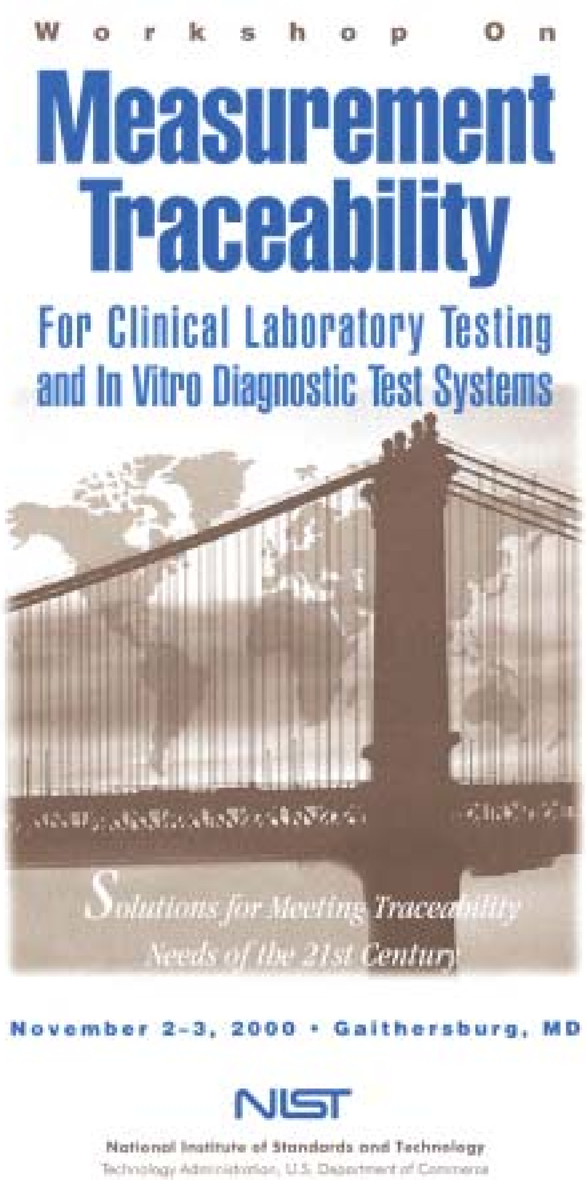
Certified Reference Materials for Laboratory Medicine

William F. Koch
Deputy Director
Chemical Science and Technology Laboratory

JCTLM Meeting
10 June, 2002
Paris, France

Greetings from CSTL



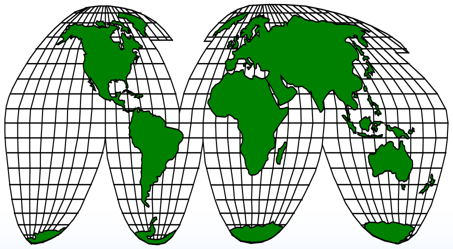
Attendees included:

- **IVD Manufacturers**
- **Regulatory Agencies and Notified Bodies**
- **Providers of Proficiency Testing Programs, Laboratory Accreditation, and Measurement Quality assessment Materials**
- **Laboratory professionals involved in standardization of laboratory methods**
- **International Standards Laboratories**

Increasing Importance and International Interest and Requirements for *Traceable* Chemical Measurements

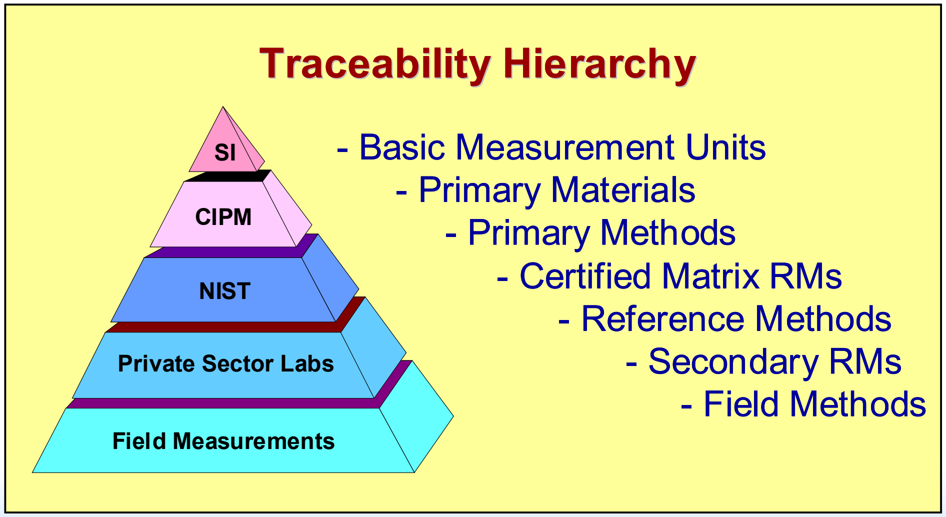
- National and International Trade
- Environmental Decision-Making

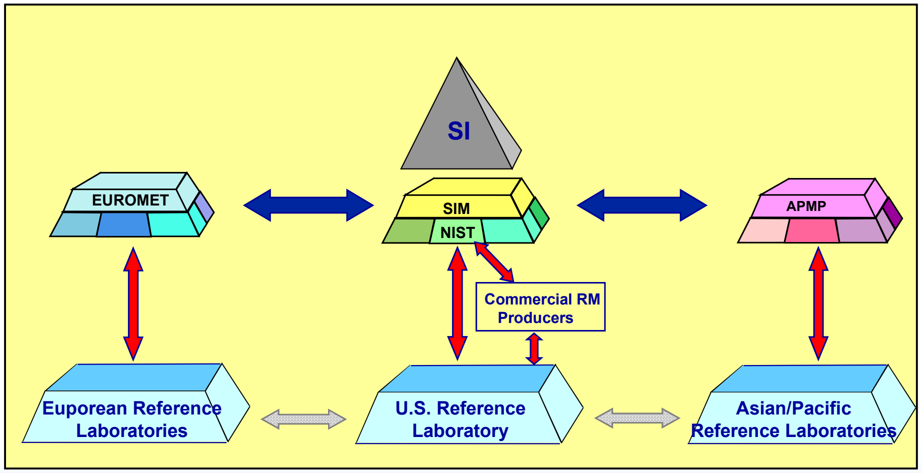
- Assessing Food Quality
- Healthcare Decision-Making



Global Confidence and Acceptance of <u>Chemical Measurement Data</u>

- Traceability to National Standards
- Assessment of Comparability among National Metrology Institutes (NMIs)
- Equivalence of Vertical Traceability Infrastructures





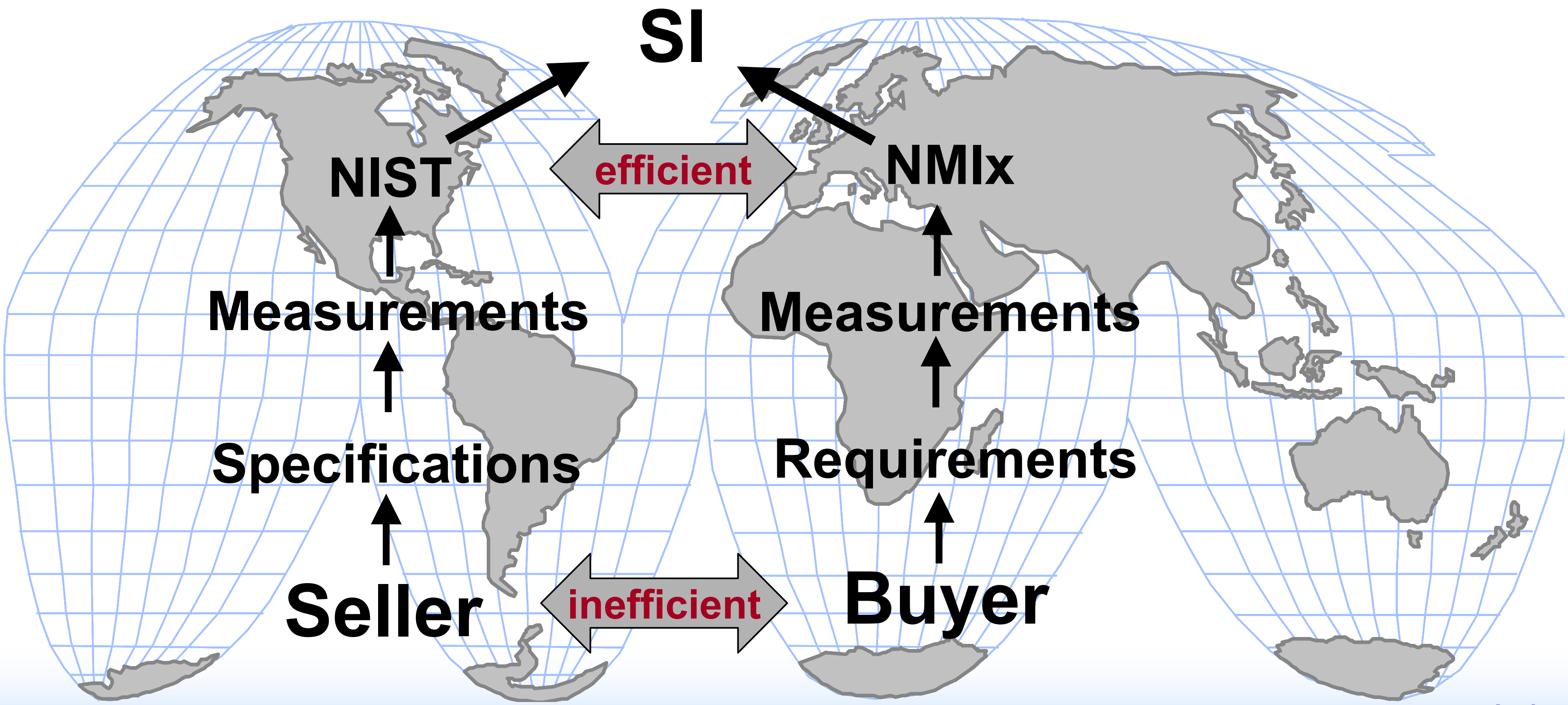
Measurement Traceability to stated references…

and global confidence in this realization

are the basis for

mutual recognition and confidence in data

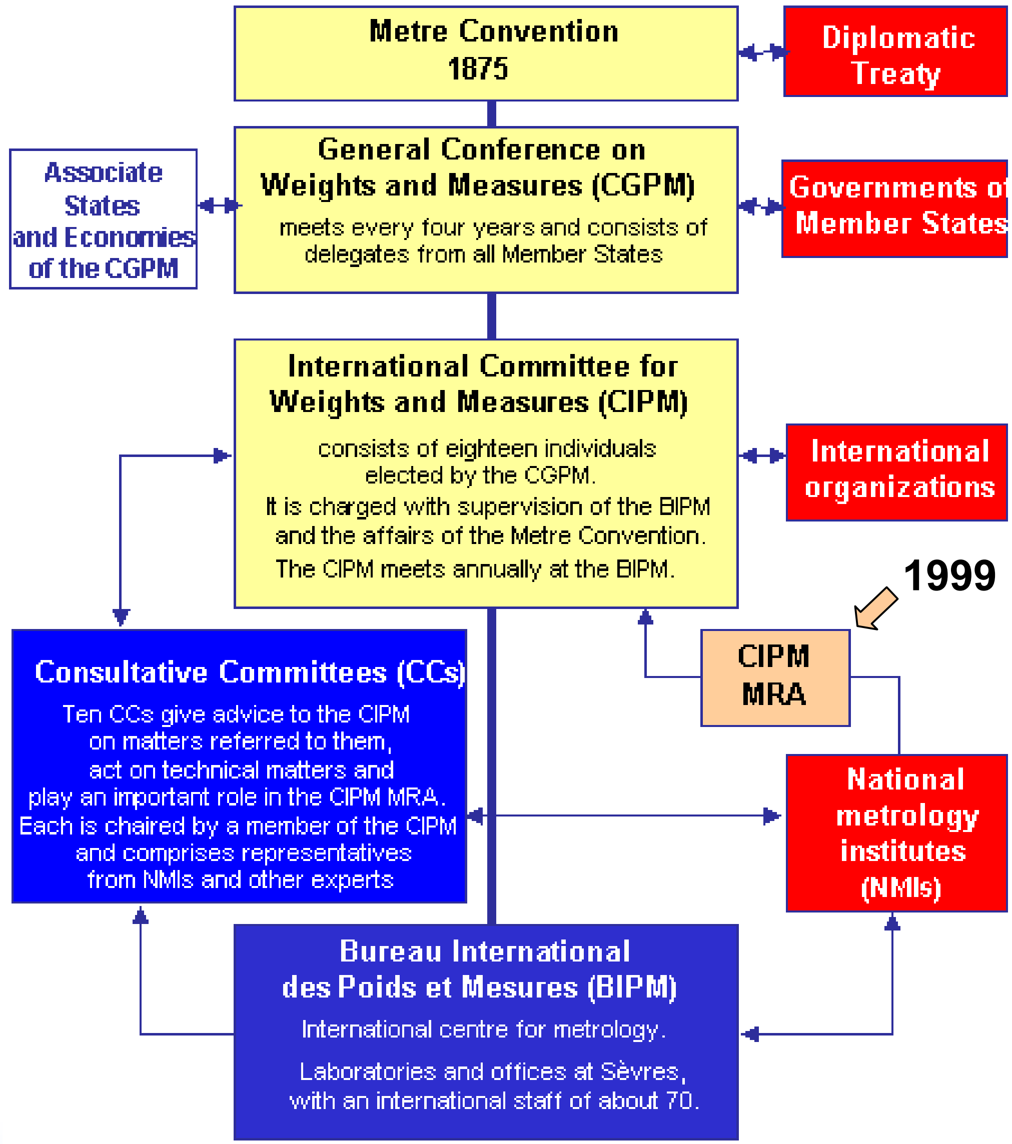
used to facilitate and underpin international trade and
decisions regarding health, safety, commerce, and/or scientific studies.



The Metre Convention

provides the framework within which the international measurement system is maintained and made available to the whole world for:

- **national and international trade**
- **manufacturing**
- **human health and safety**
- **the protection of the environment, and**
- **all aspects of science and engineering**



http://www.bipm.fr/enus/1_Convention/chain.html

Facilitating International Acceptance of Measurement Results

Mutual Recognition Arrangement (MRA) under the CIPM

- **Signed by 38 NMI Directors in October 1999; (others since)**
- **Provides and/or Facilitates:**
  - Open, transparent, and comprehensive scheme to provide reliable quantitative information on the comparability of metrology services provided by NMIs
  - Technical basis for wider agreements negotiated for international commerce and regulatory affairs
- **Requires:**
  1. Demonstration of system for assuring quality of each NMI's measurement services
  2. Evidence of *successful* participation in formal, *relevant* international comparisons: *MRA Appendix B*
  3. Declaring and documenting calibration and measurement capabilities: *MRA Appendix C*

NIST … enabling a better future

NIST Vision … **is to be the global leader in measurement and enabling technology, delivering outstanding value to the nation.**

NIST Mission … **is to develop and promote measurement, standards, and technology to enhance productivity, facilitate trade, and improve the quality of life.**

Core Values:

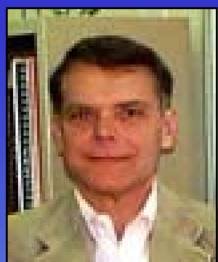
- **People …** we respect, value and support each other in all our activities.
- **Integrity …** we are objective, ethical, and honest.
- **Customer focus …**we anticipate the needs of our customers and are committed to meeting or exceeding their expectations.
- **Excellence …** we expect world-class performance and continuous improvement in all we do.

National Institute of Standards and Technology

- **Director** — Arden Bement
- **Deputy Director** — Karen Brown
  - Boulder Laboratories — Vacant
  - National Quality Program — Harry Hertz
  - Director for Administration — Jorge Urrutia
  - Technology Services — Richard Kayser
  - Advanced Technology Program — Marc Stanley (Act.)
  - Manufacturing Extension Partnership — Kevin Carr
  - Electronics and Electrical Engineering Laboratory — Wm. Anderson
  - Manufacturing Engineering Laboratory — Dale Hall
  - Chemical Science and Technology Laboratory — Hratch Semerjian
  - Physics Laboratory — Katharine Gebbie
  - Materials Science and Engineering Laboratory — Leslie Smith
  - Building and Fire Research Laboratory — Jack Snell
  - Information Technology Laboratory — Susan Zevin (Act.)

CHEMICAL SCIENCE AND TECHNOLOGY LABORATORY

Hratch G. Semerjian, Director
William F. Koch, Deputy Director



Biotechnology

V. Vilker, Act. Chief

- DNA Technologies
- Bioprocess Engineering
- Structural Biology
- Biomolecular Materials

Process Measurements

J. Whetstone, Chief

- Fluid Flow
- Fluid Science
- Process Sensing
- Thermometry
- Pressure and Vacuum
- Thermal and Reactive Processes

Surface & Microanalysis Science

R. Cavanagh, Chief

- Atmospheric Chemistry
- Microanalysis Research
- Surface & Interface Research
- Analytical Microscopy

Physical & Chemical Properties

M. Haynes, Chief

- Experimental Kinetics & Thermodynamics
- Chemical Reference Data & Modeling
- Computational Chemistry
- Experimental Properties of Fluids
- Theory & Modeling of Fluids
- Cryogenic Tech.

Analytical Chemistry

W. May, Chief

- Spectrochemical Methods
- Organic Analytical Methods
- Gas Metrology & Classical Methods
- Molecular Spectroscopy & Microfluidic Methods
- Nuclear Methods

Organized by Discipline …

Chemical Science and Technology Laboratory

Vision

A world class research laboratory recognized by the Nation as the *primary resource* for chemical, biomolecular, and chemical engineering *measurements, data, models, and reference standards* required to enhance U.S. industrial competitiveness in the world market.

Mission

As the Nation's Reference Laboratory, CSTL's Mission is to provide the *chemical measurement infrastructure* to:

- enhance U.S. industry's productivity and competitiveness;
- assure equity in trade; and
- improve public health, safety, and environmental quality.

Chemical Science and Technology Laboratory

Goals

Measurement Standards

Establish CSTL as the pinnacle of the national traceability and international comparability structure for measurements in chemistry, chemical engineering and biotechnology, and provide the fundamental basis of the nation's measurement system

Chemical and Process Information

Assure that U.S. industry has access to accurate and reliable data and predictive models to determine the chemical and physical properties of materials and processes

Measurement Science

Anticipate and address next generation measurement needs of the nation, by performing cutting-edge research

NIST Standards for Chemical Measurements

Chemical standards constitute **952** of ~1,400 NIST SRM types, and **more than 23,000** of nearly 32,000 NIST SRM Units sold in FY01

- High Purity Neat Chemicals
- Organic Calibration Solutions
- Inorganic Calibration Solutions
- Gas Mixture Standards

Complex Matrix Standards

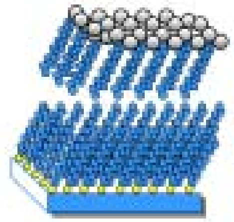
- Advanced Materials
- Biological Fluids/Tissues
- Foods/Botanicals
- Geologicals
- Metal Alloys
- Petroleum/Fossil Fuels
- Sediments/Soils/Particulates

- Optical Filter Standards
- Conductivity Standards
- Ion Activity Standards

CSTL Programs

Transportation

Biomaterials



Energy Systems

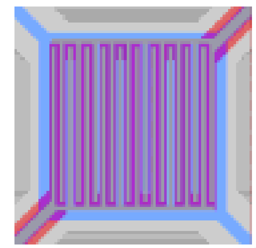
Microelectronics

Environmental Technologies

Forensics

Biotechnology

Nanotechnology

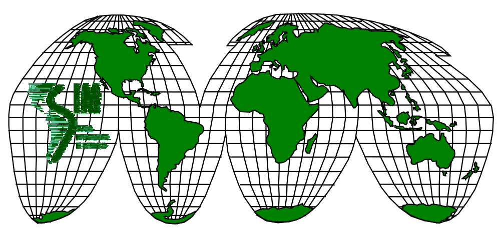


Healthcare

Chemical and Allied Products

Data and Informatics

Food and Nutrition



International Measurement Standards

Industrial and Analytical Instrument Services

… Focused by Customer-Driven Programs

Healthcare Measurements

… *supporting the national reference system for healthcare*

NIST SRMs provide anchor for CAP evaluations:

- **the peer group for grading and regulatory purposes**
- **an accuracy-based assessment for medical utility for nine analytes**

NIST Micronutrients QA Program:

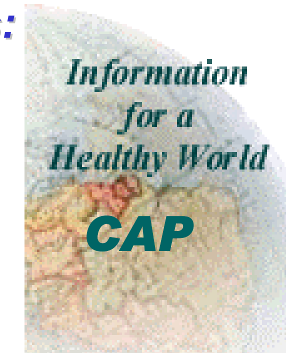
- **efficacy of nutrition in disease prevention**
- **60 labs worldwide – fee supported**

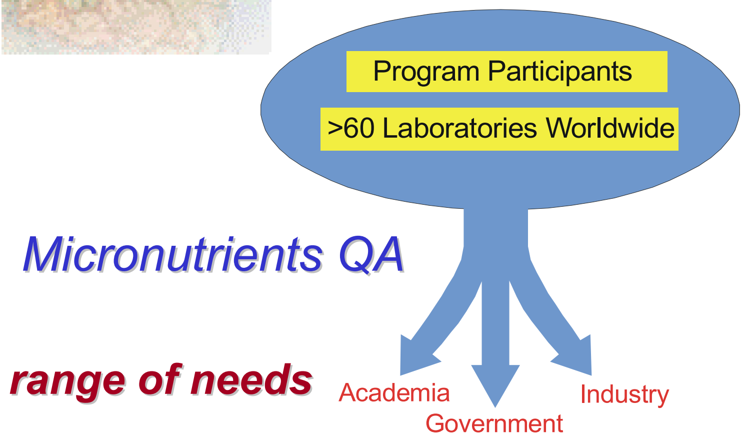
Continuous interactions with:

- **CDC, NCCLS, AACC, NCI, AdvaMed**

Expanded collaboration with:

- **NIH, FDA, CDC**





Utilize core expertise to support an ever-changing range of needs

Areas of core expertise:

- **Toxic inorganics – increased needs (Hg and Cd)**
- **Small organic markers – standards in place, measurement bias effects under study jointly with Mayo clinic to determine impact on medical decision-making**
- **Protein-based markers – increased need**
- **Electrolytes – standards in place at currently acceptable levels**
- **DNA-based markers – increased need**

Food and Nutrition

Populating the AOAC Food Triangle

Sector 1 Cholesterol and Fat-Soluble Vitamins in Coconut Oil, SRM 1563
Sector 2 Baking Chocolate
Sector 3 Peanut Butter, proposed
Sector 4 Meat Homogenate, SRM 1546
Sector 5 Baby Food Composite, SRM 2383
Sector 6 Frozen Diet, SRM 1544, Infant Formula, SRM 1846, Typical Diet, SRM 1548a
Sector 7 Frozen Spinach, SRM 2385
Juncture, Sectors 4,8,9 Fish Tissue, SRM 1946

Needs Assessment: **Interaction initiated in 1997 as a result of US FDA study regarding implementation of Nutritional Labeling and Education Act**

AOAC International requested 1-2 reference materials in each sector of the nine-sectored triangle

Quality Assurance: **Interlaboratory comparisons involve 20 laboratories from NFPA, plus other collaborating labs**

Food SRMs facilitate:

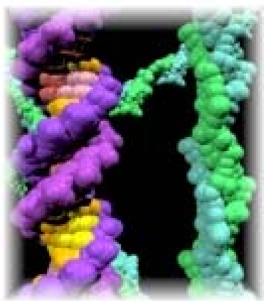
- **compliance with nutritional labeling laws**
- **traceability for food exports needed for international trade**
- **the provision of accurate labeling information**

AOAC food triangle populated with appropriate standards to meet current needs – shifting emphasis to new issues such as efficacy and purity of Nutraceuticals

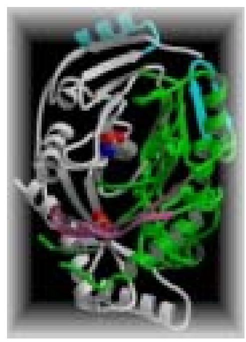
Biotechnology

… improved human health … improved agriculture
… and improved industrial processes …

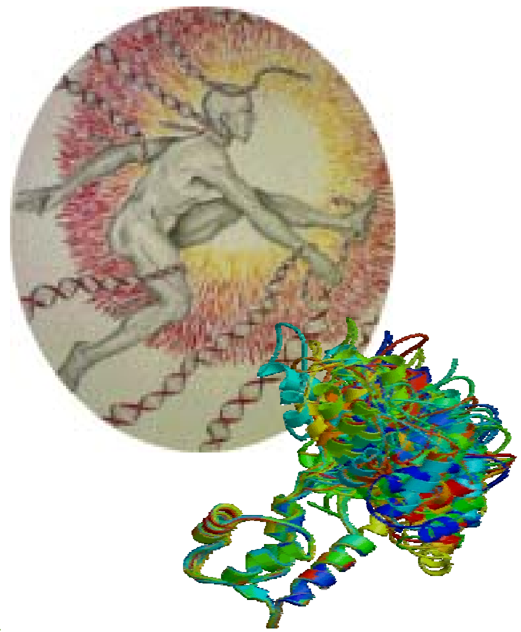
Bioprocessing



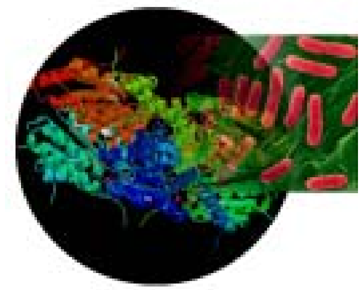
3D structures for biocatalysts



Preparative DNA Separations

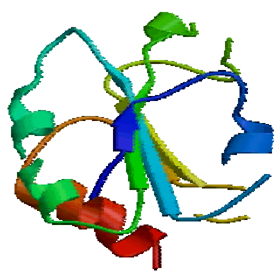


Structural Biology
Functional Genomics



E coli bacteria, and crystal structure

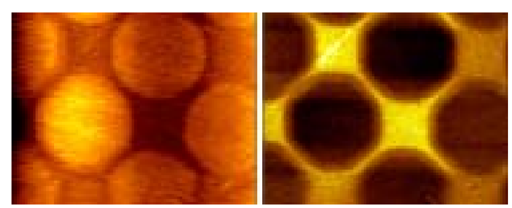
BioInformatics



Research Collaboratory for Structural Bioinformatics
PROTEIN DATA BANK
PDB

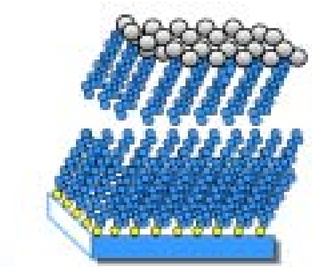
Data and Software

Biomaterials



AFM imaging of biomolecular surfaces

Hybrid Bilayers



As the US National Reference Laboratory for Chemical Measurements, NIST Maintains and Provides:

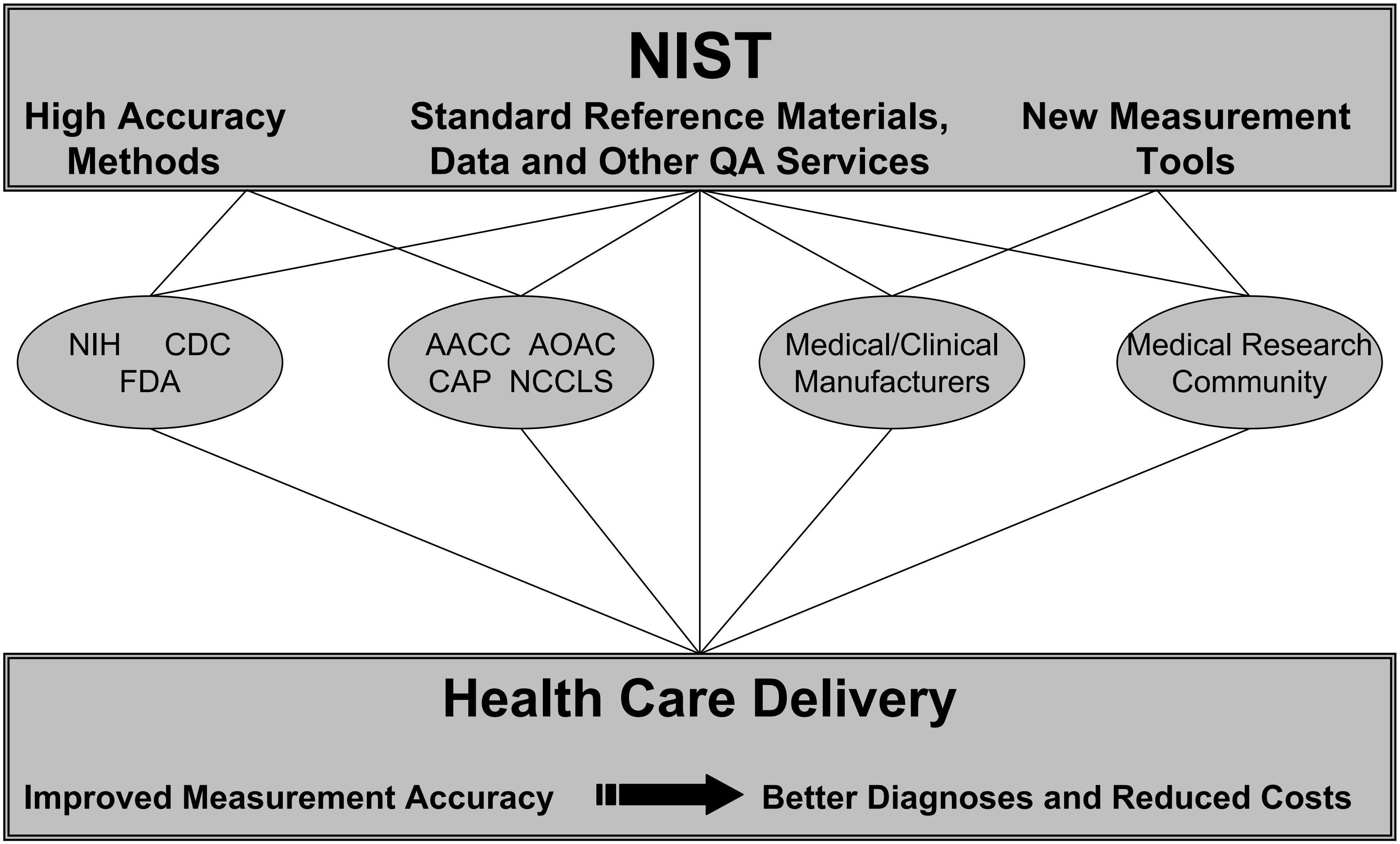
World-Class Metrologically-Based Competencies in Chemical Measurement Science

Internationally Recognized Measurement Capabilities

Tools for Achieving National Traceability and International Comparability of Measurements

- SRMs ™ and SRD
- NTRMs™
- Calibration Services
- Measurement QA and Proficiency Assessment Programs
- Reference Methods [disseminated via publications, etc.]
- Testing Services [for selected high priority needs]

NIST's Role in Health Care Measurements



The Role of CSTL

- Serving as the US Primary Reference Laboratory for Health-Related Chemical Measurements,
- CSTL Develops and Maintains the Measurements and Standards Infrastructure
- to Facilitate Accurate Decision-Making Regarding the Diagnosis, Treatment, and Prevention of Diseases.

Program Outputs and Activities

- High accuracy measurement methods
- Standard Reference Materials
  - pure primary standards
  - matrix-based materials
  - instrument calibration materials & artifacts
- Interactive measurement quality assessment/demonstration activities
- International comparison exercises with other National Metrology Institutes (NMIs)

History of the Clinical Laboratory Standards Program at NIST

Pre- 1950's	Early standards for Clinical Measurements
1960's	Development of pure, crystalline standards for calibration begun
1970's	Development of highly accurate and precise "Definitive Methods" for clinical analytes
1980's	Human serum-based SRMs for electrolytes toxic metals and small organic markers
1990's	Activities of 1980's continued with new efforts focused on toxic metals and protein-based markers
Early 2000's	Reference methods and standards to address EU IVD Directive

Definitive Methods for Clinical Analytes

ANALYTE	***METHOD***	***CONDITION***
Calcium	ID/MS	Cancer, Blood Clotting
Chloride	ID/MS, Coulometry	Kidney Function
Cholesterol	ID/MS	Heart Disease
Creatinine	ID/MS	Kidney Function
Glucose	ID/MS	Diabetes
Lithium	ID/MS	Bipolar Treatment
Magnesium	ID/MS	Heart Disease
Potassium	ID/MS	Electrolyte Balance
Sodium	Gravimetry, ICP/MS	Electrolyte Balance
Triglycerides	ID/MS	Heart Disease
Urea	ID/MS	Kidney Function
Uric Acid	ID/MS	Gout

History of the Clinical Laboratory Standards Program at NIST

-Pure Materials and Artifacts

• 1914	SRM 41, Dextrose
• 1945	SRM 186 I & 186 II, phosphates for pH
• 1967	SRM 911, Cholesterol
• 1968	SRM 912, Urea
	SRM 913, Uric Acid
	SRM 914, Creatinine
	SRM 915, Calcium Carbonate
• 1970's	21 SRMs with NIH support

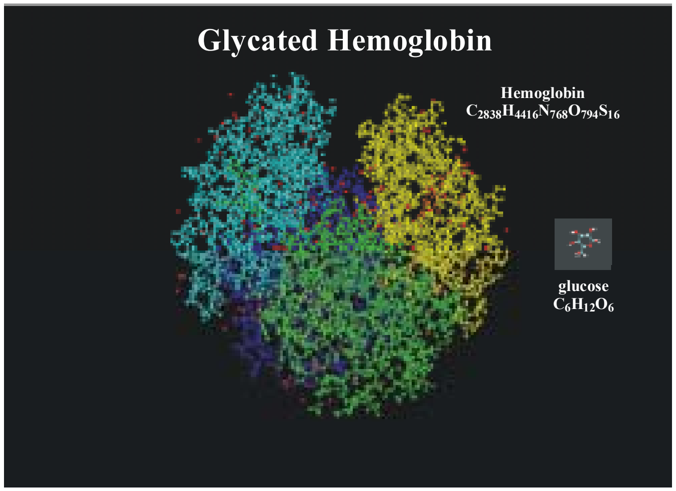
History of the Clinical Standards Program at NIST

- Selected Natural Matrix Materials

1979	SRM 900, Antiepilepsy Drug Level Assay Standard
1980	SRM 909, Human Serum
1982	SRM 1599, Anticonvulsant Drug Level Assay Standard
1988	SRM 1951, Cholesterol in Human Serum (Frozen)
	SRM 1952, Cholesterol in Human Serum (Freeze Dried)
1989	SRM 968, Fat Soluble Vitamins in Human Serum
1991	SRM 956, Electrolytes in Blood
1996	SRM 956a, Electrolytes in Frozen Human Serum
1996	SRM 965, Glucose in Frozen Human Serum
1997	SRM 1951a, Lipids in Frozen Human Serum
2000	SRM 966, Toxic Metals in Blood
	SRM 2070a, Toxic Elements in Human Urine

Standards for Clinical Diagnostic Markers: New Measurement Challenges

New health markers have some or all of the following properties:
- Very low concentration in blood
- Lack of certified reference compounds for calibration
- High molecular mass (>20,000 daltons)
- Protein heterogeneity
- Separation and identification difficult
- Unstable
- Blanks are severe problem at analyte level
- Most appropriate form to measure is not known



❖ Establish Reference Systems for New Clinical Markers - Highest Priorities

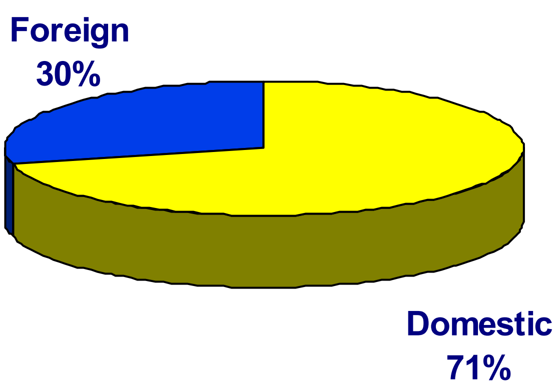
Prototype Method Being Critically Evaluated		*Research on-going*	
Homocysteine	Risk of Heart Disease	Troponin-I	Myocardial Infarction
Folates	Neural Tube Defects	Glycated Hemoglobin	Diabetes Status
Bilirubin	Liver Function	TSH	Thyroid Function
Cadmium & Mercury	Toxic Metal Poisoning	Speciated Iron	Hemochromatosis, Anemia
Cortisol	Endocrine Function	PSA	Prostate Cancer
Thyroxine	Thyroid Function	Trinucleotide Repeat	Fragile X Syndrome: Mental Retardation
p53 DNA	Cancer Marker		

Standardization necessary before medical diagnostic benefit can be fully realized.

Clinical SRMs in FY98
59 Types - 3244 Units Sold

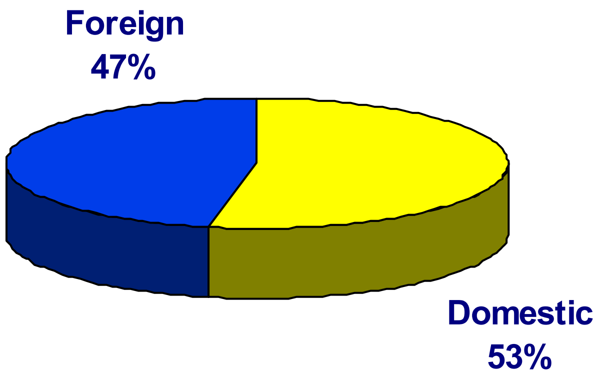
SRM 968b, Fat Soluble Vitamins & Cholesterol in Serum

320 units sold



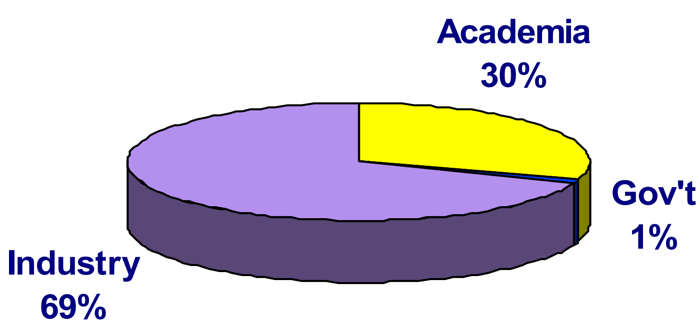
SRM 909b, Human Serum

258 units sold

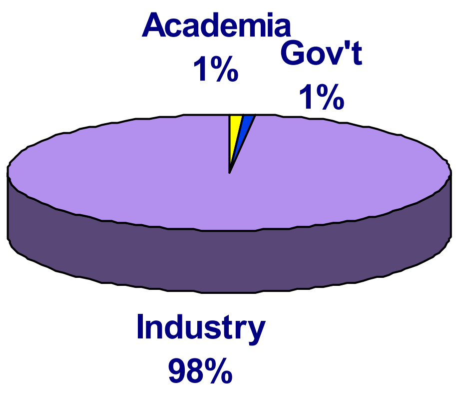


Clinical SRMs in FY98
Profile of Domestic Customers

SRM 968b, Fat Soluble Vitamins & Cholesterol in Serum



SRM 909b, Human Serum



Results of NCCLS-AACC Survey of Problem Analytes – 2001

Clinical laboratory personnel were asked to rate problem analytes based upon three criteria:

Inconsistent results between different methods
Results questioned by physician
Lot-to-lot shifts

Rank order from respondents:

1. Troponin I
2. PSA
3. Glucose
4. Creatinine
5. Calcium
6. *HCG*
7. Glycated Hemoglobin
8. Free T4
9. Bilirubin
10. Potassium
11. *Amylase*
12. TSH

Value-Assignment of Reference Materials

As a CRM Provider, NIST has:

- described seven modes currently used at NIST for value-assigning SRMs and RMs for chemical measurements
- defined data quality descriptors used at NIST for these SRMs and RMs
  - NIST Certified Value
  - NIST Reference Value
  - NIST Information Value
- linked these modes to the three data quality descriptors

NIST Special Publication 260-136
Standard Reference Materials

Definitions of Terms and Modes Used at NIST for Value-Assignment of Reference Materials for Chemical Measurements

W. May, R. Parris, C. Beck, J. Fassett, R. Greenberg, F. Guenther, G. Kramer, and S. Wise
Analytical Chemistry Division
Chemical Science and Technology Laboratory

T. Gills, J. Colbert, R. Gettings, and B. MacDonald
Standard Reference Materials Program
Technology Services

National Institute of Standards and Technology
Gaithersburg, MD 20899-8390

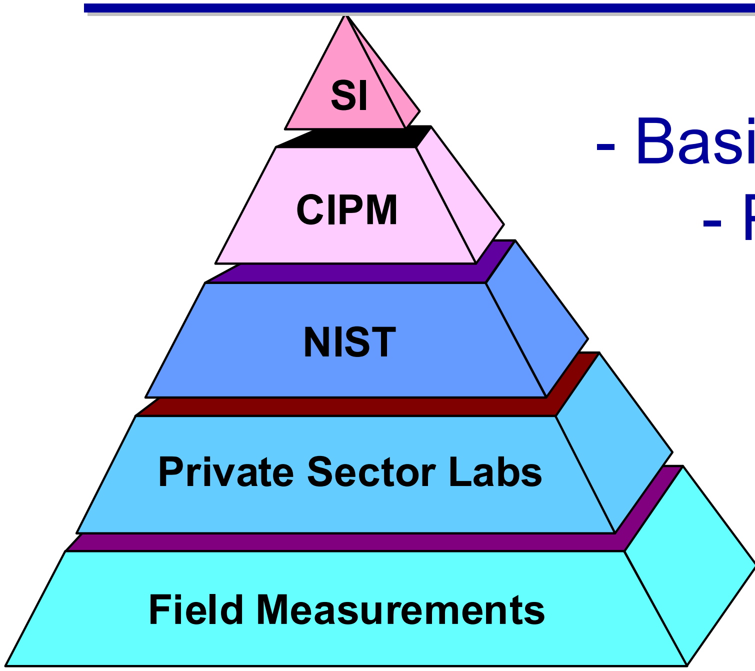
U.S. DEPARTMENT OF COMMERCE, William M. Daley, Secretary
TECHNOLOGY ADMINISTRATION, Dr. Cheryl L. Shavers, Under Secretary for Technology
NATIONAL INSTITUTE OF STANDARDS AND TECHNOLOGY, Raymond G. Kammer, Director

Issued January 2000

Modes Used at NIST for Value-Assignment of Reference Materials for Chemical Measurements

Mode	Certified Value	Reference Value	Information Value
1. **Certification at NIST Using a Primary Method with Confirmation by Other Method(s)**	✓		
2. **Certification at NIST Using Two Independent Critically-Evaluated Methods**	✓	✓	
3. Certification/Value-Assignment **Using One Method at NIST** and Different Methods by Outside Collaborating Laboratories	✓	✓	
4. Value-Assignment Based On Measurements by Two or More Laboratories Using Different Methods in Collaboration with NIST		✓	✓
5. Value-Assignment Based on a Method-Specific Protocol		✓	✓
6. Value-Assignment Based on NIST Measurements Using a Single Method or Measurements by an Outside Collaborating Laboratory Using a Single Method		✓	✓
7. Value-Assignment Based on Selected Data from Interlaboratory Studies		✓	✓

Measurement Traceability Hierarchy



- Basic Measurement Units
- Primary Materials
- Primary Methods
- Certified Matrix RMs
- Reference Methods
- Secondary RMs
- Field Methods

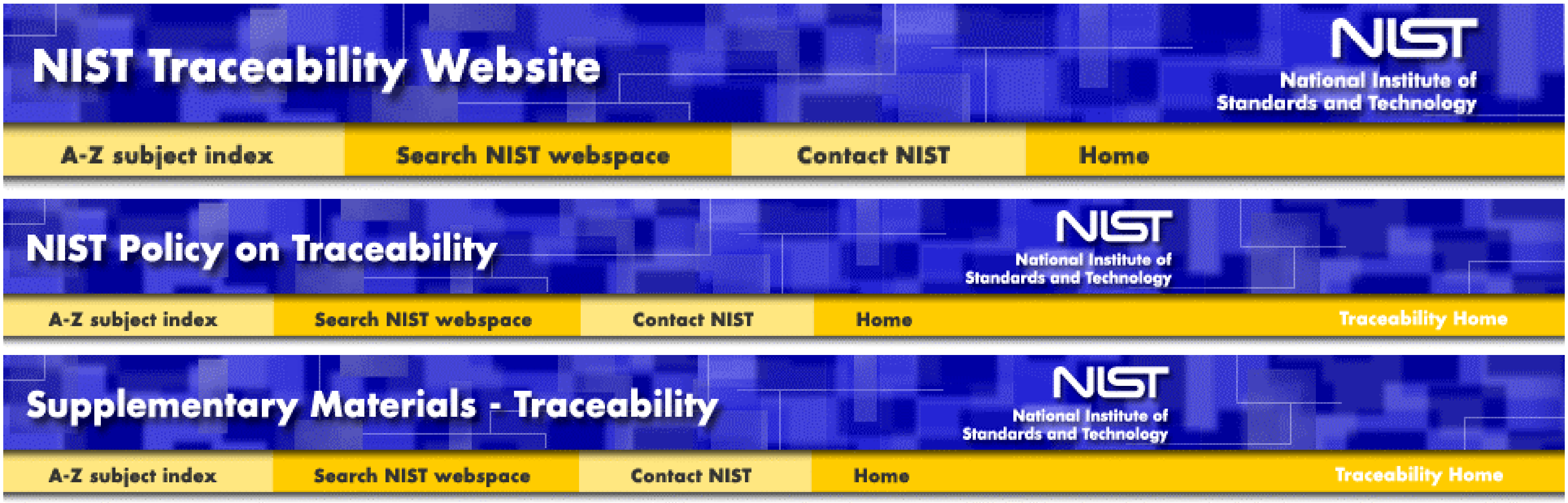
What is meant by the phrase "traceable to NIST"?

According to the internationally recognized VIM definition, traceability is a property of the result of a measurement or the value of a standard by which that result or value is related to standards, not to institutions.

Accordingly, the phrase "traceable to NIST", in its most proper sense, is shorthand for **"results of measurements that are traceable to reference standards developed and maintained by NIST".**

Measurement Traceability – NIST Policy and Supplementary Materials

http://www.nist.gov/traceability/



- Definition of Key Terms in the Statement of Policy
- Frequently Asked Questions (FAQs)
- Examples of NIST Programs in Traceability
- Glossary of Terms
- References
- Checklist for Traceability through Calibration

What is NIST's role in measurement traceability?

- to provide practical access to the seven base units of the International System of Measurements (SI), including amount of substance, mass, length, and time, by realizing and disseminating those units through measurement services;
- to similarly provide access to what are in effect U.S. national standards of various other measurement quantities of economic importance to the United States; and
- to collaborate on development of standard definitions, interpretations, and recommended practices with organizations that have authority and responsibility for variously defining, specifying, assuring, or certifying traceability.

How do I make my measurement results traceable to NIST?

To achieve traceability of measurement results to standards maintained by NIST, you need to reference your measurement results through an unbroken chain of comparisons, including determining the uncertainties at each step, to NIST standards as the stated references.

These stated references may be, for example, standards developed and maintained by NIST:

- broadcast signals controlled or monitored by NIST (such as standard time and frequency signals),
- NIST Standard Reference Materials, or
- NIST-Traceable Reference Materials.

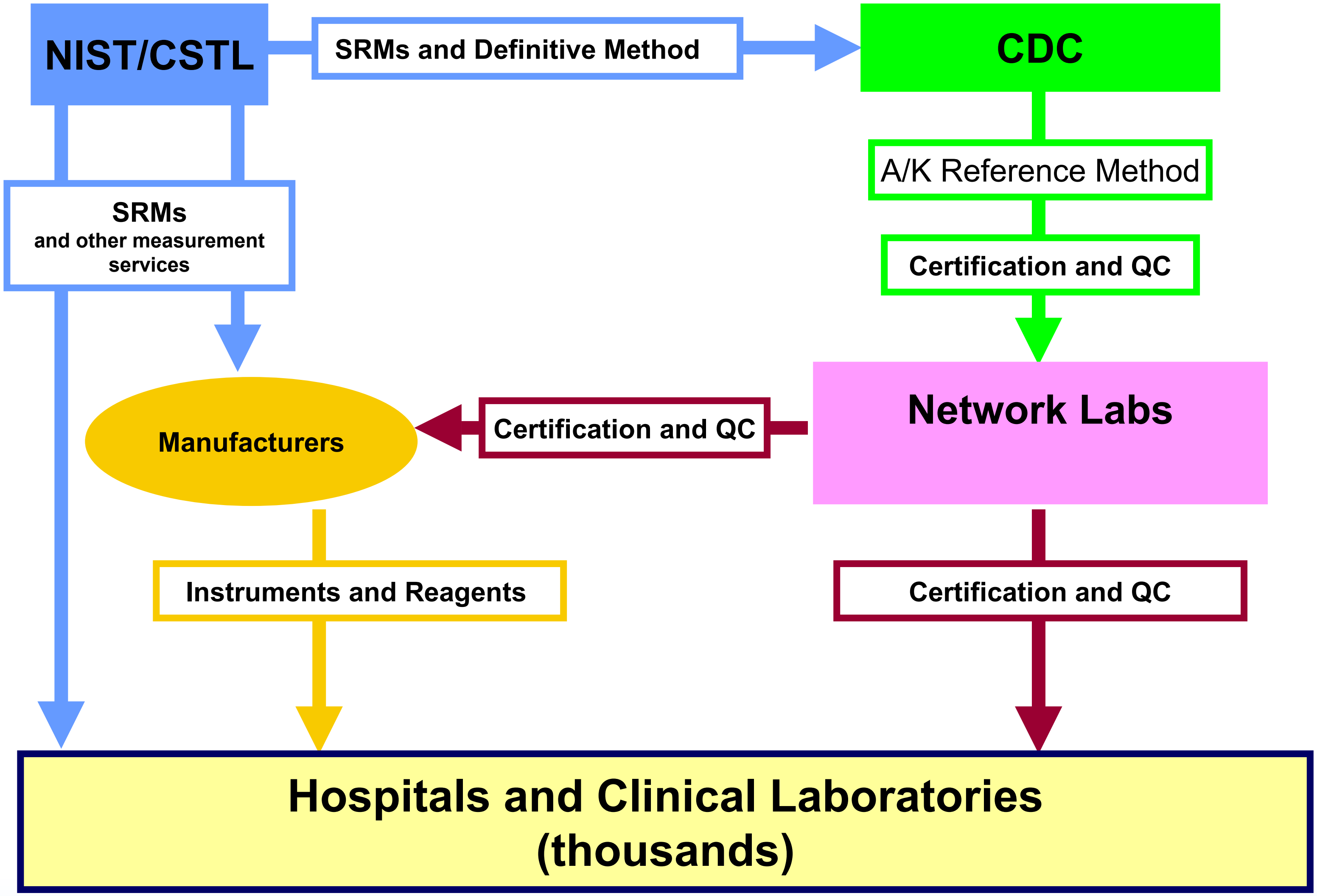
The chain of comparisons may be short, if the user has instruments or artifacts calibrated by NIST or acquires standards from NIST and references measurement results to those. It may be longer, if the user references other comparisons in a chain of comparisons back to stated references developed and maintained by NIST.

National Reference System for Clinical Chemistry

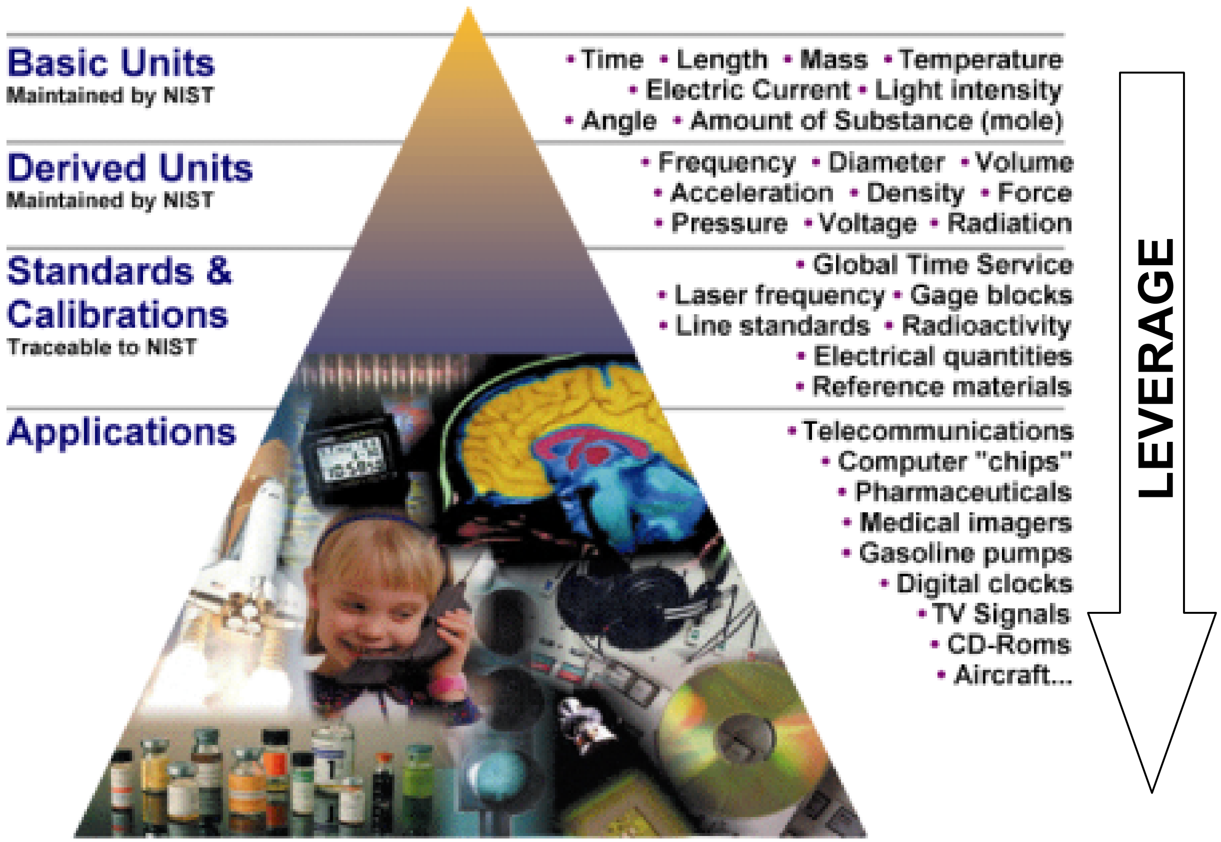
Hierarchy of Methods for Cholesterol

- Definitive (NIST)
  - Highest accuracy and precision
  - Thoroughly tested for bias
  - Generally not within the capability of clinical laboratories
  - Used for primary RMs and validation of reference methods
- Reference (CDC Network)
  - Carefully tested *vs* definitive method; high accuracy and precision
  - Within capability of most clinical labs, but too time consuming
  - For secondary RMs and validation of field methods
- Field (Clinical Labs)
  - Routine clinical use
  - Sufficient accuracy and precision for reliable diagnosis
  - Simple, rugged and cost-effective

Cholesterol Reference System



Impact of NIST Measurement and Standards Programs

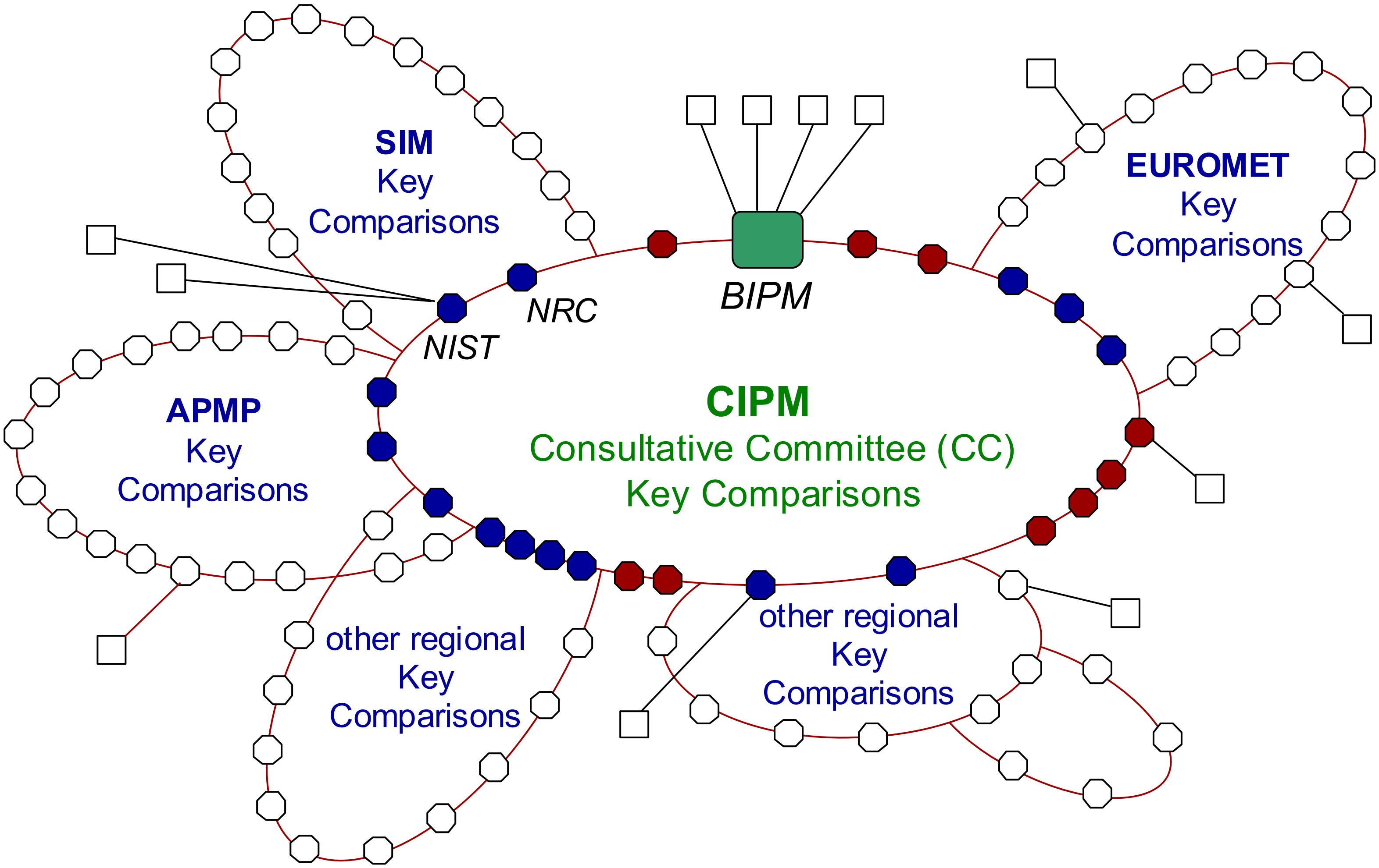


Approx. $500 M/yr NIST investment (0.7% of federal R&D)

Undergirds ~$10 B/yr of private sector investment in measurements and standards

Impacts U.S. economy - More than half of $7.6 T/yr U.S. GDP in sales supported by measurement

Framework for International Comparability Assessment



CCQM Comparisons: Categories

General Studies

- pH
- conductivity
- elemental and anion solution mixtures
- purity assessment: organics and inorganics

Health

- clinical diagnostic markers in serum
- toxic elements in blood

Food

- nutritional constituents in food digest
- contaminants in food

Commodities

- lead in wine
- composition and calorific value of natural gas
- sulfur in fuel oil

Environment

- biological tissues:
  - pesticide residues in fish oil (Food)
  - arsenic in fish
- soil/sediments:
  - PCBs, tributyl tin in sediment
  - lead and cadmium in sediment
- air:
  - VOCs
  - automotive exhaust emissions
  - stationary source emissions, etc.
- water: selected elements

25 CCQM Comparisons in FY01; CSTL was the lead or co-lead of 13.

Formal International Comparability Activities

Recent CCQM Studies

Clinical Diagnostic Markers in Serum

NIST Served as Pilot Laboratory for Pilot Study and Key Comparison for:

- Cholesterol
- Creatinine
- Glucose

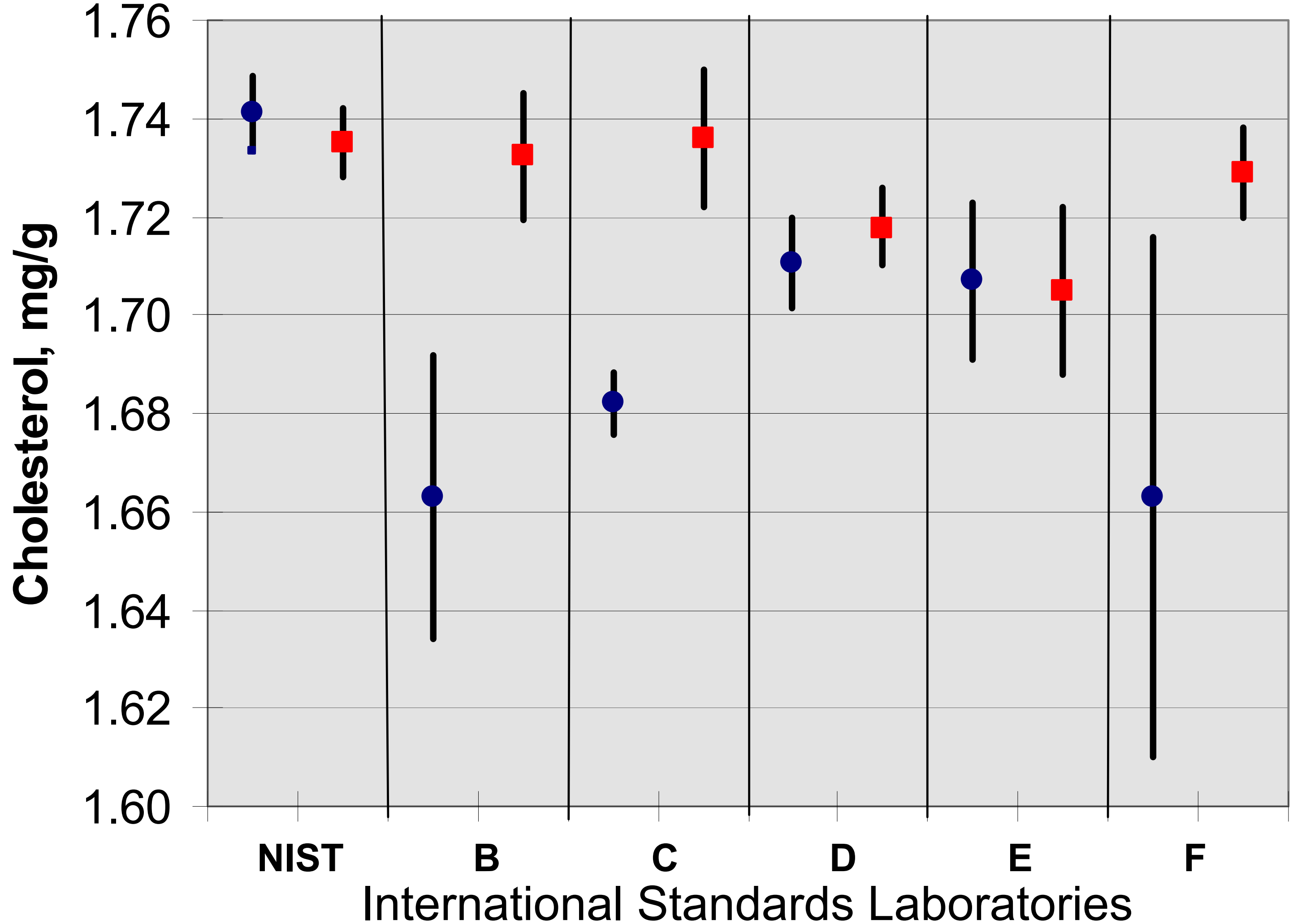
These three analytes were chosen because they present different challenges for accurate measurements. Cholesterol is lipophilic, glucose is highly water soluble, and creatinine is present at much lower concentrations. Ability to determine all of these accurately is evidence that a laboratory has the capability to measure other well-defined small organic molecules in serum.

NIST also participated in Key Comparison for:

- Calcium in Serum

CCQM – Comparison of Results for Cholesterol in Serum

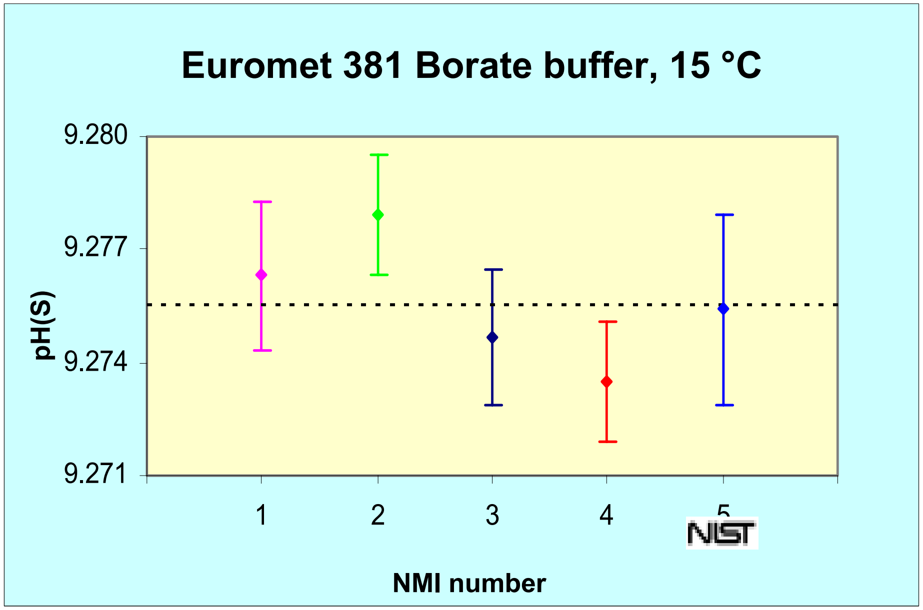
in 1999 Pilot Study • and in 2000 Key Comparison ■ (CCQM-K6.b)

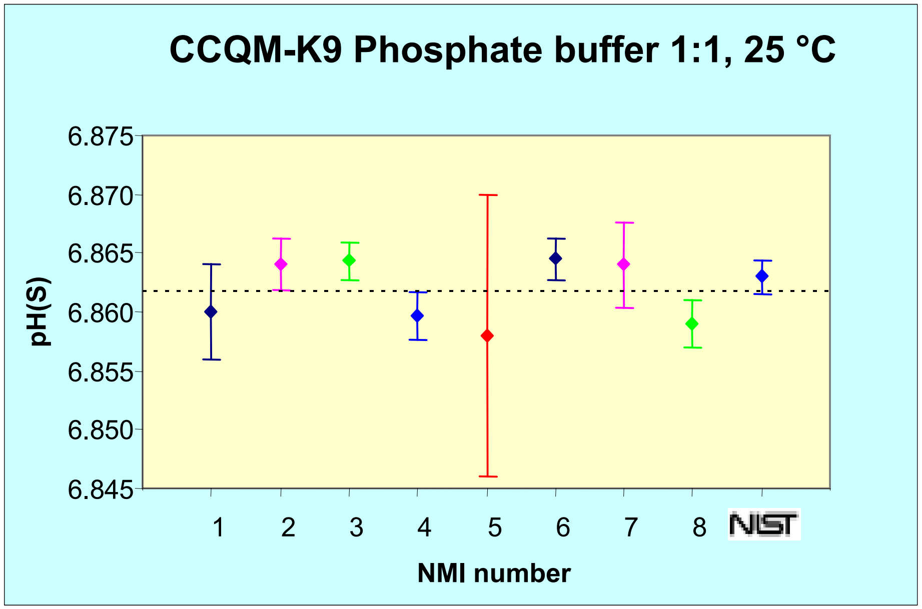


mean ± U: 1.700 ± 0.087 mg/g (pilot) 1.726 ± 0.013 mg/g (key)

International Intercomparisons

- Methodology
  - participants: national metrology institutes (NMIs)
  - identical buffer sample issued to each NMI
  - each NMI independently measures pH(S), estimates uncertainty





- Results
  - inter-NMI-recognized “degree of equivalence” for pH(S)
  - improved uncertainty assessment for pH metrology

NIST Program Vision:

- Expand existing clinical standards program to encompass all major diagnostic markers *[perhaps through more effective networking].*
    - Reference Materials to Address EU *in vitro* diagnostics Directive
    - Measurement Technologies and Transfer Standards for Point-of-Care Health-Care Diagnostics
- Expand food standards program to address GMO, adulteration and other issues of US concern.
- Establish program for credentialing commercial instrument calibrators.
- Work with the U.S. College of American Pathologists and appropriate EU counterparts to establish trans-Atlantic Clinical Laboratory Chemical Measurements Proficiency Demonstration Program.

Health Care Measurements:

… *supporting the national reference system and the IVD industry*

❖ Maintain and Refine Definitive Methods for 12 Health Status Markers

Calcium	Cancer, Blood Clotting
Chloride	Kidney Function
Cholesterol	Heart Disease
Creatinine	Kidney Function
Glucose	Diabetes
Lithium	Antipsychotic Treatment
Magnesium	Heart Disease
Potassium	Electrolyte Balance
Sodium	Electrolyte Balance
Triglycerides	Heart Disease
Urea	Kidney Function
Uric Acid	Gout

❖ Establish Reference Systems for New Clinical Markers - Highest Priorities

Troponin-I	Myocardial Infarction
Gylcated Hemo.	Diabetes Status
Homocysteine	Risk of Heart Disease
P_{53} DNA	Breast Cancer
TSH	Thyroid Function
Speciated Iron	Hemochromatosis, Anemia
Human Serum Alb.	Renal Failure
PSA	Prostate Cancer
Cadmium & Mercury	Toxic Metal Poisoning
Cortisol	Endocrine Function
Thyroxine	Thyroid Function
Folates	Neural Tube Defects

Characteristics of current markers:

- Relatively small well-defined molecular or elemental species

Measurement Challenges for new markers:

- High molecular mass proteins (>20,000 daltons)
- Heterogeneity of the protein
- Separation of different forms of the proteins
- Serum matrix complex; analyte level low
- Stability of analytes
- *Standardization necessary before medical diagnostic benefit can be realized*

Assessing Needs and Setting Priorities for Health Status Markers: How do we Proceed??

Global Action Plan for Addressing IVD Directive: NIST Proposal

- **NIST would develop and maintain reference methods and SRMs for up to 40% of the "A" list analytes**
- **NMIs in the EU, Japan and Australia would develop reference methods and CRMs for the remaining 60%**
- **Mechanisms for mutual recognition of reference methods and assigned values for CRMs to be established:**
  - **Collaboration between NMIs**
  - **Independent Development with Verification**

Classes of Analytes:

"A list" - approximately 100 well-defined chemical species, potentially traceable to SI units

"B list" – less well defined, potentially not traceable to SI units, and number >500 (for example: method dependent analytes such as liver enzymes)