125 Jahre genau
1887 - 2012

Helmholtz-Symposium on the occasion of the completion of PTB's first 3×42-1 years

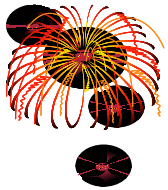
"Metrology, the Universe and Everything"

Tuesday, March 27, 2012 Stadthalle Braunschweig, Germany

Metrology for "Stuff"
– Chemistry, Biology and Materials –

and its impact on commerce, innovation and quality of life

Dr. Willie E. May
Associate Director for Laboratory Programs & Deputy Director
National Institute of Standards and Technology



Happy Anniversary PTB!!

Here's to the next 125!

From NIST

Outline

§ Congratulatory Comments from NIST

Director, Pat Gallagher

§ Brief History of Metrology and Some of its More Common Practices and Applications

§ Metrology for “Stuff”: Its Impact on Productivity, Innovation and Quality of Life

- Chemical Structure and Composition
- Materials Properties
- Bioscience/Health

The Need for Metrology: Recognized Through the Ages

The ancient Egyptians were well known for their measurement capabilities

- **Standard unit of length** - the length of Pharaoh's forearm plus the width of his palm
  - **The Cubit**
- **The "Royal Cubit Master"**
  - **Primary standard** in granite
- **Realization of the Cubit: A stick of wood**
  - **Working Standard** / Comparability
- **Re-calibration of cubit stick required on each full moon**
  - **Calibration / Traceability**
  - Severe penalty for non-compliance

Uniformity of length measurement was achieved to a relative accuracy of 0.05% over a distance of 230 meters

In addition to the well known Royal Cubit for length measurement, a host of other accurate measurement standards existed. For example in mass:

Predynastic

Stone mass standard

(5,000 to 7,000 years old)

The Deben,

12g, 27g, 93.3 g

(3,000 to 5,000 years old)

Standards in Medieval Times

"Throughout the realm there shall be the same yard of the same size and it should be of iron"

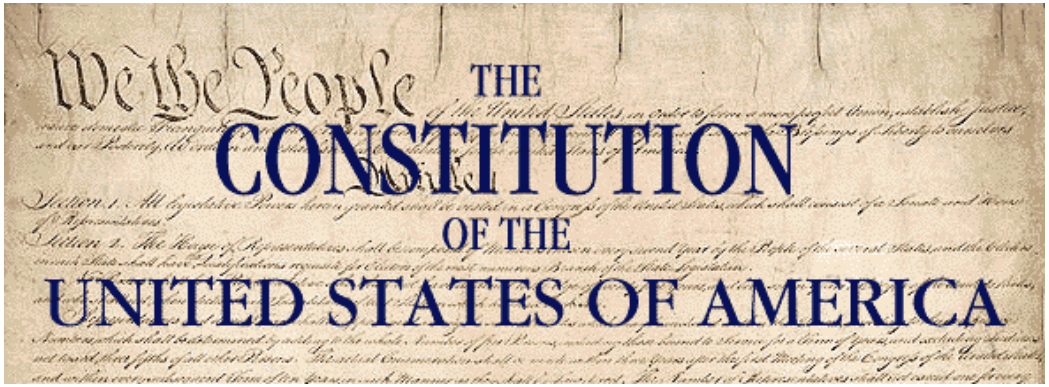
Assize of Measures, 1196

Magna Carta of 1215

"There shall be standard measures of wine, ale, and corn (the London quarter), throughout the kingdom. There shall also be a standard width of dyed cloth, russett, and haberject, namely two ells within the selvedges. Weights are to be standardised similarly."

U.S. Federal Role in Metrology

The Constitution of the United States



Article 1, Section 8: The Congress shall have the power … *to coin money, regulate the value thereof, and of foreign coin … and fix the standard of weights and measures … (1788)*

"Foreign traders had begun to voice concern that goods might not be assigned a proper quantitative value at American custom-houses and that, as a result, assessed duties might be unfair and uneven from port to port."

John Quincy Adams (1817)

International Metrology Infrastructure: The Early Years

International Metrology Infrastructure

20 May 1875

The Meter Convention, an intergovernmental treaty signed by representatives of 17 nations, established an organization structure for member **governments to act in common accord on all matters relating to units of measurement**.

- It established a scientific and permanent International Bureau of Weights and Measures (BIPM) operated under the direction of an International Committee of Weights and Measures (CIPM) controlled by General Conference for Weights and Measures (CGPM).

In subsequent years, National Metrology Institutes were established

1887 PTB (PTR)

"to supervise and direct calibration and to establish metrological standards"

1900 NPL

"for standardising and verifying instruments, for testing materials and for the determination of physical constants"

1901 NIST (NBS)

"for custody of the standards; the comparison of the standards…; the construction … of standards; the testing and calibration of standard measuring apparatus; solution of problems which arise in connection with standards; the determination of physical constants and the properties of materials …"

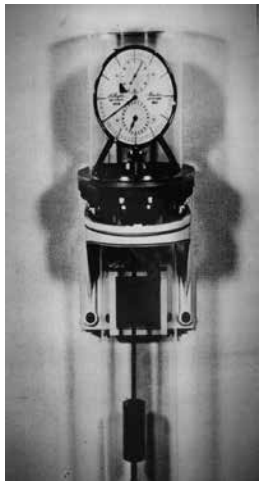
Early Emphasis on Physical Metrology

- During the past 100+ years, National Metrology Institutes have developed sound programs for **physical metrology** focused on the realization of SI units for time, mass, length, temperature, electricity, etc.

- **Physical Metrology is vital to wide ranging sectors that impact our daily lives**

Advances Have Led to Life-changing Innovations

pendulum clock
1 s in 3 years
(1904)

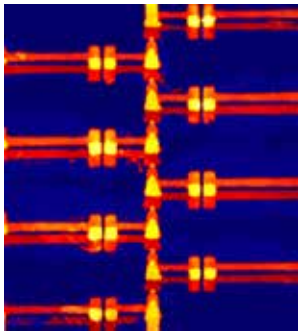


second

NIST F1
atomic clock
1 s in 30 million
years
(1999)

silver voltameter
current standard
(1910)

ampere



single
electron
counter
(20xx)

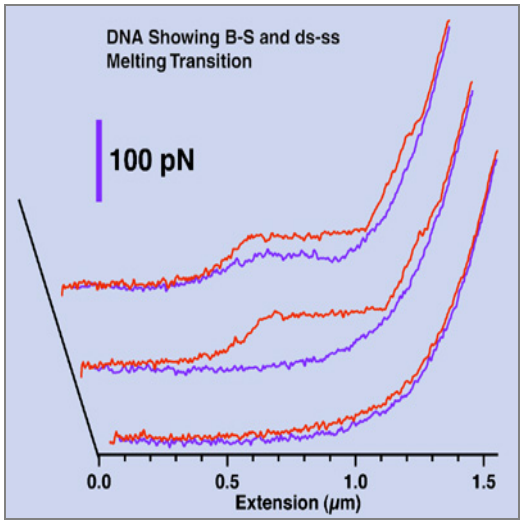
physical artifact
(1889)

kilogram

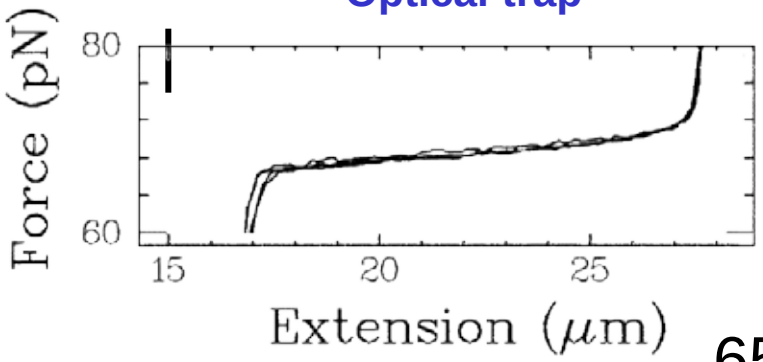
electronic
kilogram
(20xx)

DNA as an Intrinsic Force Standard

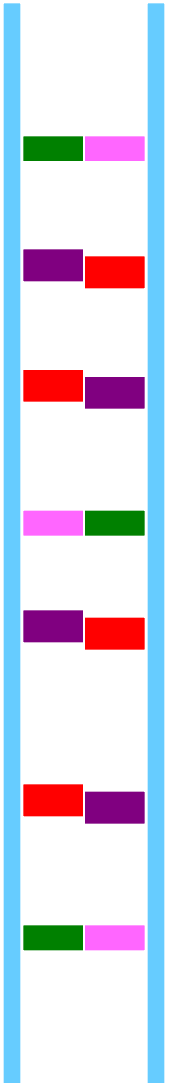
AFM



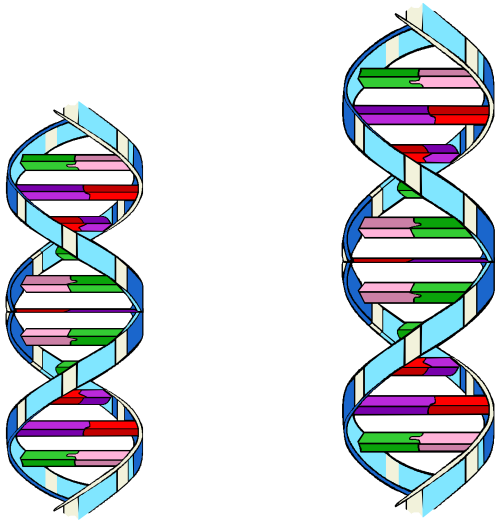
Optical trap



65 pN



- DNA can be manufactured to atomic precision anywhere in the world.
- The force required to induce DNA transition is used as a biophysics “standard” – but firm metrological basis does not exist
- NIST is working to measure the DNA transition force with traceable metrology using approaches based on both optical and AFM techniques.



Metrology

§ science of **measurement** and its application

(ISO/IEC Guide 99:2007, *International Vocabulary of Metrology - Basic and General Concepts and Associated Terms (VIM), 2.2)*

§ The science of metrology is based on a number of principles that can be appropriately applied to any type of measurement:

– not only in physics, but chemistry, biology, and materials science as well

In addition to manufacturing and trade, Metrology for "Stuff" addresses a broad range of contemporary issues

"Missing Micrograms Set a Standard on Edge" – NY Times

"Trouble in Toyland, toxic and hazardous toys" – NBC News

"Up to 20% of published work using human cell lines are known to be misidentified"
- Nature Editorial

"Meaningful nanotechnology EHS research requires independent nanomaterial characterization"
- Nanowerk

"Vitamin D Testing: What's the Right Answer?
– Clinical Lab News

"Pipeline Corrosion and Safety Issues Take Spotlight" - Reuters

WSFA 12 News

Concerns Arise over Lead in Dental Crowns
Posted: March 3, 2008 07:45 PM EST

Body of Evidence: New Fast, Reliable Method to Detect Gravesoil
– Science Daily

"Rare Earth Metals Leave Toxic Trail to Toyota, Vestas" – Bloomberg Business Week

"The trials of new carbon: commercialization is neither quick nor easy." - Nature

"Medical Devices Approved Too Soon?" - ABC News

In Fact, Metrology for Stuff Impacts Areas of Global Importance, such as:

- **Advanced Materials**, from *nanomaterials* to *structural steels* to *complex fluids*
- **Assessment of the Environment and Climate**, from the measurement of automotive exhaust emissions and other pollutants to assessment of climate change and the health and safety aspects of man-made nanomaterials
- **Biomedical and Health**, from clinical diagnostics to tissue engineering to the more efficient manufacturing of biologic drugs
- **Electronics**, from semiconductors to organic electronics
- **Energy**, from characterization and performance of fossil and alternative fuels to next-generation renewables
- **Food Safety and Nutrition**, from contaminant monitoring to ensuring the accuracy of nutritional labels
- **Physical Infrastructure**, from the aging of the country's bridges and pipelines to the quality of our drinking water
- **Manufacturing**, from lightweight alloys for fuel-efficient automobiles to bio- and chemical manufacturing
- **Safety, Security and Forensics**, from gunshot and explosive residue detection to ensuring the performance of body armor materials and DNA-based human identity testing

Metrology Program for Chemical Measurements

pays significant dividends to a Nation's Economy and Quality of Life for its citizens through underpinning decisions regarding:

- Transactional Efficiency in National and International Trade
- Fact-based Environmental Decision-Making
- Assessment of Food Safety and Nutritional Content
- **Informed Healthcare Decision-Making**
- Reliability of National Security-Related Measurements and Data
- Innovation and Industrial Competitiveness

A Context for the Importance and Complexity of Chemical Measurements

§ According to a study released by the Council for Chemical Research, **chemistry is core or important to virtually all industrial sectors and technology areas**

– ***"Measuring Up: Chemical R&D Counts for Everyone", CCR, 2006***

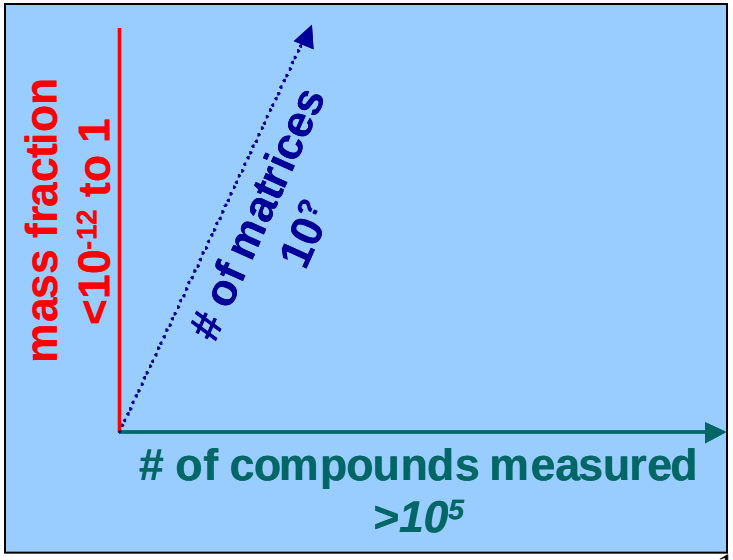
§ **For metrology in chemistry** the task is to determine the quantity of a **specific chemical entity in a given matrix** and not merely "amount of substance" *(i.e., requires confirmation of identify as well as amount)*

§ **Chemical measurements are multidimensional**

– a large number of chemical entities (>10^5)

– in a broad range of matrices ($10^?$)

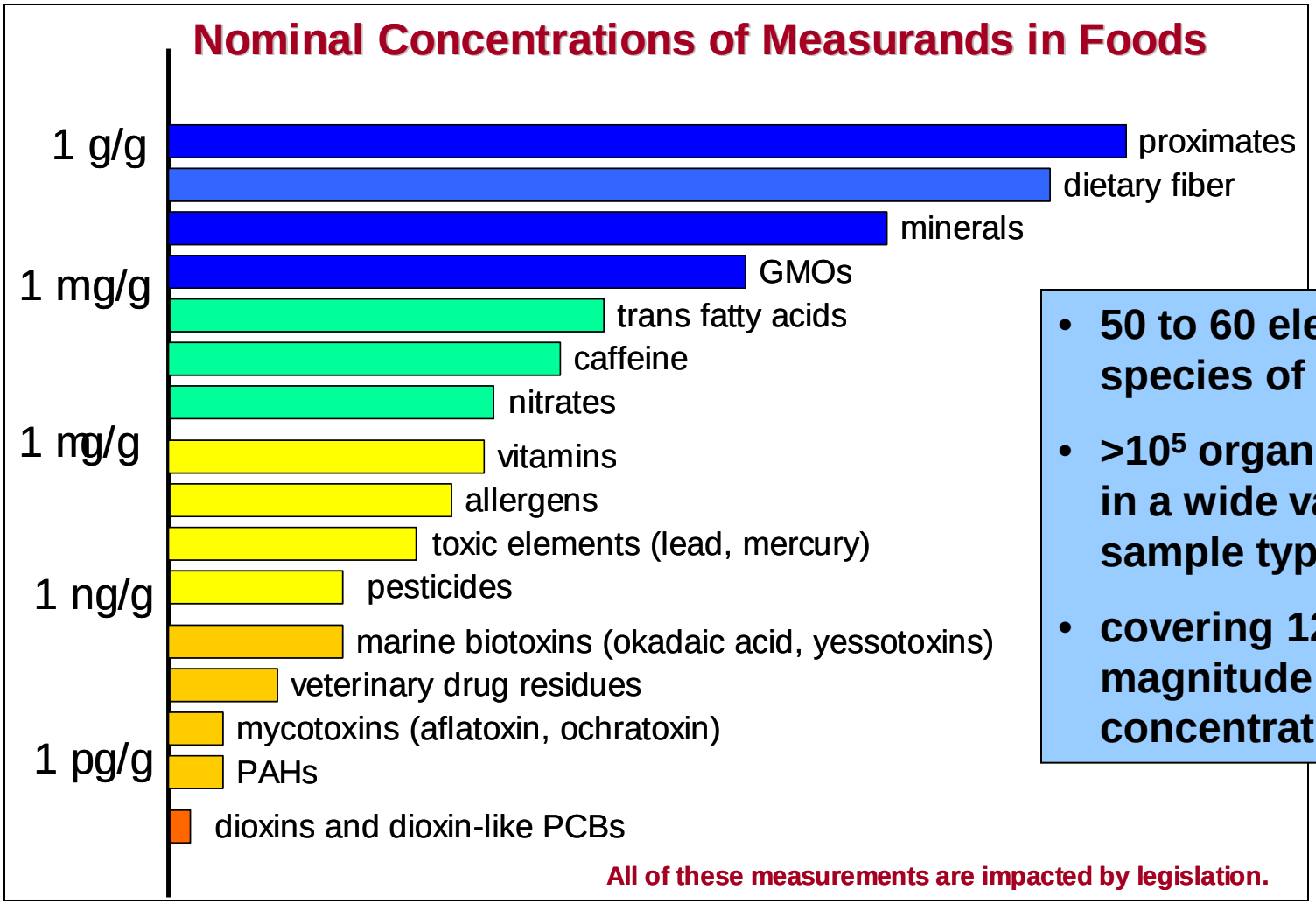
– and mass fractions ranging from <10^{-12} to 1



... an example of this complexity

Regulated Classes of Chemicals in Foods

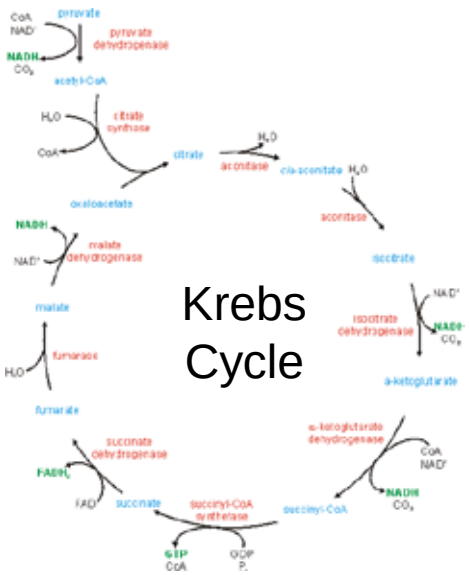
(there are multiple measurands within each class)



- **50 to 60 elemental species of importance**
- **>10^5 organic species in a wide variety of sample types**
- **covering 12 orders of magnitude in concentration.**

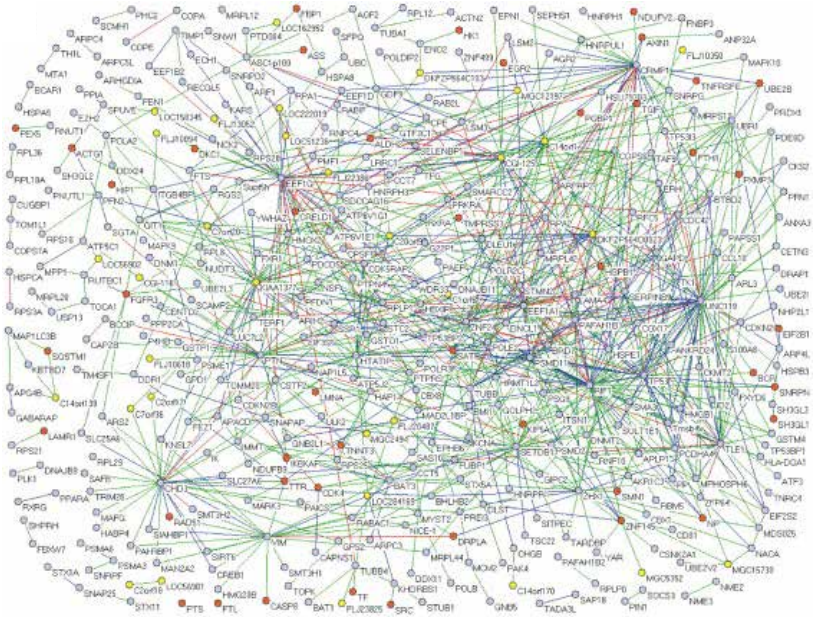
Facilitating Innovation in the "Biosciences" is Hard

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? Trial and Error

Why Is This Important?

Better measurement and modeling tools can lead to effective predictive toxicology for new drug candidates and can:

- minimize adverse health effects
- eliminate the adverse economic impact associated with recalls

$2.5 B world-wide sales in 2003

For example:

Rofecoxib (Vioxx™) provided effective treatment for arthritis sufferers.

The inability to predict which individuals were most at risk for experiencing serious side-effects, e.g., heart attack and stroke caused this highly effective and profitable product to be **taken off the shelf for all – not just those at risk.**

Better measurement science and standards can improve reliability of testing and improved diagnostic power.

Why Is This Important?

Better measurement science and standards can improve reliability of testing and improved diagnostic power.

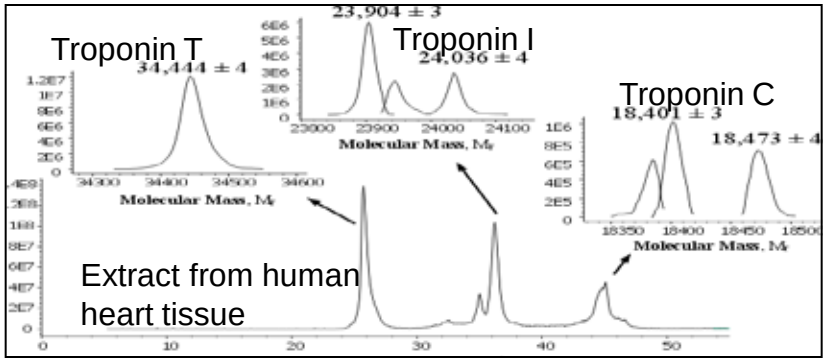
For example:

Troponin I has the potential to be a very specific biomarker for heart attack.

- Although all report results as Troponin I, different commercial tests measure different things.
- The lack of agreement of results from these tests limits diagnostic utility.

Assay Manufacturer	Conc. ng/mL	# Labs
A	19.9	115
B	6.7	489
C	0.85	27

From G. S. Bodor, Denver Health and Hospitals -- personal communication



Healthcare: Lack of Standards Has Economic and Quality-of-Life Implications

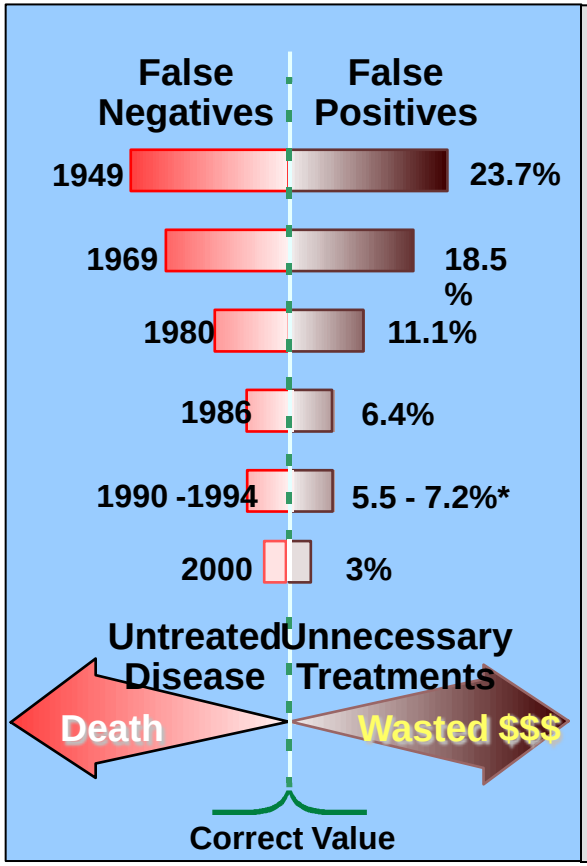
U.S. Spends ~ $2.5 trillion on Health Care Annually of which 10-15% is associated with measurements

- ~ 70% of health care decisions are based on results from clinical laboratory measurements
  - *Yet, standards exist for only 10% of the 700 routinely performed clinical laboratory tests*
- 60 million CT tests performed annually to measure changes in lesions are limited by ability to discern only large changes in size/metabolism
  - *This is a direct consequence to lack of standards to monitor equipment performance*
- Costs of repeat measurements amounts to 1.5 B US$ per year in Germany according to the German Health Report of 1998 (www.gbe-bund.de)

Measurement Bias also Affects Quality of Life and leads to

- Incorrect diagnosis and treatment
- Impairment of patient well-being

Improved Cholesterol Measurement Accuracy Saves Health Care Dollars



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)*

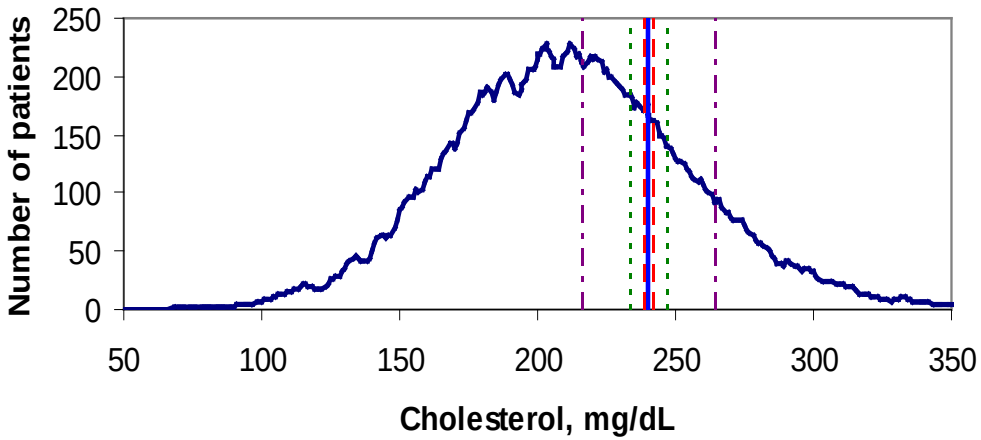
1988 – New Suite of Cholesterol in Serum SRMs at Medical Decision Points

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

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

***Data from GAO and CAP**

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

The New York Times

"Quest Acknowledges Errors in Vitamin D Tests"

"The nation's largest medical laboratory company provided possibly erroneous results to thousands of people who had their vitamin D levels tested in the last two years, the company has acknowledged. " "When the Quest tests have been inaccurate, the reading has typically been too high, although not in all cases."

By ANDREW POLLACK, NY Times, JANUARY 7, 2009

NIST SRM 972 - Vitamin D in Human Serum

- Vitamin D deficiency has long been associated with osteoporosis and an increased risk of bone fractures; has recently been linked to increased risk of other common diseases.
- Clinical labs perform hundreds of thousands of tests for vitamin D each year, and recent studies have shown that different labs often provide different results for the same samples.
- MML scientists developed SRM 972, "Vitamin D in Human Serum," to provide a foundation for increased accuracy for vitamin D measurements
    - SRM 972, issued 9 Jun 2009, contains four serum samples with NIST assigned values for three vitamin D metabolites; 25(OH)D2, 25(OH)D3, and 3-epi-25(OH)D3

>1300 units sold in first 21 months

Major purchasers: Quest Diagnostics (666); Perkin Elmer (97); Kaiser Permanente (12); Vanderbilt University (11); CDC (9); Waters Instruments (9)

Prostate Specific Antigen (PSA)

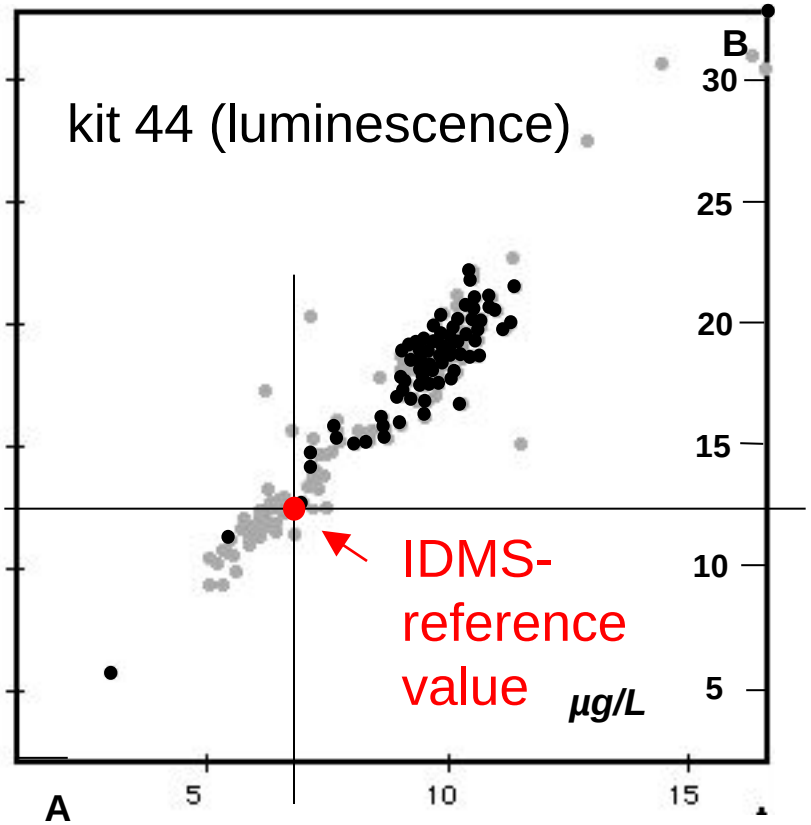
- >37,000 deaths annually in U.S. from prostate cancer
- Blood tests for PSA are used to screen for the likelihood of prostate cancer
- PSA is a heterogeneous protein that occurs both free and complexed
- Immunoassays are the approach favored for routine measurement of PSA
- Wide variability among the results from immunoassays (see below)
- High incidence of false positives and false negatives

# of Labs	- Low -	- Med.-	-High-	-Mean-	- S.D. -	%RSD	95% Confidence Range
2672	10.8	19.4	34.5	19.67	2.14	10.9	15.39-23.95
2653	7.2	9.8	18	9.92	1.11	11.2	7.70-12.14
2689	5.3	7.3	12.8	7.36	0.79	10.7	5.78-8.94
2509	2.1	3	4.7	3.03	0.33	10.8	2.37-3.69
2504	0.6	0.7	1.5	0.73	0.11	14.5	0.51-0.95
2591	0.1	0.2	0.8	0.24	0.1	40.2	0.04-0.44

From: http://www.cooleyville.com/cancer/capsava.htm

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.

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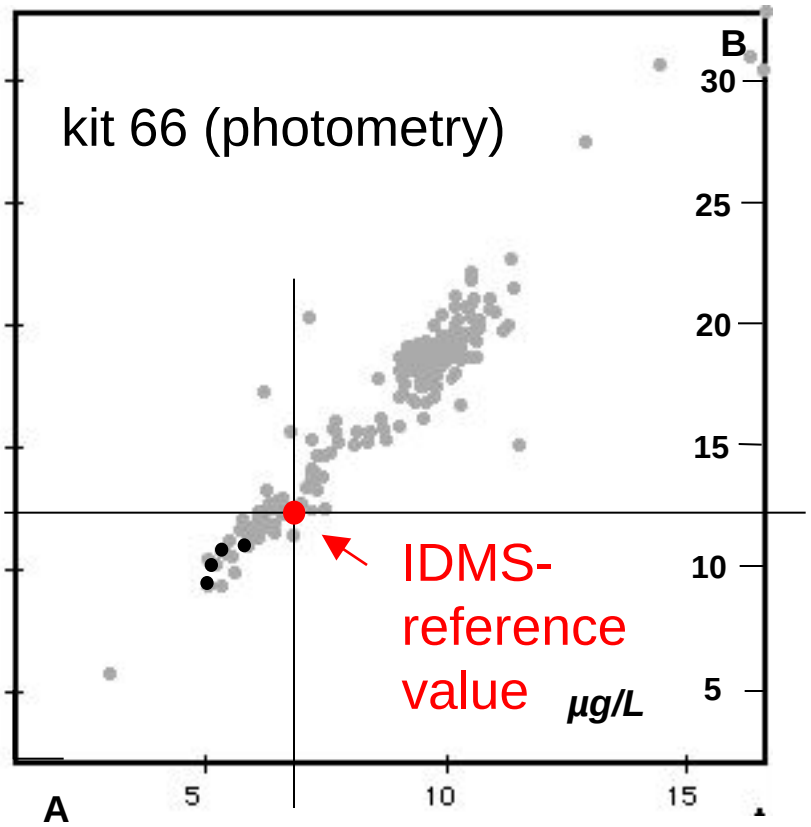

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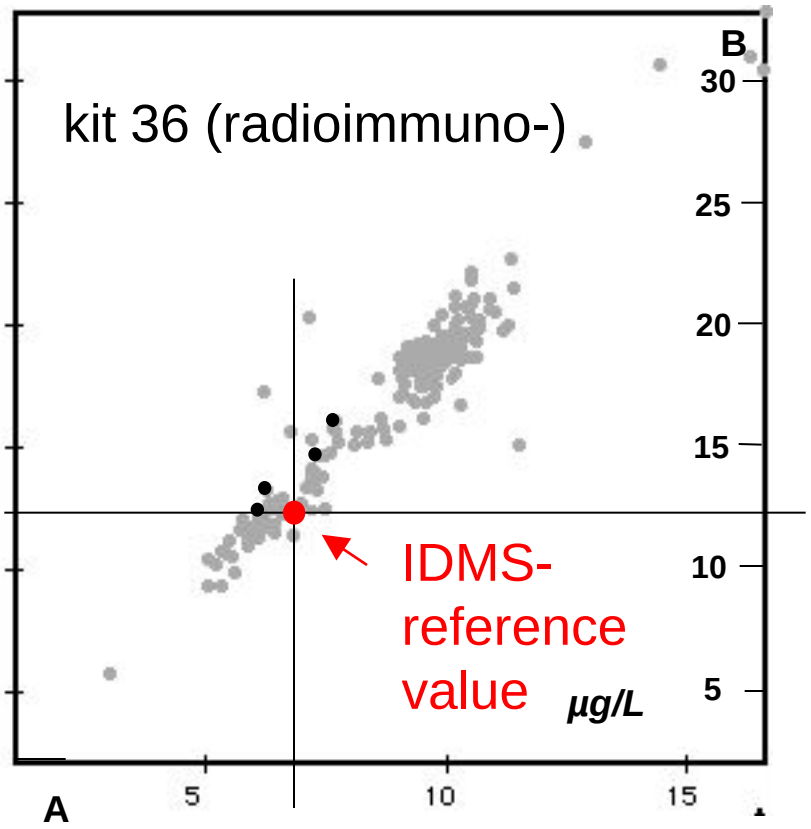

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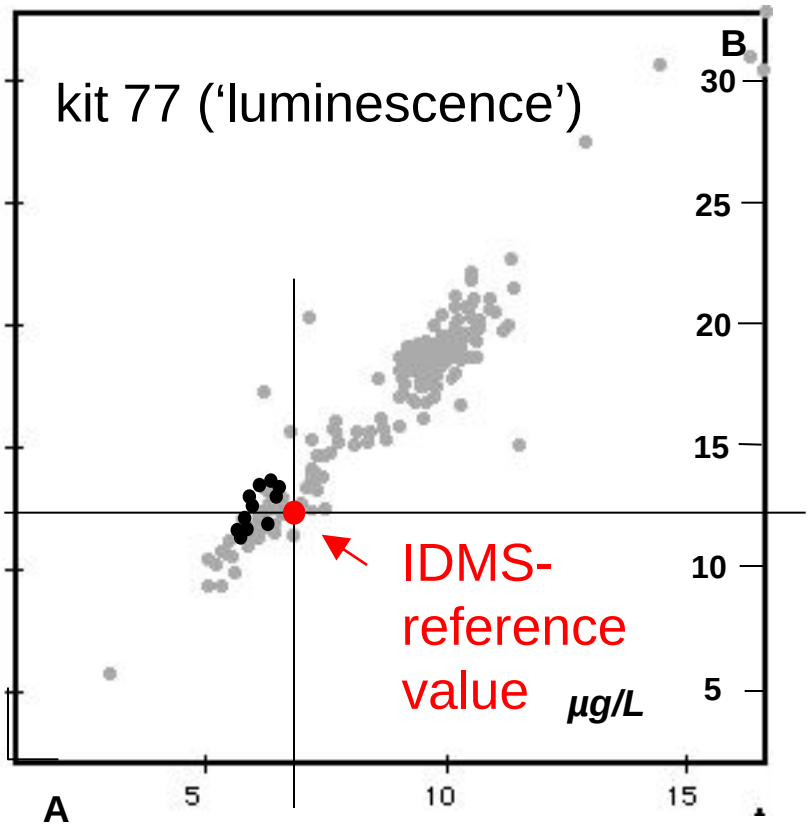

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What is "Personalized Medicine"?

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

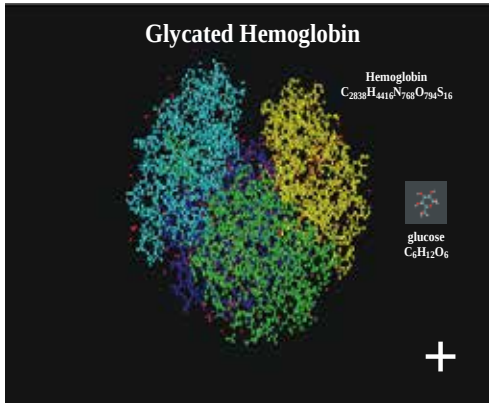
Personalized medicine can address questions of the common man/woman -

- **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: Standards for Genetics Testing

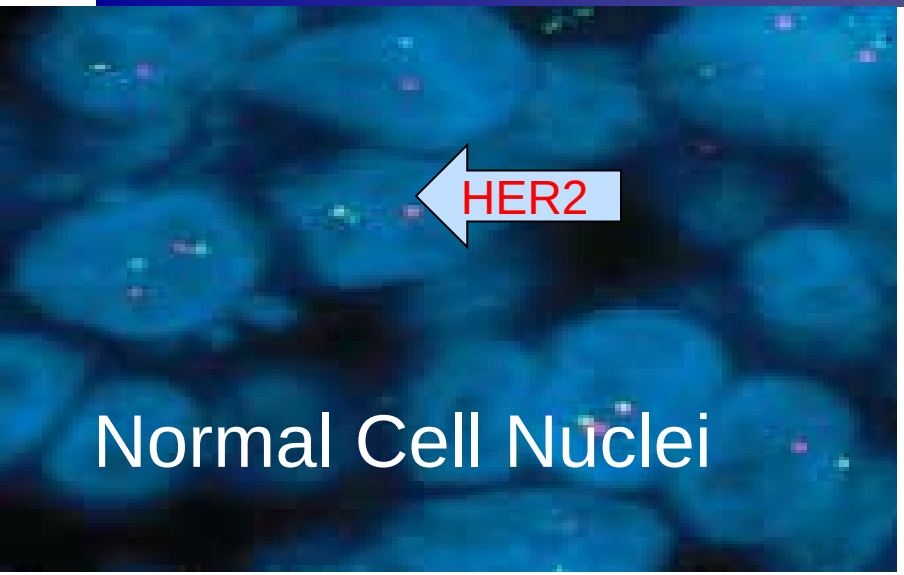
Reference systems for markers that typically exhibit:

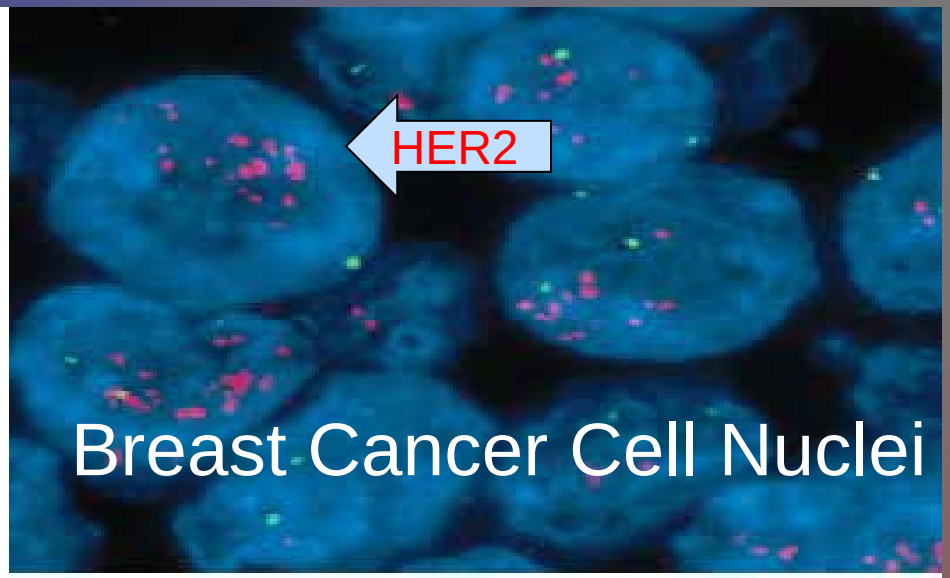
- **High molecular mass (>20,000 daltons)**
- **Heterogeneity, low concentration, instability of analyte form**
- **Cannot all be determined using GC- ID/MS or ICP/MS-based methodologies**
- **Such as the following:**



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**





"The college of American Patholigists and the American Society of Clinical Oncology, which issued guidelines for the Her-2 …. estimated that around 20% of Her-2 testing may be inaccurate"

HER2 Tests

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/SB119941325367266813.html

Goal: Identify unique biomolecular profiles and anatomical features that are indicative of the onset and progression of disease

Future Challenge

One Visionary's perspective

The premise is that:

- organ-specific blood proteins will provide a window into health and disease state
- perhaps 50 major organs each secreting protein blood molecular fingerprint
- 10 -50 organ-specific proteins per organ
- the levels of each protein in a particular fingerprint will report the status of organ
- need to quantify 500-2500 blood proteins from a droplet of blood

Lee Hood
Institute for Systems Biology

Measurements and Standards for Biologic Drugs

The Cost of Protein therapeutics is one of the fastest growing components to the overall cost of health care in the U.S. (~$90B, 180,000 jobs 2010)

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

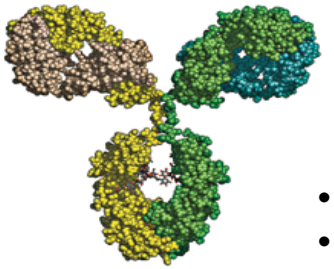
These drugs have proven to be **very therapeutic and substantially improve patients' health and quality of life.** However, they are **very expensive and generics are not currently available in the U.S.**

President Obama has charged FDA with establishing a pathway for approval of generic biologic drugs

NIST has been asked by both FDA and the industry to apply its unique combination of expertise in the physical, chemical, and the biological measurement sciences **to underpin the development and regulatory approval of Biologic Drugs.**

Prozac

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



Rituxan: Biologic Drug

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

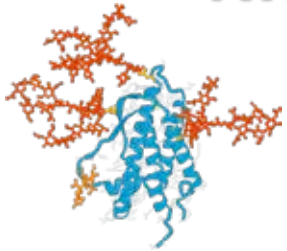
Top Ten Biologic Drugs and Their Global Sales

Total World-wide Biologic Market: ~150 billion

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

*July 2010 to June 2011; Source: IMS Health

NIST Program in Biomanufacturing Metrology



Measurement science, tools & standards to support manufacturing & regulatory approval of biologic drugs

Program Areas:

1. **Protein structure: higher order structure, post-translational modifications**
   - **"Structural Sameness"** of the manufactured biopharmaceutical

2. **Measurements & standards for protein stability, aggregation, & particles**
   - **Propensity** of the biopharmaceutical **to induce an Immune Response in Patients**

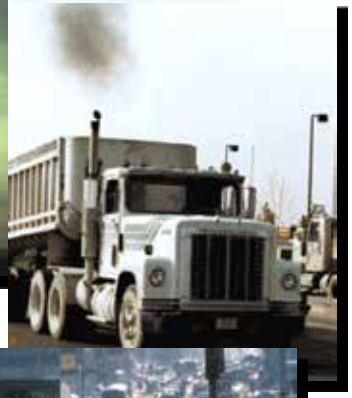
3. **Measurement tools & science to understand production cell variability**
   - **Complex Inner Workings of Cells** used in the production of Biologic Drugs

Congressional Subcommittee Hearing - Need for Measurement Standards to Facilitate R&D of Biologic Drugs, Sept. 2009

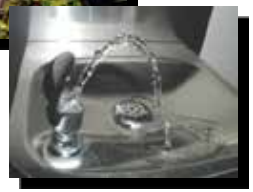
(From L to R): ***Dr. Anthony Mire-Sluis (Amgen)***
Dr. Patrick VJJ Vink (Mylan)
Dr. Steven Kozlowski (FDA)
Dr. Willie May (NIST)

Environmental Measurements

Climate Change Assessment; Green House Gases, Aerosols, Stationary and Mobile Source Emissions; Air Quality



Environmental monitoring (including specimen banking and Gulf Oil Spill damage assessment; drinking & wastewater



Quality and Health of the Marine Environment; Links to Human Health

Green Sustainable Manufacturing & Processes; Sustainable Sediment Management

National Reference System for Environmental Measurements

- Measurement Research
- Standards Development
- Quality Assurance Activities
- International Activities

the U.S. Climate Discussion

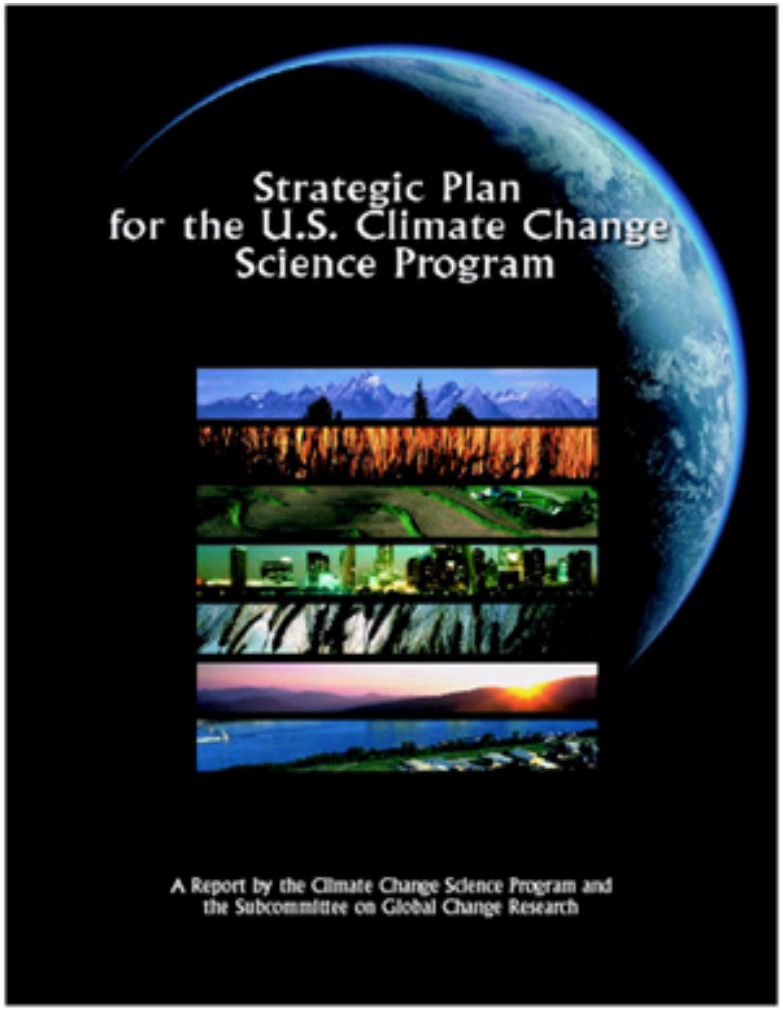
- **Climate change is a major issue for the U.S. and the World; greenhouse gas emissions are a major driver.**

- **Controversy around particular aspects of the discussion indicate that measurement results of undisputable quality and scientific integrity are needed to better inform policy decisions and mitigation strategies both nationally and internationally.**

- **Climate change observations require improved measurement capabilities because of the small changes that occur over long time periods and in the presence of significant variations in the parameters of interest.**

Calibrations/Measurements Should be Tied to National and International Standards

"… Instrument calibration, characterization, and stability become paramount considerations. Instruments must be tied to national and international standards such as those provided by the National Institute of Standards and Technology (NIST)..."



NMI Support for Global Monitoring Program

Traceability to NOAA Stds.

World Meteorological Organization (WMO)

MoU being developed

International Committee for Weights and Measures (CIPM)

Global Atmospheric Watch (GAW)

International Bureau of Weights and Measures (BIPM)

National Oceanic and Atmospheric Administration

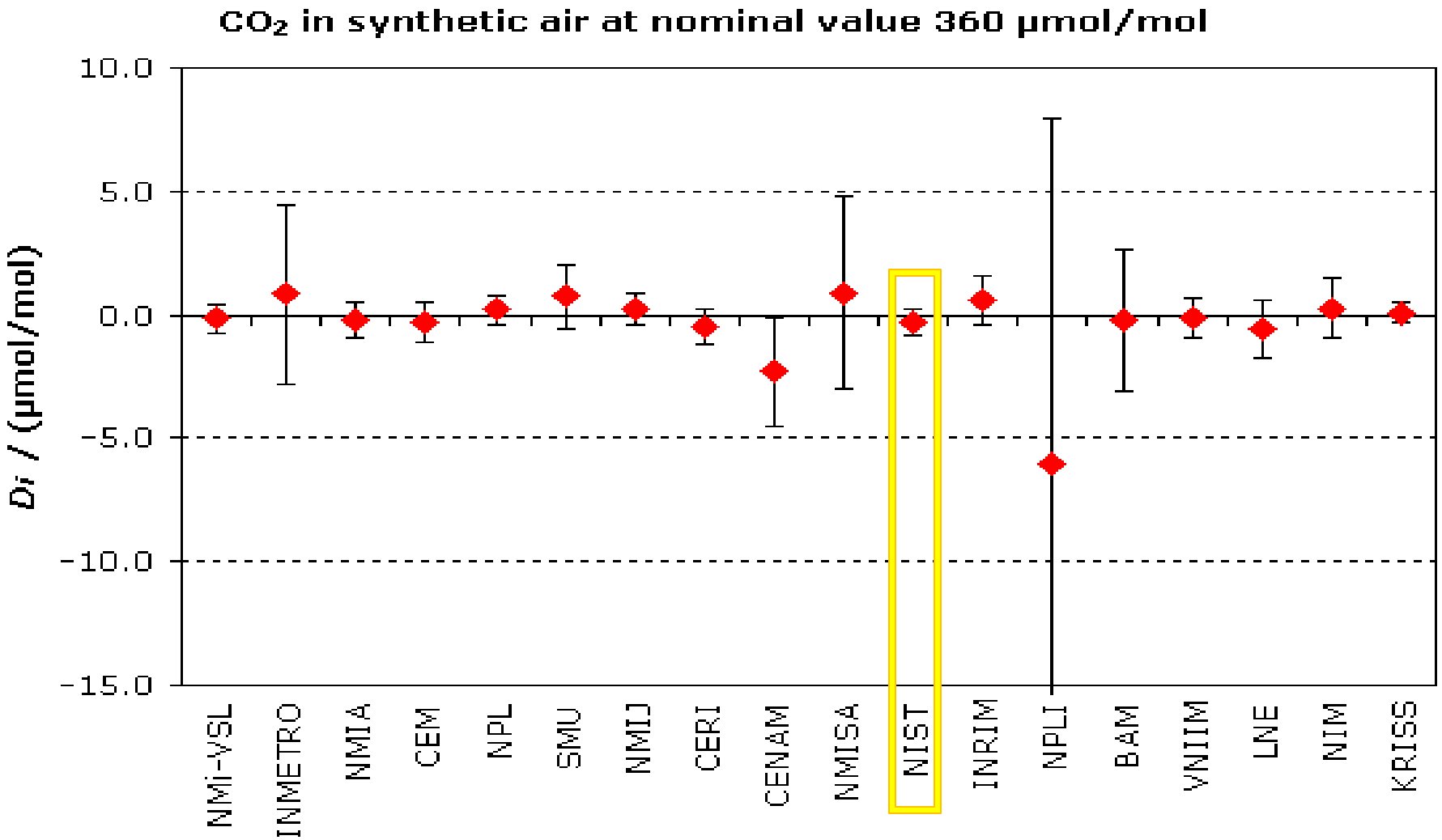
National Institute of Standards and Technology

Traceability to SI

The GAW can get traceability via linkages to NMI Community

Results of International Key Comparison

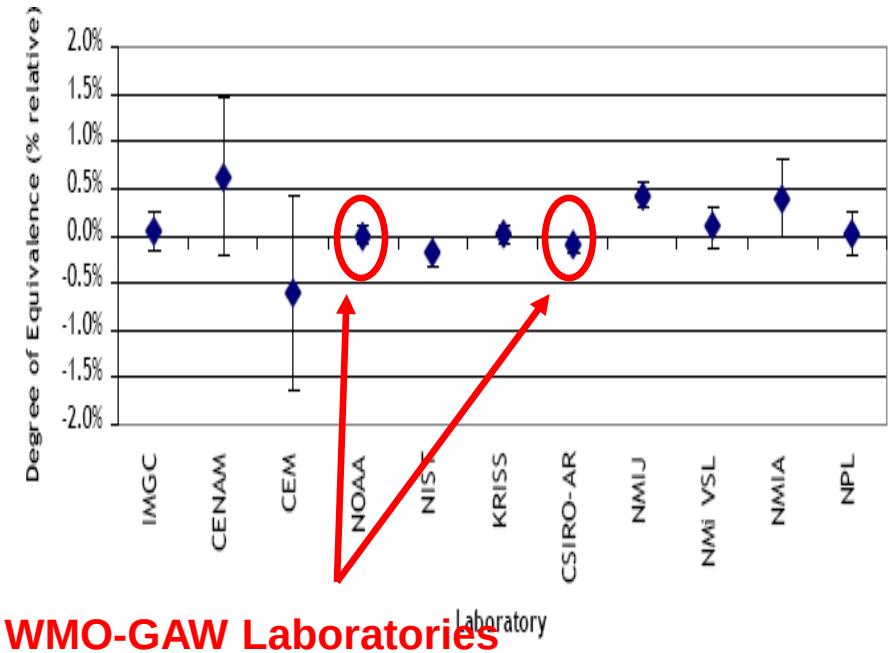
Participation restricted to NMIs



Results from Pilot Study

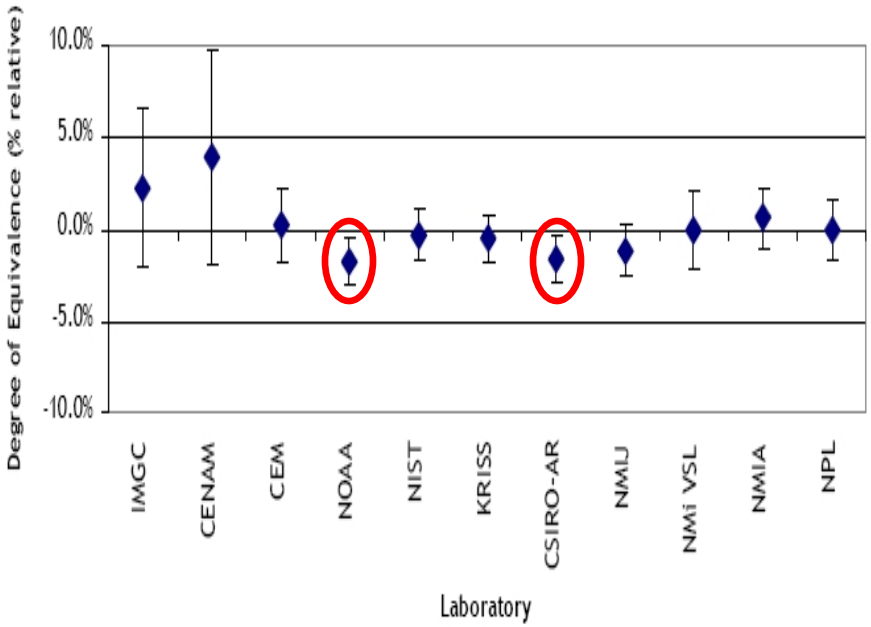
Preliminary to Key Comparison; other expert laboratories allowed to participate

CCQM-P41, Carbon dioxide, 365 µmol/mol (2003)



WMO-GAW Laboratories

CCQM-P41, Methane 1.8 µmol/mol (2003)



Comparison coordinated by NMi-VSL (NL)

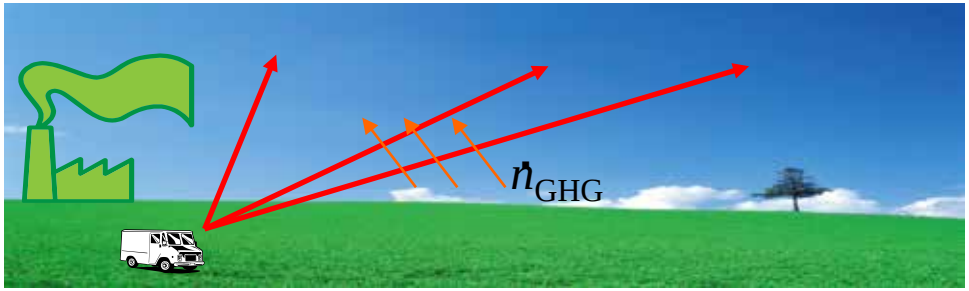
- Both NOAA and NIST represent the U.S. in treaty organizations regarding climate measurements.

Optical Remote Sensing

High Accuracy Spectroscopy Application

§ Configurations

- **Multi-path observations combined with:**
  - **tomographic reconstruction approaches and GPS time stamping provide 3D plume flux determination**
- **Ground based – vehicle or tower**
- **Airborne**



§ Payoffs

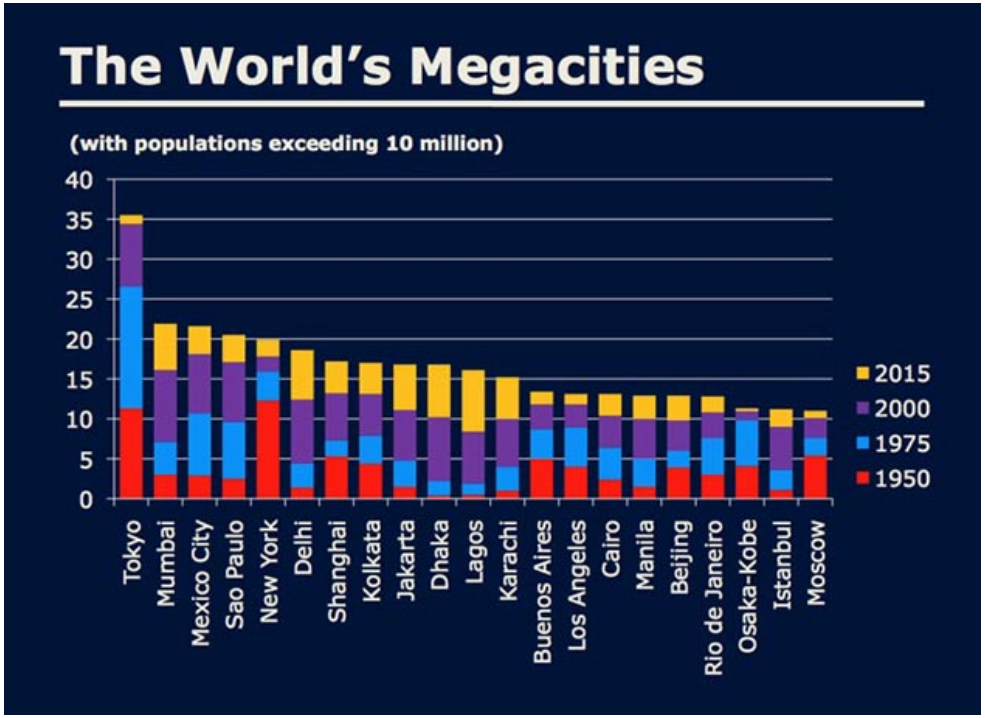
- **Enable GHG quantification for geographically distributed sources & sinks**
- **Point source verification at physical point of emission** – [My Emissions or Yours?]

Measurement Science Advancing Measurable, Reportable, and Verifiable (MRV) Greenhouse Gas Mitigation Activities

- Measurable & reportable emissions form the basis for a country's GHG Inventory (Bali Action Plan, UNFCCC Conference of the Parties, 2007 (COP 13))
- Transparent verifications of inventories and mitigation activity using measurements independent of the reporting entity are essential for international acceptance of these reports
- Metrological advances based on sound scientific principals are needed for these measurements and for verification of measurement results

Atmospheric GHG Flux Measurement

- **The Indianapolis Flux Experiment –** Surface-based, dense observing networks coupled with advanced analytical tools and atmospheric boundary layer dynamics measurements & models
  - Measure GHG mixing ratio at various heights in the atmospheric boundary layer
  - Augment numerical weather forecasting models with boundary layer dynamics measurements – 3D wind speed & direction, energy flows, and related atmospheric parameters, to determine GHG transport & flux
- **Performance Goals – Demonstrate Measurement Capability to:**
  - Locate stationary emission sources within 1 km^2, and
  - Estimate emission source strength to within 20% or less of stated inventory of an entity
- **Areas of Application:**
  - Major industrial GHG emission sources – electric and industrial energy production plants
  - Characterization of urban GHG domes and remote sensing calibration
  - Forests and estuaries – CO_2 sequestration and methane emission determination



Dense Observing Networks

MegaCity Extension

- **The top 40 MegaCities have aggregated GHG emissions that rank 3rd behind U.S. and China.**
- **These cities are represented by the C40 Organization**
  - **Formed by the cities Mayors**
  - **Mayors of NY and Sao Paolo current chairs**
  - **58 cities currently are members**
  - **Clinton Climate Initiative Partnership**

http://www.megacitiesproject.org/

Measurement Challenges for Enforcement of Food Regulations: *Four Key Areas*

1) Incurred residues and contaminants in food

Hormones
Natural and synthetic
Antibiotic
Chloramphenicol, sulphonamides, penicillin, in milk, tissue linking rapid tests to reference methods,
.....
Chloramphenicol in milk + others

Biogenic amines In fish
histamine, putrescine, cadaverine, tyramine

3-MCPD Soya sauce and vegetable hydrosolates,

PAHs, dioxins and dioxin like PCBs in a suitable matrix

Nitrates in lettuce, spinach,
Nitrates/Nitrites in cured meat

Heavy metals and trace elements Hg, Cd, Pb, Cu, Fe
Tin in canned food
.....
Nitrates in lettuce and inorganic

2) Labeling and nutritional legislation

Vitamins, A, D, E, C, B vitamins

Amino acids
.....
Vitamin A or D in a milk powder or processed food

SO_2, sorbic or benzoic acid

Other, caffeine in soft drinks
.....
Sulphur dioxide in processed food
Sorbic or benzoic acid

Protein, fat, ash, etc.
Butter fat in spreads
GMO presence in seeds, maize or processed food
Fat in a milk product or other matrix
GMO

3) Indigenous contaminants

Mycotoxins

Aflatoxins nuts/milk, infant formula,
Ochratoxins in coffee, cereals, beer,
Patulin in apple juice
Fusarium mycotoxins in cereals
.....
Aflatoxin M1 in milk

Shell fish toxins

Mouse bioassay (reference method)
Okadaic acid

4) Tariff classification

Butterfat (methyl ester of butyric acid),
Individual sugars,
Caffeine or theobromine, chocolate
Fat in milk powder
Protein in meat
.....
Butterfat (butyric acid methyl ester) in mixed spread, chocolate or cream liqueur
Caffeine/theobromine in chocolate (

RECENT EVENTS IN CHILEAN PRODUCTS

Alert Notifications of Chilean Products to EU, Years 2007-2009

PESTICIDES

- Carbaryl in wine

HEAVY METALS IN SEAFOOD

- Cd in frozen mussels
- Hg in frozen swordfish

MICOTOXINAS EN FRUTAS

- Patulin in mashed apples

FUNGICIDA EN FRUTAS

- Tiabendazole in apples
- Azinphos-methyl in grapes

Temporary Closure of markets due to the presence of residues

- Crystal violet in salmón, UE (Oct 2006)
- Leucomalaquite green in salmón, Taiwan (Oct 2007)
- Emamectin / Ivermectin in salmon,Canada (Oct.2007)
- Abamectina in salmon, Germany (Oct 2008)
- Amphenicol in Salmon, Canada (April 2008)
- Dioxin in pig meat, Korea (July 2008)

Fuente: Rapid Alert System for Food and Feed (RASFF)

IMPACTS FROM UNRELIABLE MEASUREMENTS

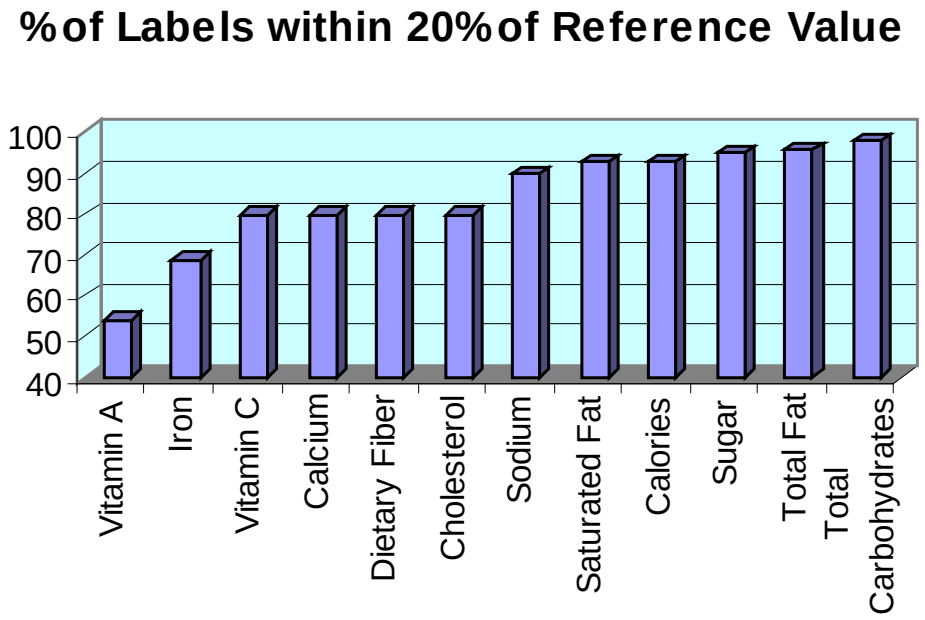
ECONOMICAL LOSSES DUE TO TEMPORAL CLOSURE OF INTERNATIONAL MARKETS TO CHILEAN EXPORTS

Due to unreliable measurements, it is likely that certain residues in foods such as antibiotics, pesticides, or heavy metals might result in higher concentration values than those established by international regulations. This might cause a temporal closure of certain destination markets. If it is assumed that, on average, such closure can last 2 months, and that re-establishment of normal trade can be achieved in 4 months, then the economic losses would be approximately:

• Temporal closure of grapes market in	USA	$ 161M
• Temporal closure of salmon market in	USA	$ 198M
	Japan	$ 176M
	UE	$ 77M
• Temporal closure of pig meat market in	Japan	$ 161M

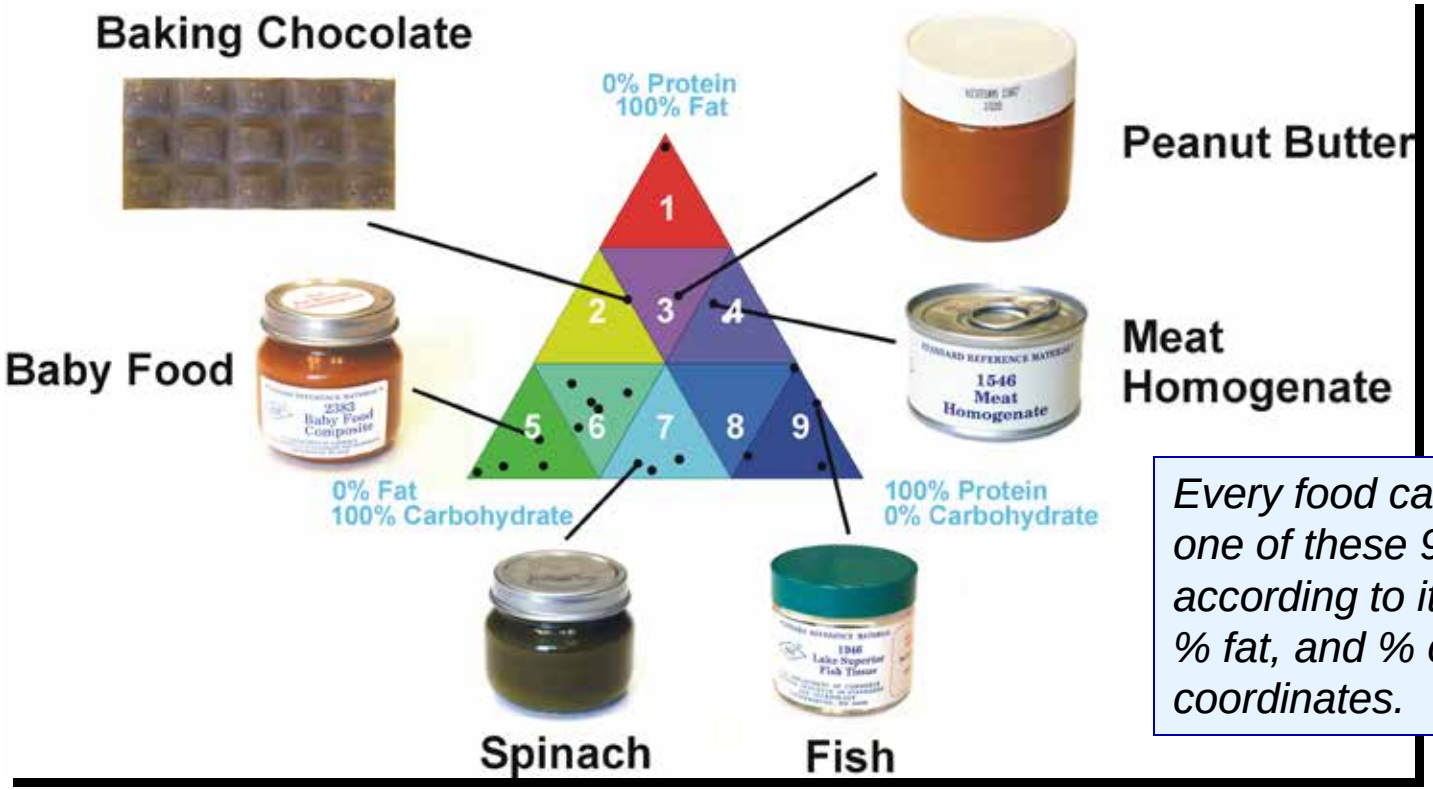
US Food and Drug Administration (FDA) Study on Nutrition Label Accuracy

US FDA sent 300 foods to a commercial reference laboratory to test accuracy of information on the nutrition labels of the food packages (1996)



SRMs for Nutrients and Contaminants in Food

Examples of Food-matrix Standard Reference Materials by Sector



Every food can be placed in one of these 9 sub-triangles according to its % protein, % fat, and % carbohydrate coordinates.

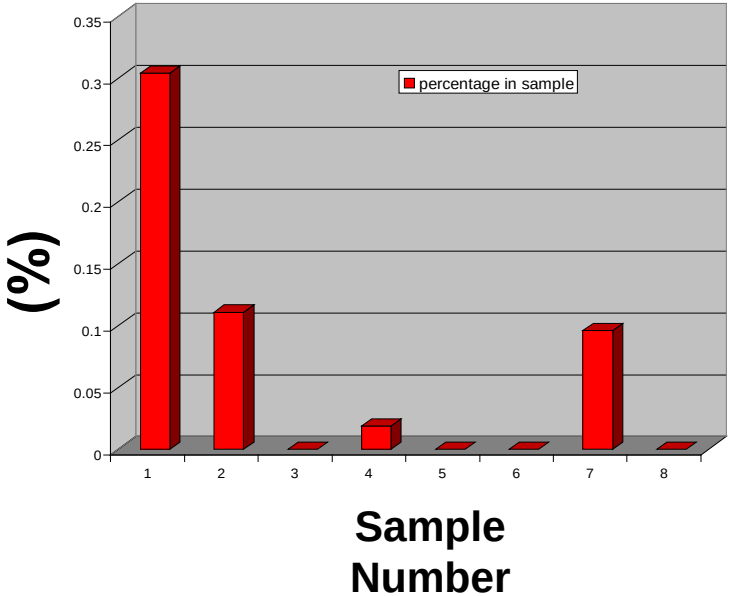
- Most food analysis labs provide analyses for **a similar set of analytes but in a wide range of food types** (matrices)
- Matrix differences and concentration differences are the primary measurement challenges.
- By providing **SRMs** certified for these common food analytes **in each of the major sections of the "food triangle"**, NIST covers most of the field of CRMs needed for the validation of these measurements of foods.

Dietary Supplements and Functional Foods

$100 billion Industry in North America alone and growing worldwide

Measurement Traceability increasingly required to:

- support label claims - truth in advertising
- **facilitate regulatory control and/or compliance**
- support public health and safety
- assess conformance with import/export requirements



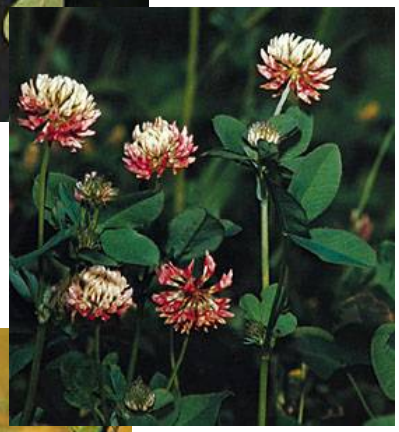
I. Khan, University of Mississippi

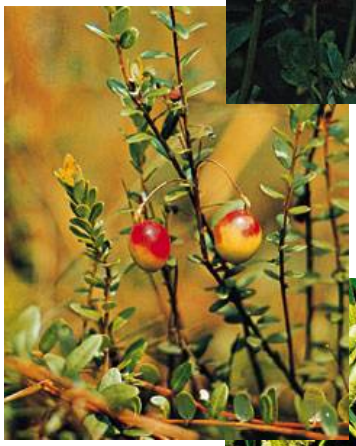
Eight commercial products sold as **Valerian Supplements** were analyzed in one Laboratory for valerenic acid content as shown below:

NIST is working with the National Institutes of Health's Office of Dietary Supplements and the US Food and Drug Administration to produce SRMs for:

Botanical Supplements

- **Ephedra**
  - Alkaloids
- **Green Tea**
  - Catechins
  - Caffeine
  - Theanine
- **St John's Wort**
  - Hypericin
  - Hyperforin
  - Flavonoids
- **Bitter orange**
  - Adrenergic amines
- **Soy, Kudzu, Red Clover**
  - Isoflavones
- ***Ginkgo biloba***
  - Gingkolides/Bilobalide
  - Flavonoid Aglycones
- **Saw Palmetto**
  - Fatty Acids
  - Phytosterols
- **Black Cohosh**
  - Triterpene glycosides
- **Cranberries**
  - Anthocyanins
  - Procyanidins
  - Organic acids
- **Blueberries, Bilberries**
  - Anthocyanins





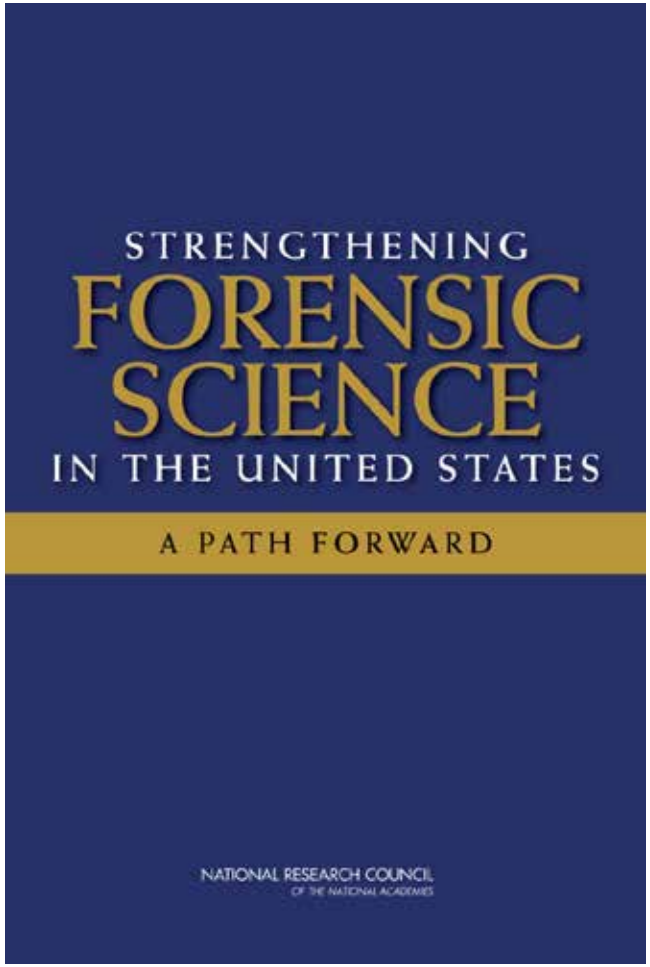
Forensics

- Crime Scene Investigations
- Standards for Drunk Driving Testing
- Drugs of Abuse in Urine and Hair
- Sports Medicine
- DNA-based Human Identification
- Explosives Detection
- **Estimating Drug use within the Population**

Helping Ensure the "Science" in Forensic Science

- Landmark forensics report by National Research Council of the National Academies
- Issued in Feb. 2009

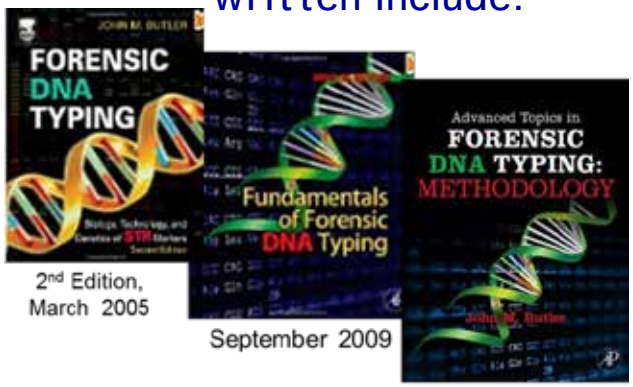
"With the exception of nuclear DNA analysis, no forensic method has been rigorously shown to have the capacity to consistently, and with a high degree of certainty, demonstrate a connection between evidence and a specific individual or source."



NIST Scientist named as Author with Highest-Impact in Legal Medicine & Forensic Science

NIST's John Marshall Butler has been identified as the world's number one "High-Impact" author in the area of Legal Medicine and Forensic Science during the period of 2001 to 2011.

In addition, textbooks he's written include:



2nd Edition, March 2005

September 2009

August 2011

High-Impact Authors in Legal Medicine & Forensic Science, 2001 to 2011

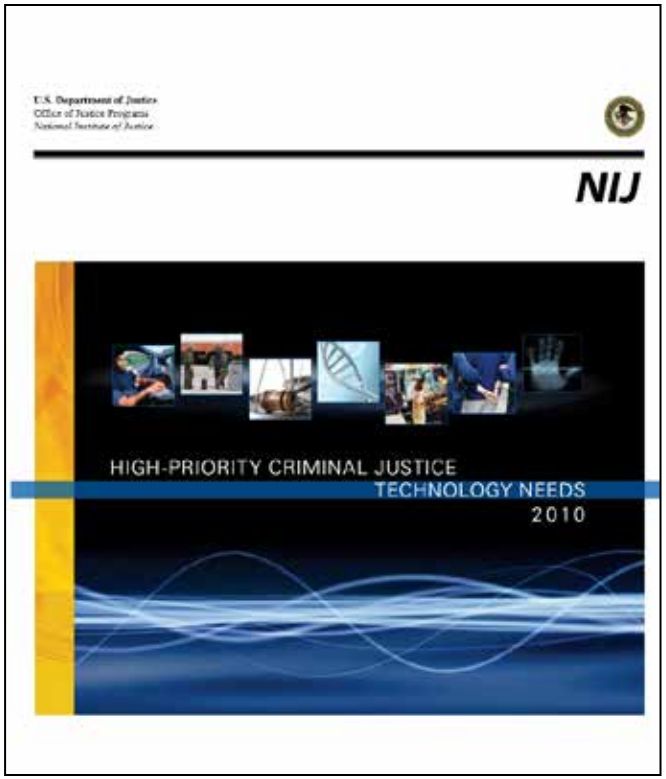
(Listed by citations per paper, of authors who published >= 20 papers)

Name	Institution	Papers	H-Index	Cites per paper
John M. Butler	Nat. Inst. of Standards & Technology, U.S.	36	17	27.8
Mechthild Prinz	Office of Chief Medical Examiner, NYC	24	14	26.0
Manfred Kayser	Erasmus University, Rotterdam	23	11	25.2
Peter Gill	University of Strathclyde, U.K.	39	17	23.1
Peter Vock	University of Bern	26	13	21.5
Lutz Roewer	Inst. Legal Med. & Forensic Sci., Berlin	36	14	21.3
Kathrin Yen	Ludwig Boltzmann Inst., Graz, Austria	24	13	20.7
Martin J. Sonnenschein	University of Bern	23	13	20.1
Peter M. Schneider	University of Cologne	44	17	19.8
Thomas J. Parsons	Int'l. Comm. on Missing Persons	30	11	18.5

(http://sciencewatch.com/ana/fea/11julaugFea/)

2010 US Dept. of Justice Report Identifies High-Priority Criminal Justice Technology Needs by Area

- **Confirming the Guilty and Protecting the Innocent**
- **Protecting the Public**
- **Ensuring Officer Safety**
- **Improving the Efficiency of Justice**
- **Enabling Informed Decision-making**



Examples include:

Need for improved capability to expand the information that can be extracted from traditional types of forensic evidence such as:

- Identification or characterization of:
  - Biological markers that may reveal more information about the source of biological evidence
  - new substances or chemical constituents of forensic importance
- Improved tools for examining aged, degraded, limited, damaged, inhibited or otherwise compromised DNA evidence
- **Tools to expand the utility of y-chromosome and mitochondrial DNA**
- Physical separation of cells or components in mixtures from two or more individuals or sources
- Tools that provide a quantitative measure/statistical evaluation of forensic comparisons such as in examination of documents, firearms, toolmarks, etc.

Metrology for Next-Generation DNA Sequencing

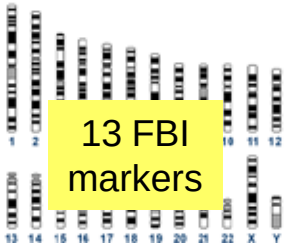

Daily News

Sunday, March 23, 2021

Crime Report

DNA evidence obtained from the crime scene indicated that the suspect is a Caucasian female with blue eyes, blond hair, height between 5'5" and 5'9" with a possible Nordic ancestry. Further analysis indicated that the victim may be closely related to the suspect.

Current Human Identification



Next-Generation DNA Sequencing has the potential to utilize the information from the entire genome for Human Identification

Would allow:

✔Externally visible traits

✔Biogeographical ancestry

✔Kinship analysis

✔Resolve DNA mixtures

- Current human identity (ID) tests provide a "DNA fingerprint" and the sex of an individual
- Using "Next Generation" DNA sequencing, we want to know ***"What does the perpetrator look like?"***

- NIST is developing the underpinning measurement science and standards to support next generation DNA sequencing
- Needed before users can rely on data
- Need to establish DNA sequence metrology
  - new concepts needed for traceability, uncertainty, validation

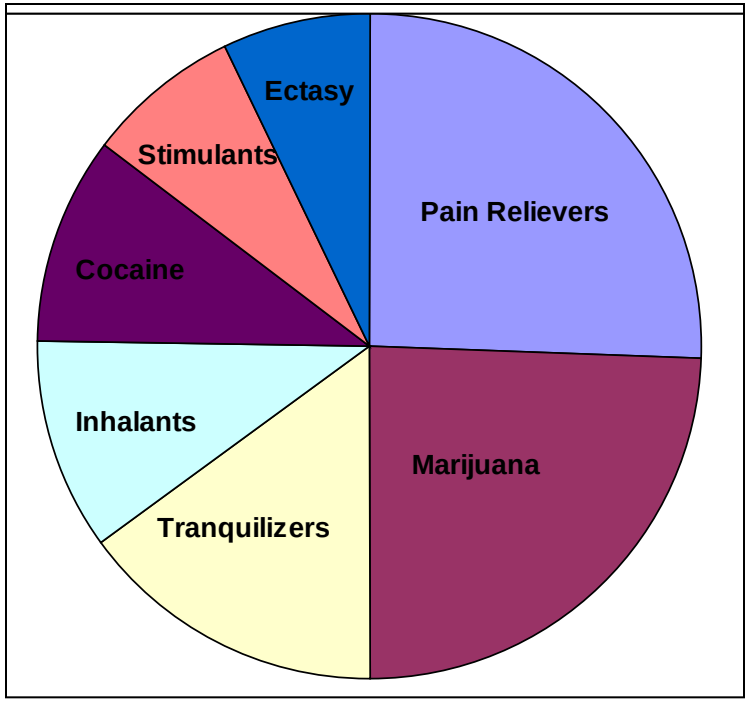
Customers in addition to legal community include: Biomedical Research, Pharmaceutical R&D, Personalized Medicine, Sequencing Technology Developers

Drugs of Abuse in the US

Scope of the Problem

- According to a 2005 survey on *Drug Use and Health: National Findings*:
  - **~22 million Americans aged 12 or older were classified as having a substance or drug dependency**

- Surveys, crime statistics, and production of drugs are typically used to estimate drug consumption rates

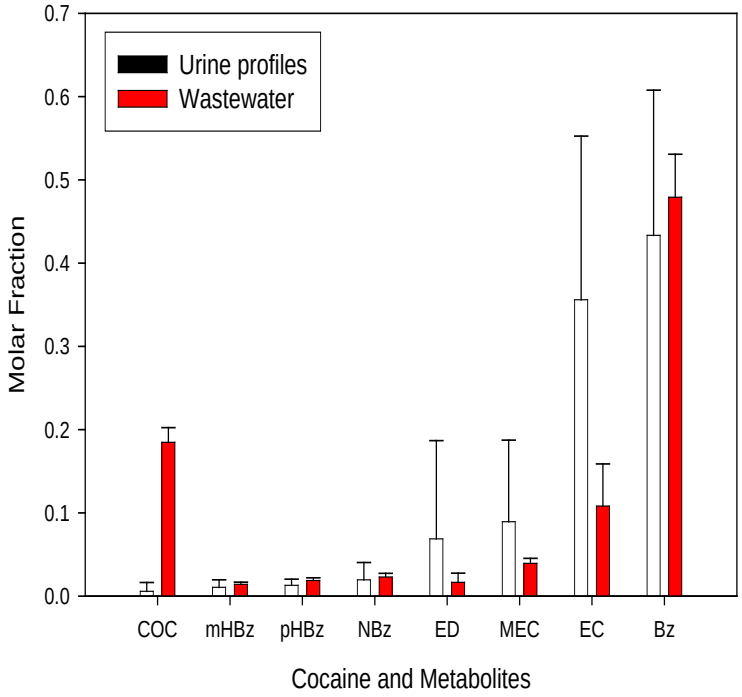


2005 Specific drug use among Americans 12 and older

Voluntary information may provide an underestimate of drug use

Wastewater Analysis as a Tool to Estimate Drug Use

- Urine is one of the most common matrices used for drug screening
- Wastewater provides an unbiased reservoir for drugs and drug metabolites excreted from humans in urine
- Illicit drug use at the community/metropolitan level may be estimated through chemical measurements of drugs and drug metabolites in wastewater
- Method is indirect, non-intrusive means to monitor drug usage within a population



Preliminary Results from Small U.S. City

- Cocaine
  - 12 metabolites
- Ecstasy
  - 3 metabolites
- Methamphetamine
  - Amphetamine
- OxyContin

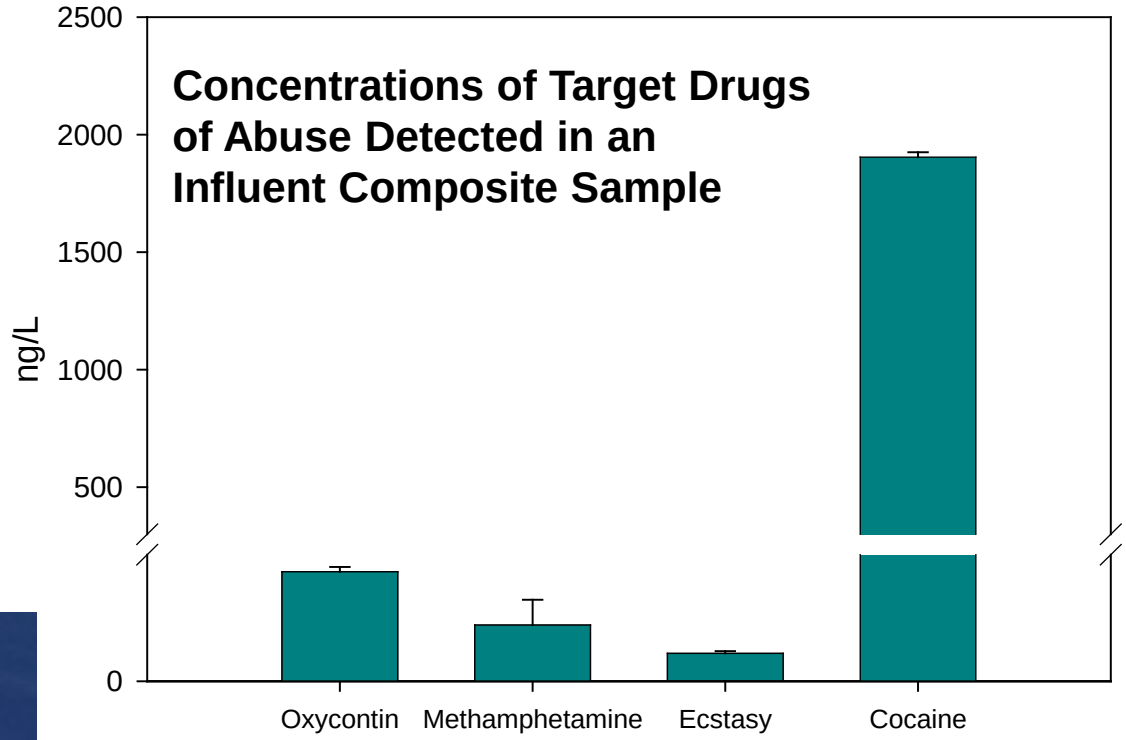


Photo Source:
www.lesliecreemla.co.uk/policing.asp

Metrology Program for Measurement of Materials Properties

pays significant dividends to a Nation's Economy and Quality of Life for its citizens through the underpinning of:

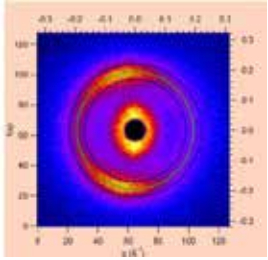
- **Informed design of materials with desired properties**
- Assessment of the properties, performance, and reliability of products
- Prediction of reliability, "length of service", and performance properties over time

As well as in:

- Transactional Efficiency in National and International Trade
- Innovation and Industrial Competitiveness
- Construction and Physical Infrastructure

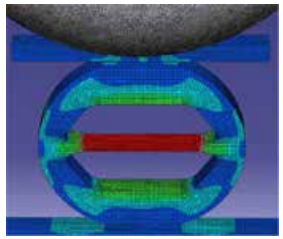
Measurements of Materials Properties: Diverse types

- **Composition and structure measurements**
  - Sub-nanometer electronic scale to the sub-millimeter microstructural scale
  - Use of all forms of probing radiation
  - Techniques: *diffraction, reflectivity, scattering, spectroscopy, imaging*



SANS structural mapping

- **Mechanical property measurements**
  - Sub-nanometer to macroscopic scale
  - Modes of mechanical deformation: *elastic, plastic, fracture, viscous*



Theta platform for mechanical testing

- **Magnetic property measurements**
  - Includes magnetization, hysteresis, domain motion

Magnetic domain imaging microscope

- **Thermal property measurements**
  - Includes thermodynamics and transport
- **Chemical property measurements**
  - Includes equations of state, solubility, chemical transport and reactions
- **Electrical and optical property measurements**

Automotive Lightweighting

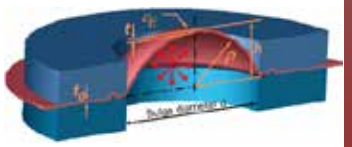
Industry Goal - CAFE of 39 MPG by 2016

Auto industry needs to *incorporate advanced lightweight alloys in automobiles to help meet increased fuel efficiency requirements*

Industry Needs

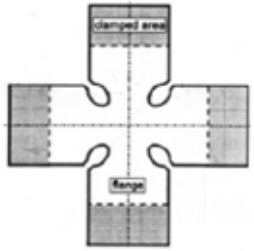
- Data and models the auto industry uses to optimize the design and manufacture of traditional metal parts are not applicable.
- So, US industry is spending $10 million+ on trial-and-error testing to optimize manufacturing protocols for these advanced alloys

- Material property data/models/tests are needed that are applicable for these materials. E.g.,:
  - Methods to assess "strain" on a material under manufacturing conditions, i.e., stretches and bends in multiple directions simultaneously and not just one at a time
  - predicting springback, when a part changes shape after it it has been formed
  - determining the crashworthiness of lightweight alloy components



NIST:

- developing methods to measure multiaxial metal forming that are more representative of actual manufacturing conditions
  - NIST materials deformation data now is being used directly by industry to more efficiently develop forming protocols for lightweight alloys



- led the development of ASTM 2462: Springback Cup Test, recently adopted for industry use
- developing high-rate deformation tests to better assess performance in crashes

Emerging Industrial Sector: Organic and Flexible Electronics Manufacturing

Industry Need

- Flexible, polymer-based electronic devices are compatible with versatile solution processing methods with potential in displays, photovoltaics, sensors, logic, lighting, and radio-frequency identification tags. Their market is predicted to be $10 to $30 B globally by 2015.
- Manufacturing is hindered by poor reproducibility & highly process-dependent properties.

NIST program focuses on:

- Developing an integrated suite of nondestructive measurement methods to evaluate organic-based electrical devices and tie both the electrical performance and interfacial morphology of the active molecules in the device to their chemical structure, fabrication methods, and processing parameters.
- Providing the measurement link for the structure - processing - performance paradigm will rationally accelerate product development, enable standard measurements, and provide a basis for quantitative comparisons

NIST, e.g.,

- Has provided this emerging industry sector with measurements to help understand why selected organic semiconductors are high-performers (as the charge mobility of Merck's pBTTT vs. P3HT).
- Provided measurements that illuminated the impacts of thermal treatments and coating methods on the materials structure & device performance of organic photovoltaics.

Manufacturing Renewable Polymers

The $100B US plastics industry want to replace petroleum based materials with bio-based, degradable alternatives to produce high-quality commodity and specialty polymers.

Industry Need

- Bio-based polyesters are one of the fastest growing polymer markets, but replacement of toxic catalysts with efficient well-controlled processes remain a key challenge to long-term, large scale manufacturing of these materials

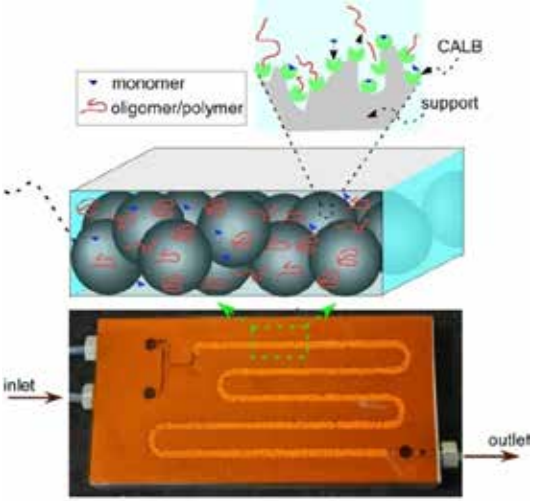
Objectives

- Quantitative characterization of polymerizations of bio-based feedstocks via enzyme catalysis
- Models, separation protocols and reference materials that support reliable manufacturing of well-defined bio-based polymers with functional main chains

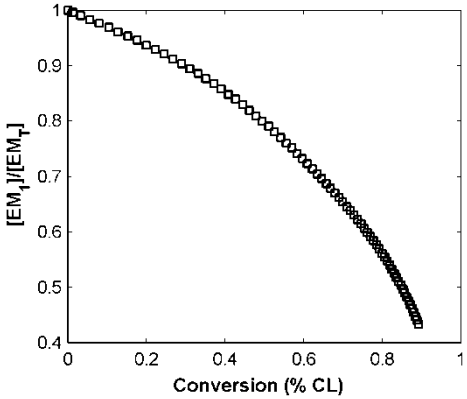
Accomplishments

- Microfluidic platforms that assess the efficiency of enzyme catalysis of polyesters in flow reactors
- In-situ Raman probes for measuring (co)monomer conversions
- New kinetic model for lipase catalyzed polymerizations captures entire mass distribution

PLA-based compostable packaging



Microfluidic measurement platform



Kinetic models for bio-based polymer synthesis help industry better design polymer manufacturing processes

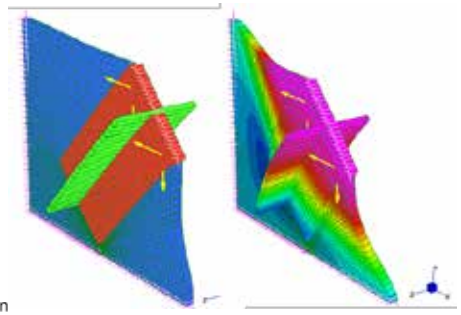
Partners: NYU-poly POLYTECHNIC INSTITUTE OF NYU VT

Physical Infrastructure

NIST is: *Providing the measurement tools that enable the nation to prioritize the repair and replacement of aging physical infrastructure (e.g., bridges, pipelines, nuclear facilities)* ***and to manufacture more resilient infrastructure components.***

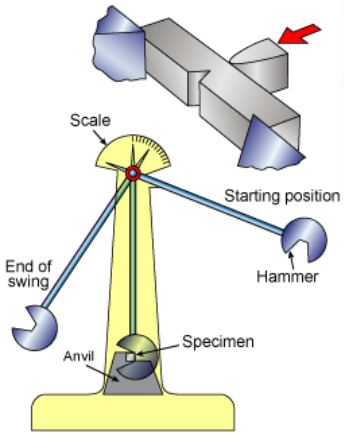
Industry Needs

- Science-based tools to guide material selection and joining approaches
- Standards for ensuring material quality
- Standards for inspecting performance during use
- Data and predictive models to assess material response (e.g., extreme conditions)



NIST Accomplishments and Impact

- NIST SRMs underpin quality control testing for $10B of construction steel annually
- NIST data and test methods are used by pipeline industry to ensure safe use of high-strength steels and new weld materials
- NIST calibrations establish baseline performance for sensors used to detect changes in materials and joints
- NIST data, measurement tools, and models predict lifetimes for new construction materials



Ideally, a National Metrology Institute (NMI)

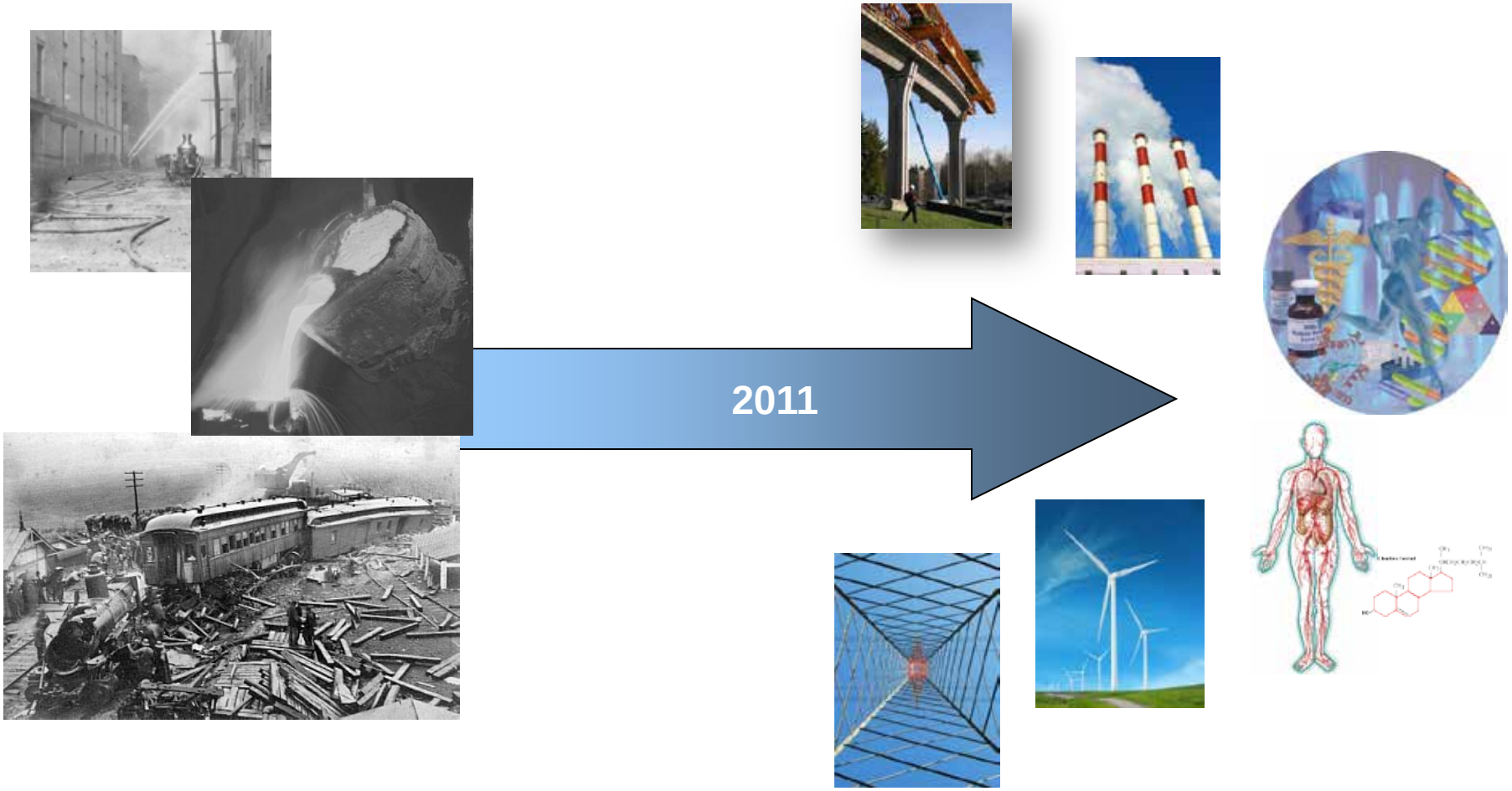
- **Is seen as its country's ultimate reference point for measurements and standards** *to support industry, science and technology enterprise, national defense, national and international commerce, and quality of life for its citizens*

- **Has some enabling legislation in support of this role that is recognized within its country**

- **Has its programs well-aligned with its country's strategic priorities**

More and more,

in addition to supporting the realization of SI units, **NIST, PTB and other leading NMIs are focusing a significant portion of their research and measurement services activities on *Quality of Life, Economic ,and Social Sustainability***



Thanks for Your Attention

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Questions and Comments?