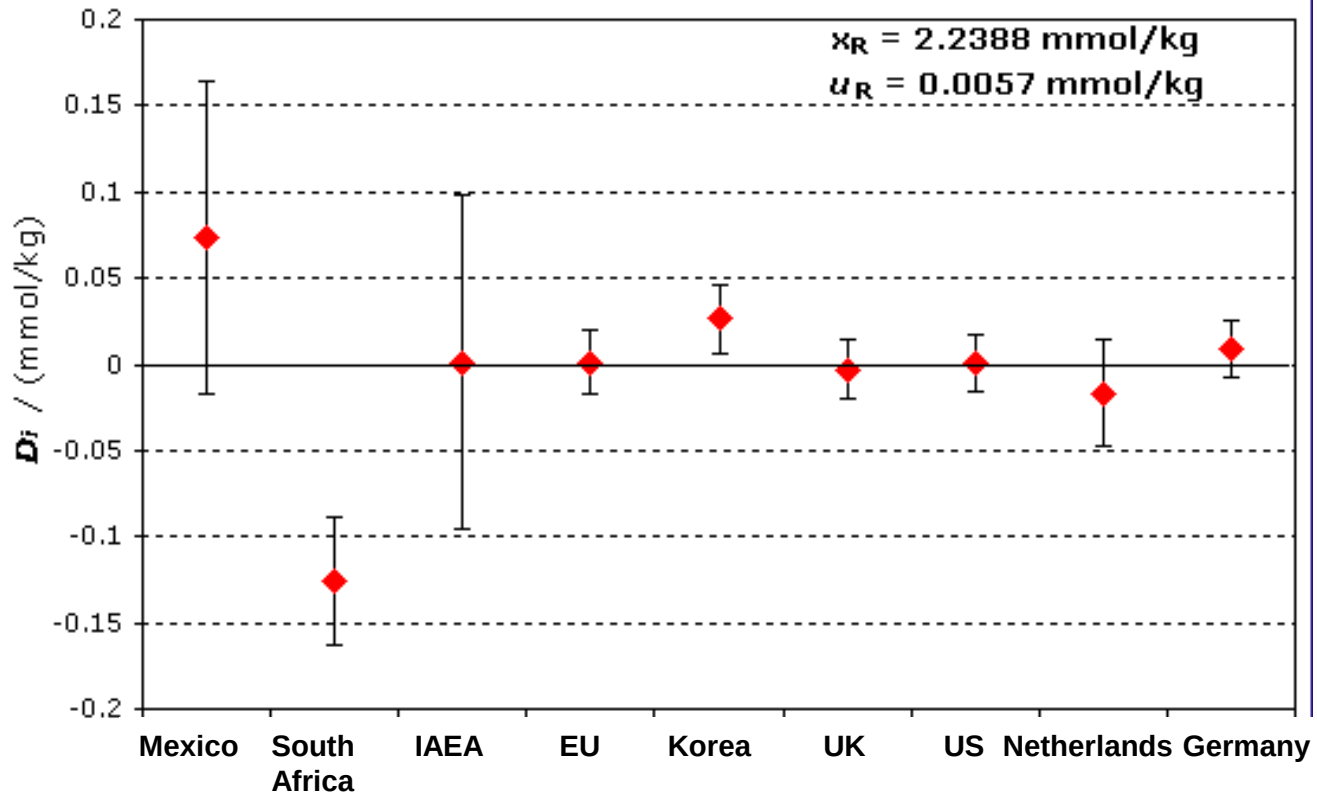
Comparison of value-assignment of CRMs



CCQM-K14: Calcium in Serum

MEASURAND : Amount content of Ca in human serum
NOMINAL VALUE : ~ 2 mmol/kg

Degrees of equivalence D_i and expanded uncertainties U_i (k = 2) expressed in mmol/kg

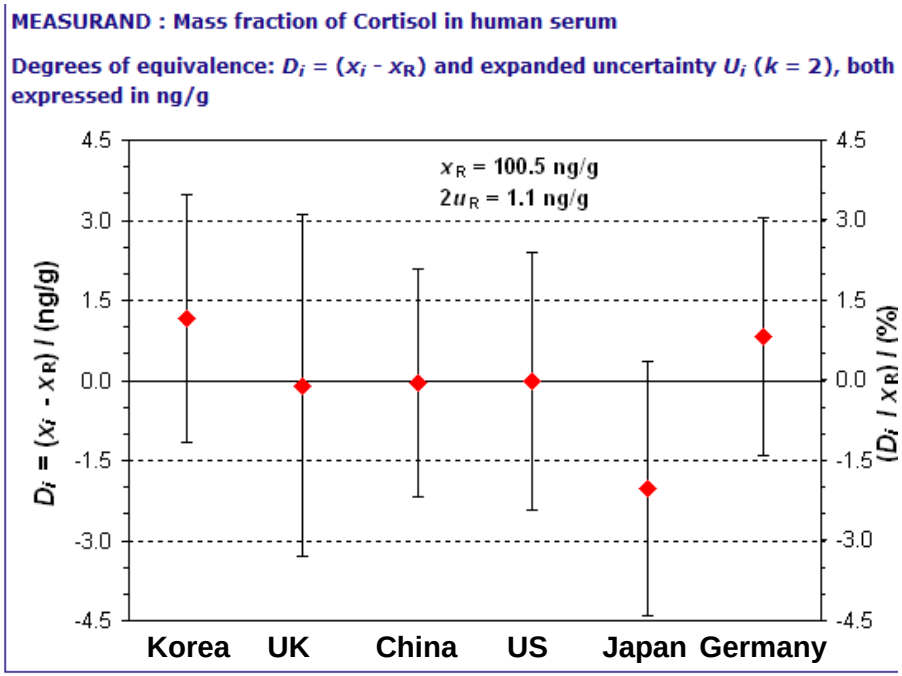


Metrologia, 2004, 41, Tech. Suppl., 08003

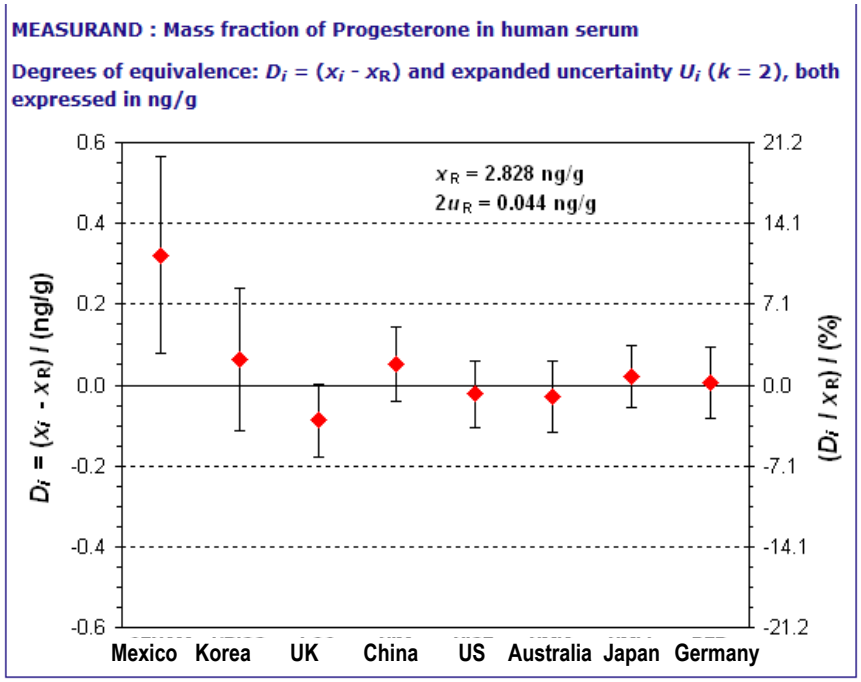
Steroid hormone measurements

-- to help in the diagnosis, treatment and prevention of breast, testicular and prostate cancers

CCQM-K63.a Cortisol in human serum



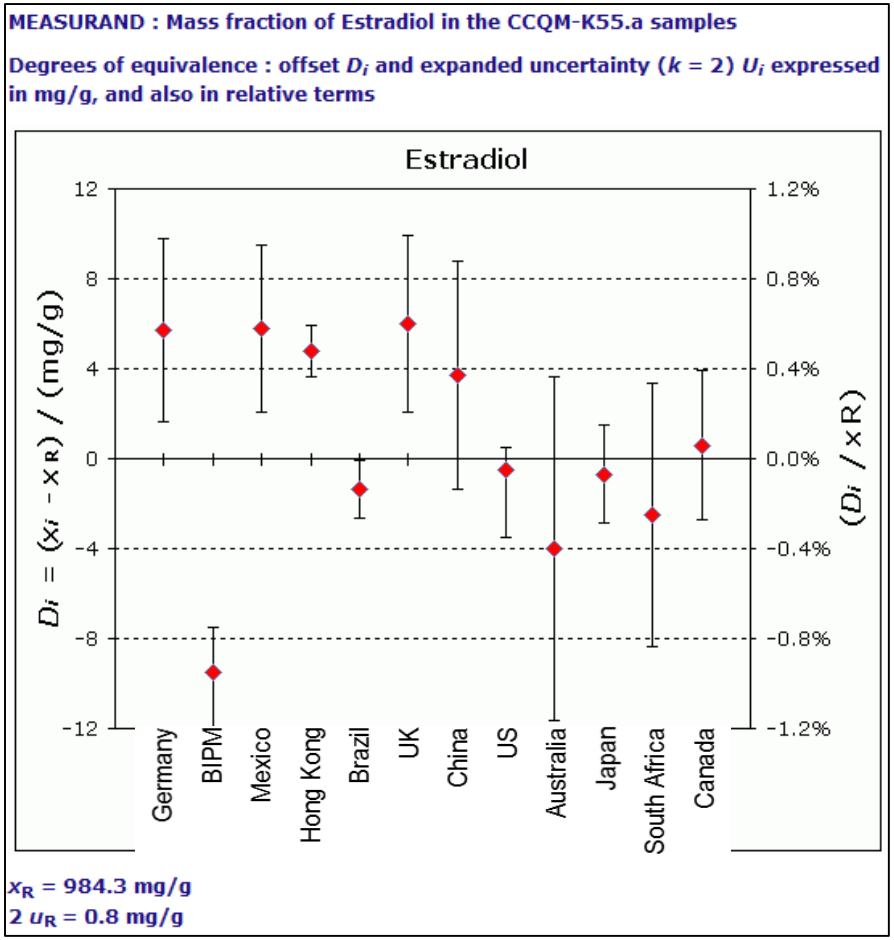
CCQM-K63.a Progesterone in human serum



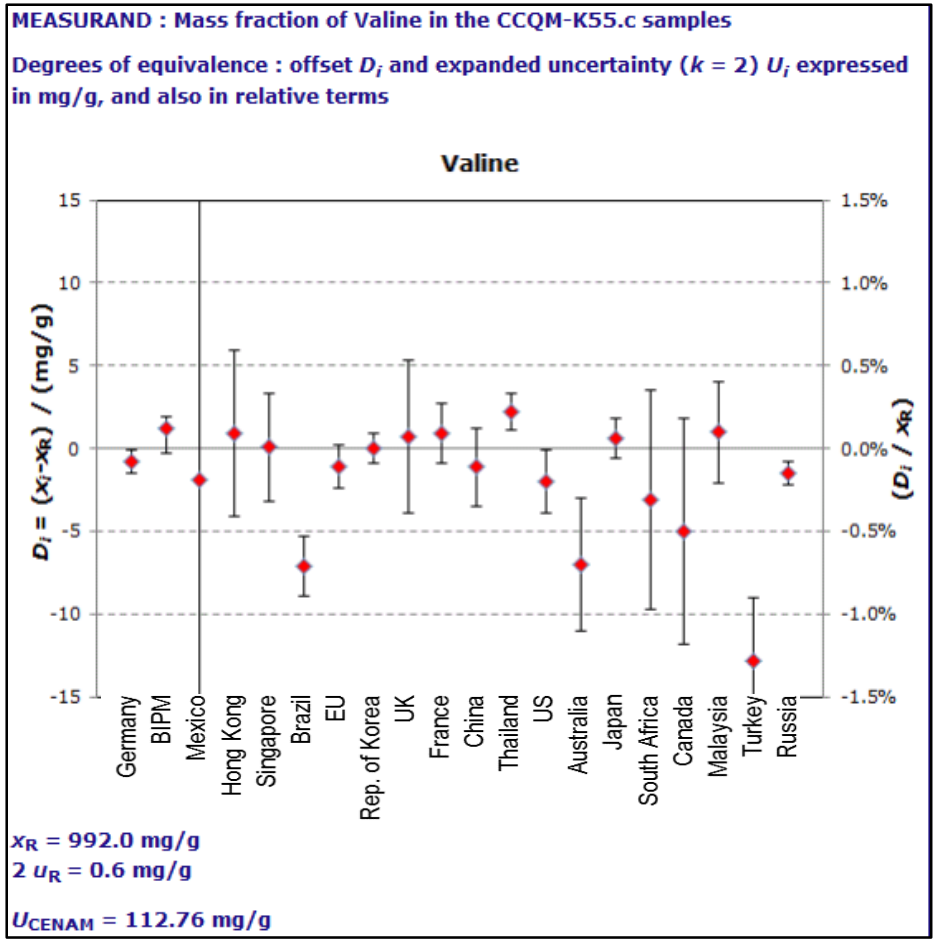
Metrologia, 2010, 47, Tech. Suppl., 08017

Purity Assessment of High-Purity Materials – critical for Metrological Traceability

K55.a 17β-Estradiol



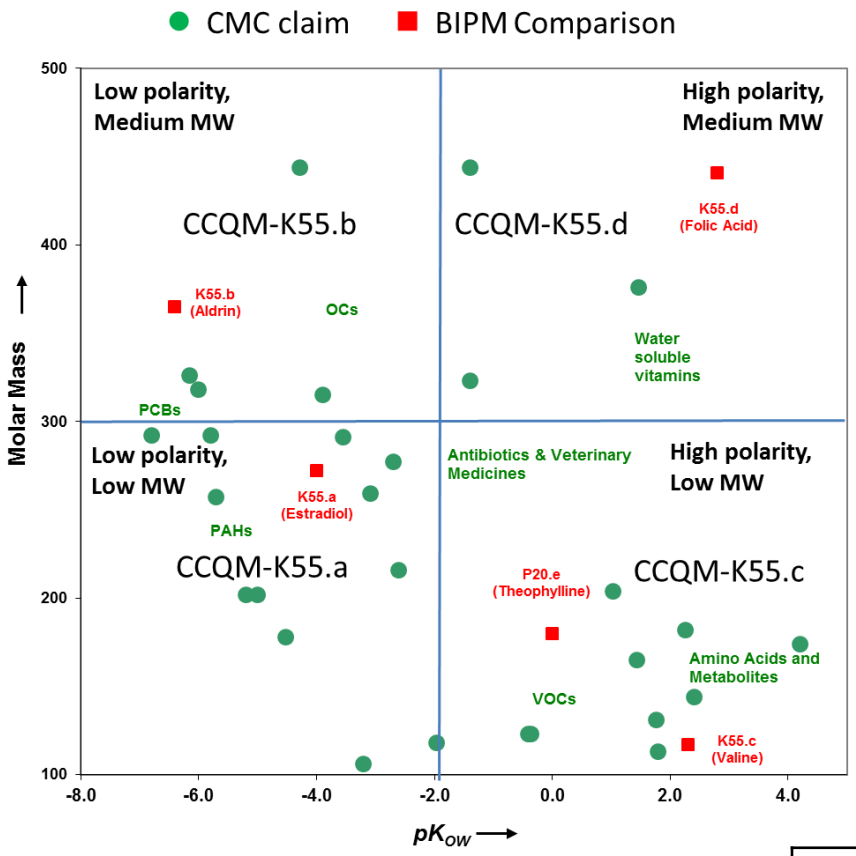
K55.c Valine

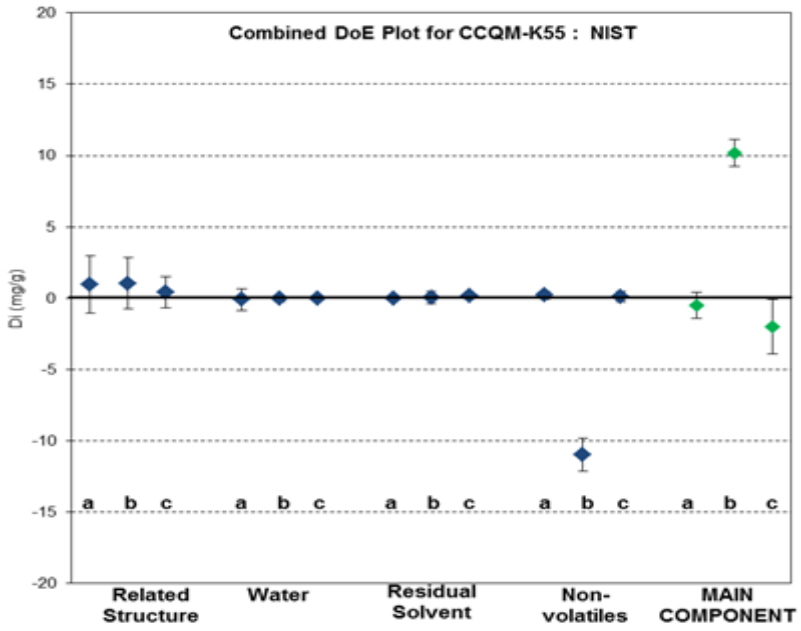


Metrologia, 2012, 49, Tech. Suppl., 08009
CCQM-K55.a Final Report, 2012, 33 pages

Metrologia, 2014, 51, Tech. Suppl., 08010
CCQM-K55.c Final Report, 2014, 64 pages

CCQM Activities Support Provision of Primary References for Clinical Diagnostic Analyses





Comparisons have assisted in establishing and or validating NMI capabilities for establishing primary references for organic molecules with molecular weight less than 500 Da. Standard uncertainties are less than 1 mg/g for purities greater than 950 mg/g.

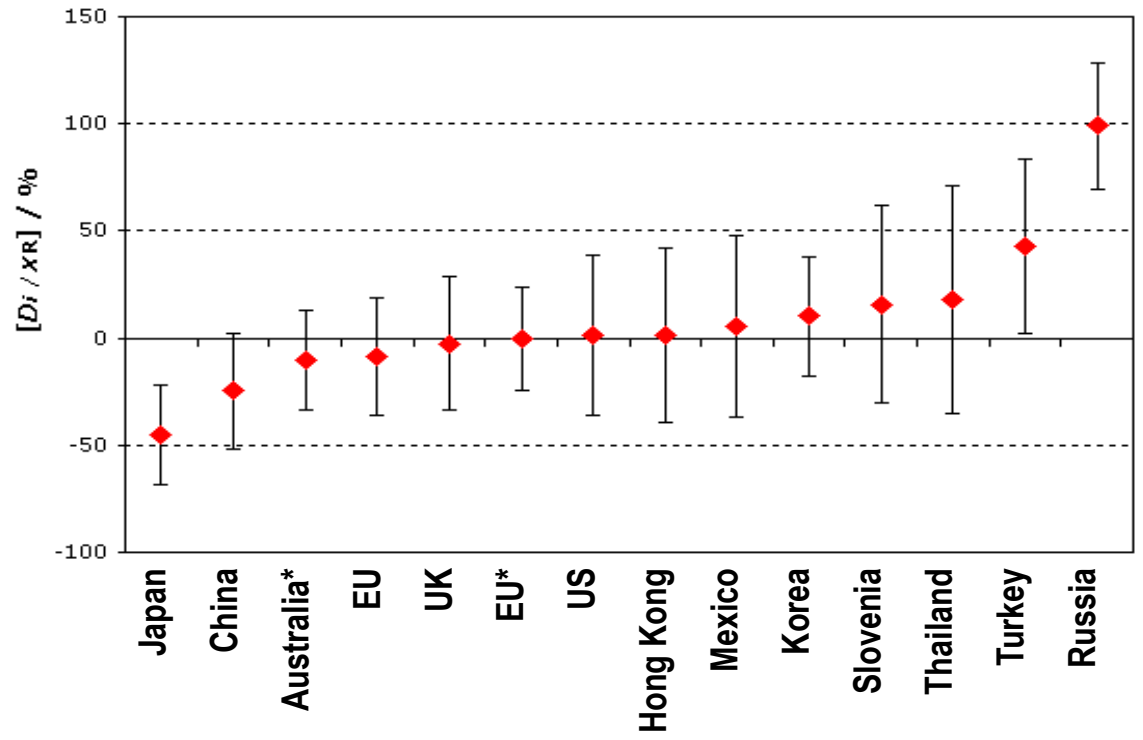
MW range	*Polarity*	*Sector specific Purity KC/Pilot study*
100 to 300	$pK_{ow} < -2.0$	CCQM-K55.a, Estradiol
100 to 300	$pK_{ow} > -2.0$	CCQM-P20.e, Theophylline; CCQM-K55.c, Valine
300 to 500	$pK_{ow} < -2.0$	CCQM-K55.b, Aldrin
300 to 500	$pK_{ow} > -2.0$	CCQM-K55.d, Folic Acid
500 to 1000	$pK_{ow} < -2.0$	CCQM-K104*, Avermectin
500 to 1000	$pK_{ow} > -2.0$	CCQM-P20.f, Digoxin

CCQM-K86: Relative quantification of genomic DNA fragments extracted from a biological tissue

MEASURAND : Ratio of number of copies of specified intact sequence segments of a length in the range of 70 to 100 nucleotides in a single genomic DNA extract

SAMPLE 1 : Mixture of dried non genetically (GM) maize seed powder and GM MON810 maize seed powder, with an assigned mass fraction value of 8.1 g/kg and associated expanded uncertainty (k = 2) of 0.7 g/kg

Degrees of equivalence: offset D_i and expanded uncertainty (k = 2) U_i given in relative terms (%)



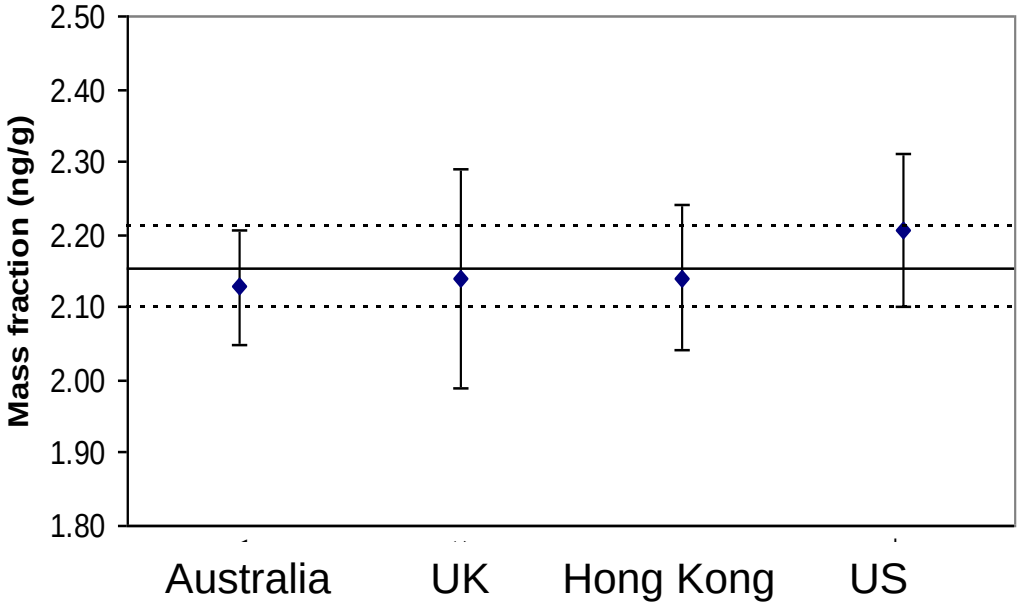
* laboratory measurement results performed using dPCR

Metrologia, 2012, 49, Tech. Suppl., 08002
CCQM-K86 Final Report, 2011, 30 pages

Results as published on 11 January 2012

CCQM-P68: Participants' Methodologies and Results

Laboratory	Method Summary	Instrumentation
NMIA	Addition of D_4-NNA, enzyme hydrolysis, solvent extraction, HPLC fractionation, TMS derivatisation	GC/HRMS
GL of HKSAR	Addition of D_4-NNA, enzyme hydrolysis, SPE and liq-liq extraction, TMS derivatisation	GC/HRMS
LGC	Addition of D_4-NNAG, enzyme hydrolysis, solvent extraction, HPLC fractionation, TMS derivatisation	GC/MS
NIST	Addition of D_4-NNA, enzyme hydrolysis, solvent extraction	LC/MS/MS



Required appropriate process design, method validation, etc., and analytical challenges include:

- Purity Assessment/value assignment of calibrant material
- Gravimetric Preparation of Calibration Solutions
- Extraction of analytes of interest from matrix
- Hydrolysis
- Derivatization
- Fractionation – separation of analytes of interest from bulk of matrix
- Chromatographic Analysis of Complex mixtures: separation of analyte from similar compounds in matrix
- Value-Assignment, including Uncertainty Determination

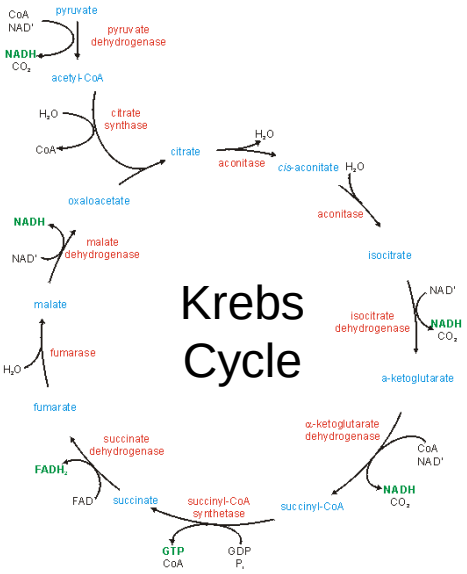
Next Areas of Priority

Assessing the Comparability of National References to support:

- Personalized/Precision Medicine
- Manufacture and Regulatory Approval of Biosimilar/Follow-on Biologics

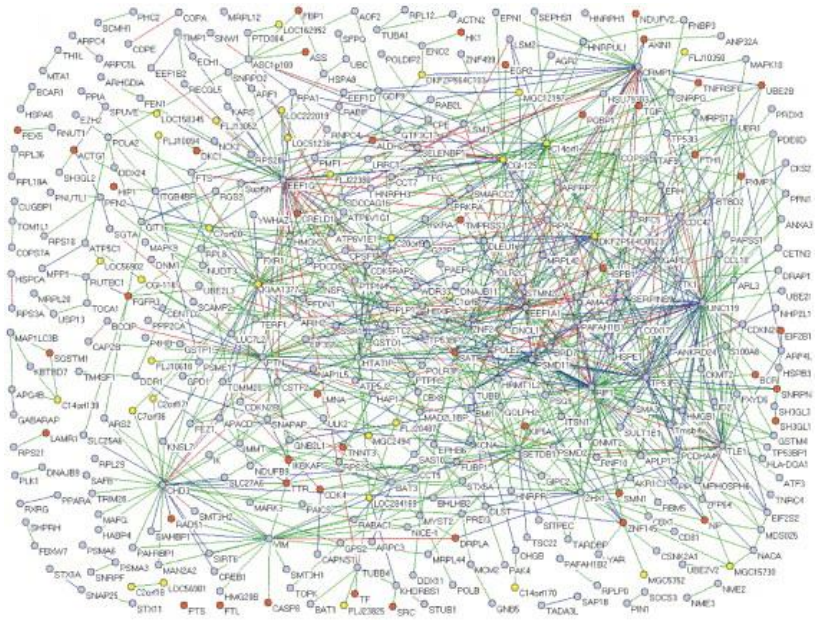
Facilitating Innovation in the "Biosciences" is Hard

Life processes are very complex and the information space is very vast



Krebs Cycle

Not as simple as we once thought



Understanding life processes requires more than physical and chemical measurements

Physical: What's the mass of Willie? 90 kg

Chemical: How much cholesterol is there in Willie's blood? 150 mg/dL

Biological: Which cholesterol-lowering drug would be best for Willie in terms of both efficacy and potential side effects? Personalized Medicine

What is “Personalized Medicine”?

The use of information and data from a patient's genotype and phenotype (level of gene expression and/or other clinical information) to:

- stratify disease
- select a medication
- provide a therapy
- initiate a preventative measure that is particularly suited to that patient at the time of administration

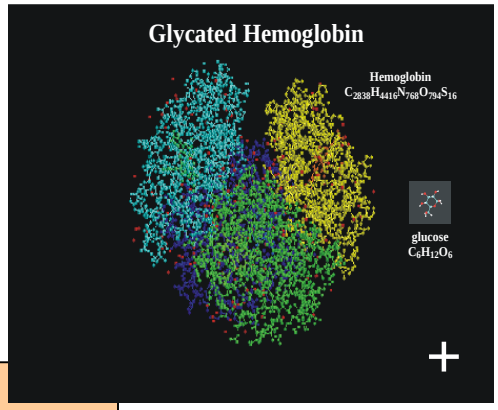
Answers are being sought such as:

- **Why do adverse drug reactions and interactions occur in some people and others not?**
- **Can I be sure that I am getting the right treatment for me**
- **Can I be sure that the generic protein drug that I get will work the same as the more expensive name brand drug?**

Laboratory Medicine: New Challenges

Reference systems for markers that typically exhibit:

- **High molecular mass (>20,000 daltons)**
- **Heterogeneity, low concentration, instability of analyte form**
- **Cannot all be determined using GC- ID/MS or ICP/MS-based methodologies**
- **Such as the following:**



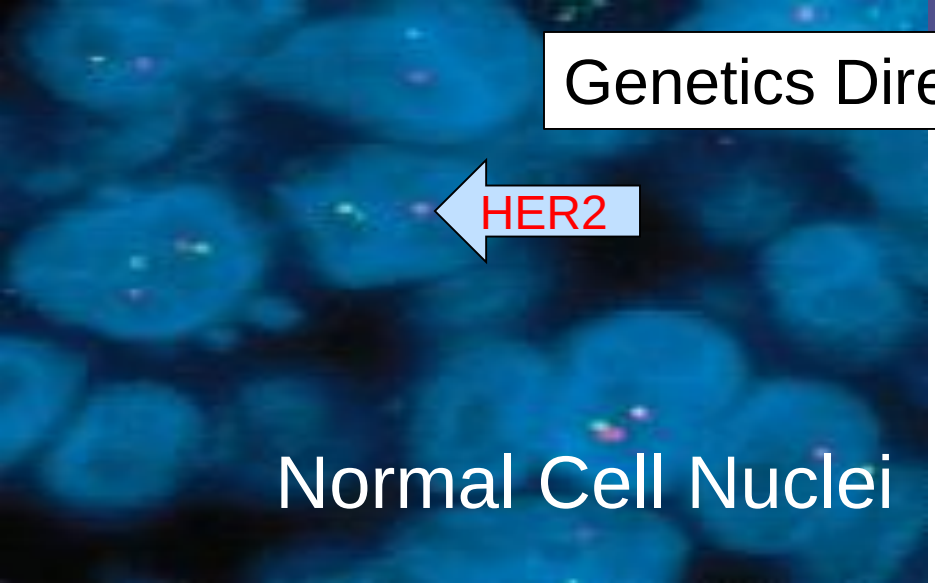
Protein Analysis

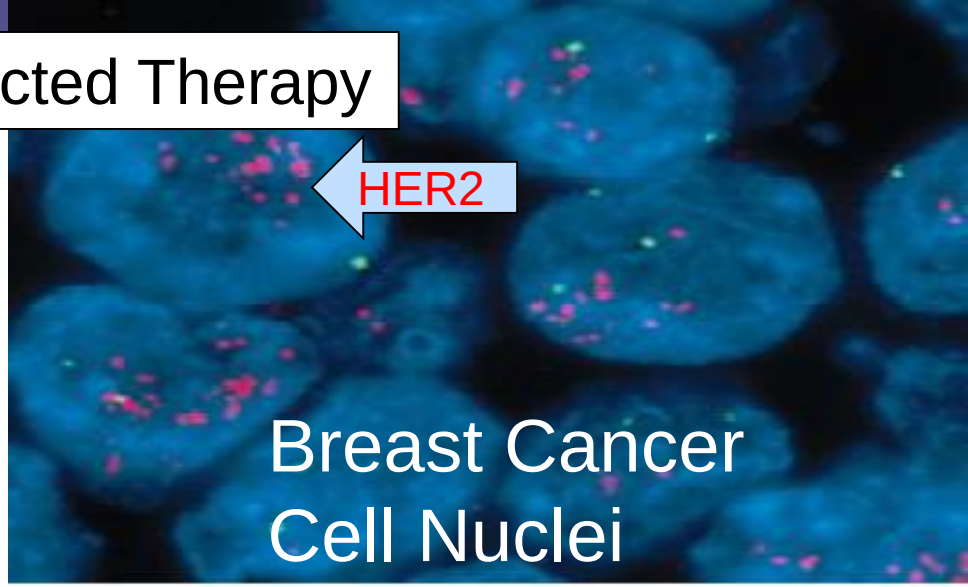
- **Single Blood Protein Biomarkers**
  - Troponin-I — *Myocardial Infarction*
  - C-Reactive Protein — *Risk of Heart Attack*
  - PSA — *Prostate Cancer*
  - Albumin — *Kidney Function*

Genetic Testing

- **Single Gene Mutations**
  - **Genetics Directed Therapy**
    - Her2-Nu — *Breast cancer*
    - CYP2C9 and VKORC1 — *Warfarin Dosage*
    - Kras — *Colon Cancer*
  - **Diagnostics**
    - DNA Triplet Repeat — *Fragile X*
    - CAG Repeats — *Huntington's Disease*
- **Genome Sequencing to support Direct to Consumer Genetic Testing**

Genetics Directed Therapy





"The college of American Patholigists and the American Society of Clinical Oncology have estimated that around 20% of HER-2 testing may be inaccurate"

HER2 Test

180,000/ year

False positive

Up to 32,000 → **Get Herceptin unnecessarily**

- Expensive
- Numerous side effects

False negative

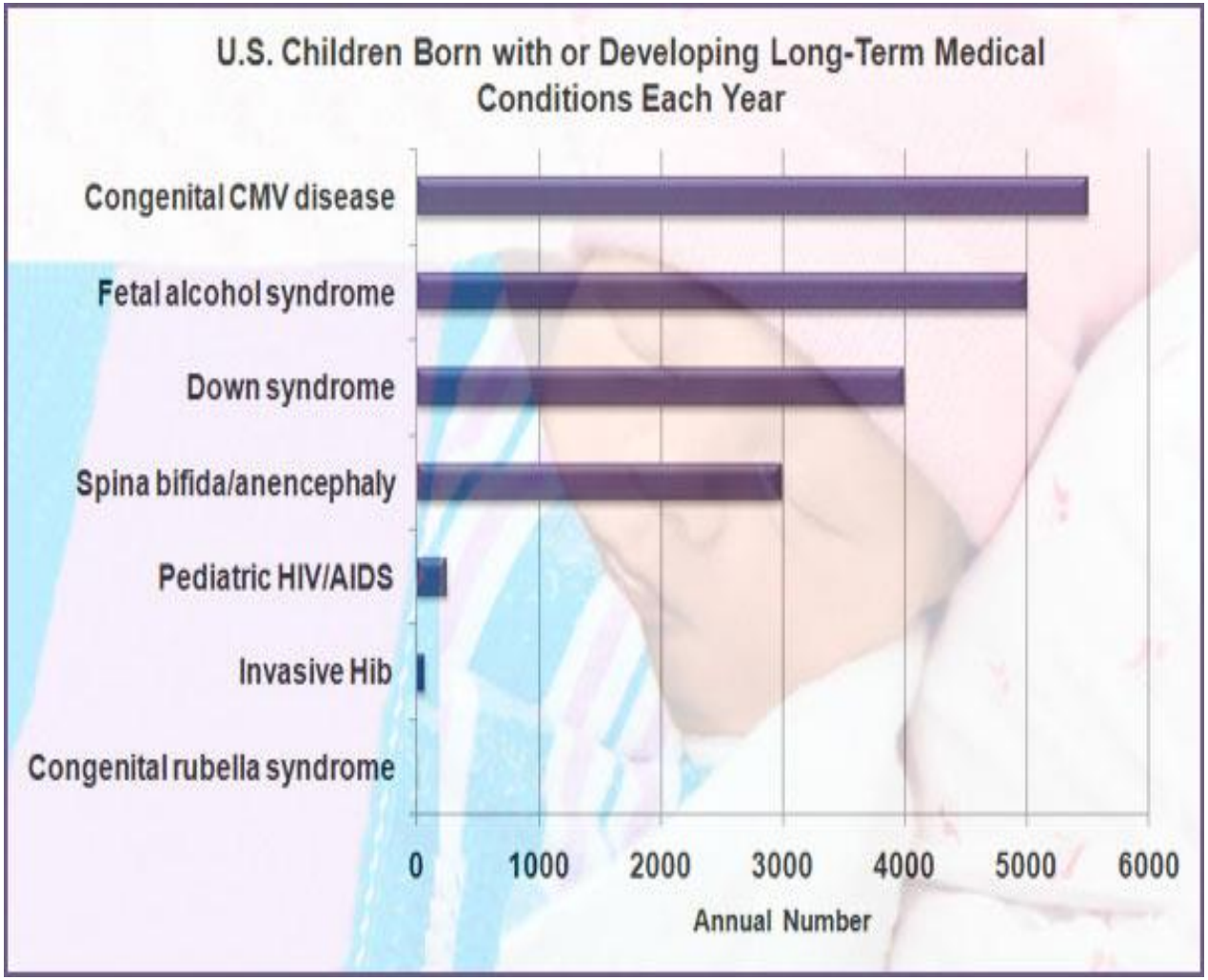
Up to 32,000 → **Herceptin Treatment withheld**

- Inappropriate treatment
- Increased morbidity
- Increased mortality

http://online.wsj.com/article/SB10001424052748704869004576011091954937268.html

Cytomegalovirus (CMV)

CMV can cause serious disease in people with weakened immune systems and in babies who are infected before birth. Congenital CMV infection causes more long-term problems and childhood deaths than Down syndrome, fetal alcohol syndrome, and neural tube defects.



Treatment for CMV, which has toxic side effects and is available only intravenously, depends on **accurate measurement of the viral load** – and interlaboratory comparisons show widely varying results.

NIST is working on development of a CMV SRM which should improve lab to lab variability, and thus treatment options.

Huntington's Disease

Classification of the trinucleotide repeat, and resulting disease status, depends on the number of CAG repeats:

Repeat Count	Classification	Disease Status
< 28	Normal	Unaffected
29-34	Intermediate	Individual will not develop HD but the next generation is at risk
35-39	Reduced Penetrance	Some, but not all, individuals in this range will develop HD; next generation is also at risk
>40	Full Penetrance	Individual will develop HD

Penetrance in genetics is the proportion of individuals carrying a particular variation of a gene that also express an associated trait.

Nationwide, an estimated 30,000 people have Huntington's Disease. Although there is no cure, knowledge of the repeat count can be used to guide treatment of clinical symptoms and give an estimate of age of onset.

NIST has issued SRM 2393, CAG Repeat Length Mutation in Huntington's Disease, to facilitate accurate genotyping of this gene.

Huntington's Disease Society of America

The NEW ENGLAND JOURNAL *of* MEDICINE

First FDA Authorization for Next-Generation Sequencer

Francis S. Collins, M.D., Ph.D., and Margaret A. Hamburg, M.D.

The FDA has also been active in addressing other regulatory issues surrounding personalized medicine.5 Along with authorizing the Illumina technology for marketing, the FDA recognizedthe need for reference materials and methods that would permit performance assessment.

As a result, the FDA collaborated with the National Institute for Standards and Technology (NIST) to develop reference materials consisting of whole human genome DNA, together with the best possible sequence interpretation of such genomes. The first human genome reference materials are expected to be available for public use in the next 12 months.

Measurements and Standards for Biologic Drugs

- **The Cost of Protein Therapeutics is one of the fastest growing components to the overall cost of healthcare. The global biological drugs market was valued at $161B in 2014 and is predicted to reach a value of 287B by 2020.**

- These **"biologic drugs" are not synthesized chemically**, but rather are made in bioreactors using living cells.

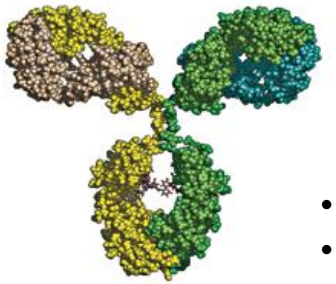
- These drugs have proven to be **very therapeutic and substantially improve patients' health and quality of life.** However, they are **very expensive and generics are not widely available**

    - **Rand researchers predict $44 billion in savings due to the approval of biosimilars over the next 10 years.**

    - **Challenges exist regarding the manufacture and regulatory approval of generic/ follow-on biologics**

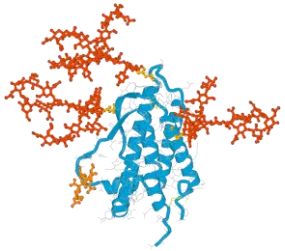
Prozac

- **Small, simple (MW = 309.3261 g/mol)**
- **Structure definitively known**



Rituxan: Biologic Drug

- **Large, complex (~150,000 kDa)**
- **Heterogeneous product**



New measurement science and standards needed to support manufacturing & regulatory approval of biologic drugs

Technical Area	*Outputs*
Immunogenicity	▪ Critical evaluation of the underpinning measurement science for protein aggregate measurements ▪ Reference methods and Standard Reference Materials for protein aggregate measurements ▪ Validated in vitro methods and models for measurement of human immune system response
Structure (3-D and PTM)	▪ Spectroscopic reference methods (reference spectra, data and standards) for measuring 'sameness' related to protein 3-D structure ▪ Reference methods, data, and standards for glycan analysis ▪ Stable Isotope Protein Labeling User Facility to support high resolution protein structural analysis
Production Cell Efficiency	▪ Reference genetic markers and methods for cell line ID ▪ Reference methods and standards to support gene expression measurements and measurement of transcriptome of CHO cells ▪ Reference methods and standards to support proteomic measurements of CHO cells ▪ Reference Data (molecular signatures) for predicting CHO cell performance in Biologic Drug manufacturing.

Developed with Input from Stakeholders:

FDA, MERCK, Genentech (A Member of the Roche Group), gsk, Lilly, MedImmune, Pfizer, AMGEN, Johnson & Johnson, biogen idec

Others:

- **USP**
- **NIBSC**
- **NIH**

Top Ten Biologic Drugs and Their Global Sales in 2011

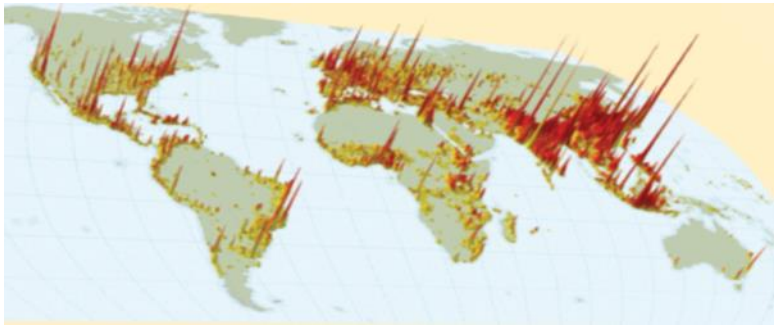
1. **Humira** rheumatoid arthritis, $6.6 billion
2. **Enbrel** rheumatoid arthritis, $6.5 billion
3. **Remicade** rheumatoid arthritis, $6.4 billion
4. **Avastin** cancers, $5.5 billion
5. **Mabthera** non-Hodgkin's lymphoma, $5.4 billion
6. **Lantus** diabetes, $5.1 billion
7. **Herceptin** breast cancer, $4.5 billion
8. **Neulasta** chemotherapy infections, $4.1 billion
9. **Lovenox** deep vein thrombosis, $3.7 billion
10. **Copaxone** multiple sclerosis, $3.6 billion

Source: IMS Health

Established in 1993:

CCQM Activities have -- without question –

- enabled NMIs to identify “spikes” of excellence within the chem/bio world that have led to establishment of strategic collaborations for both research and standards development purposes



Examples of Impact of CCQM Activities for Healthcare

- **CCQM Comparisons have:**
  - documented the degree of comparability among the measurement capabilities and measurement services provided by NMIs
  - resulted in significantly increased # of NMIs providing measurement services in HC
    - Also improved overall quality of HC CRMs available to customers
  - Provided objective data to support peer review of CMC claims

- **Symposia for Stakeholders have furthered awareness /communication**
  - Workshop on the Frontiers of Traceability in Chem/Bio Measurement (22 April 2009)
  - Pharma & Bio-pharma Workshop (4-5 December 2008)
  - International Symposium on Certified Reference Materials for Quality of Life (1 November 2006)
  - Workshop on higher-order measurement methods for physiologically significant molecules (13 April 2005)

- **Numerous workshops to provide a forum for the exchange of information within CCQM and CCQM WGs**
  - topics cover a wide range of research and measurement service delivery programs and other technical activities of the CC members and observers
  - **new opportunities for collaboration created.**

NIST, Gaithersburg

BIPM, Sevres

Thanks for Your Attention

Questions and Comments?