

**USP Enzyme Workshop
July 8 - 9, 2009
The Spalding Auditorium
USP Headquarters, Rockville, Maryland**

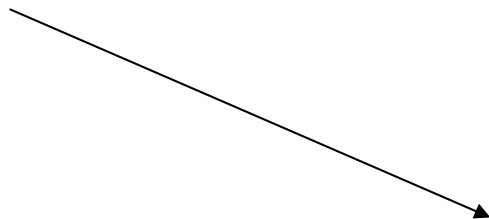
Role of the Compendia and Standards

**William Koch, Ph.D., FACB
Chief Metrology Officer
U.S. Pharmacopeial Convention**

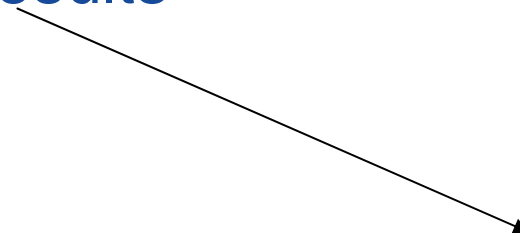


Role of the Compendia and Standards

Good Measurements



Good Results



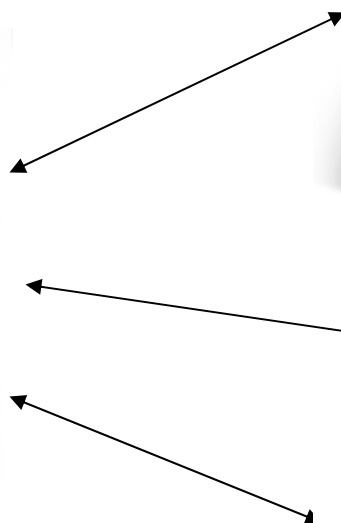
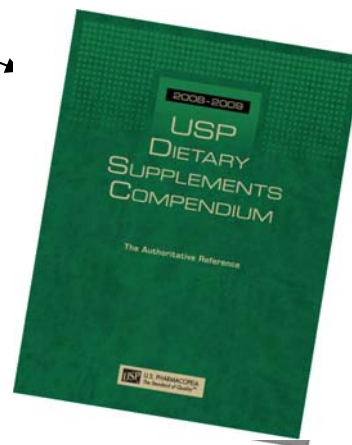
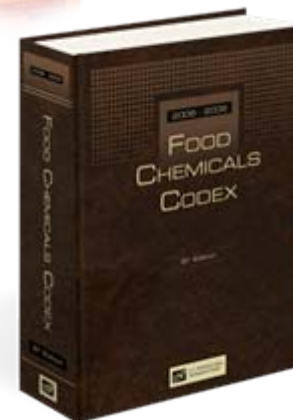
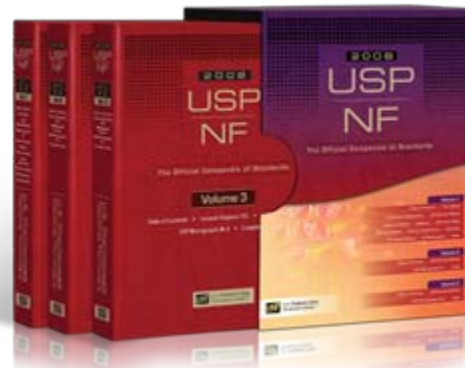
Good Decisions



Articles of Metrology

Materials

Procedures





Philosophy of Metrology

***... if you cannot measure it,
your knowledge is meagre and
unsatisfactory***

Lord Kelvin (1883)

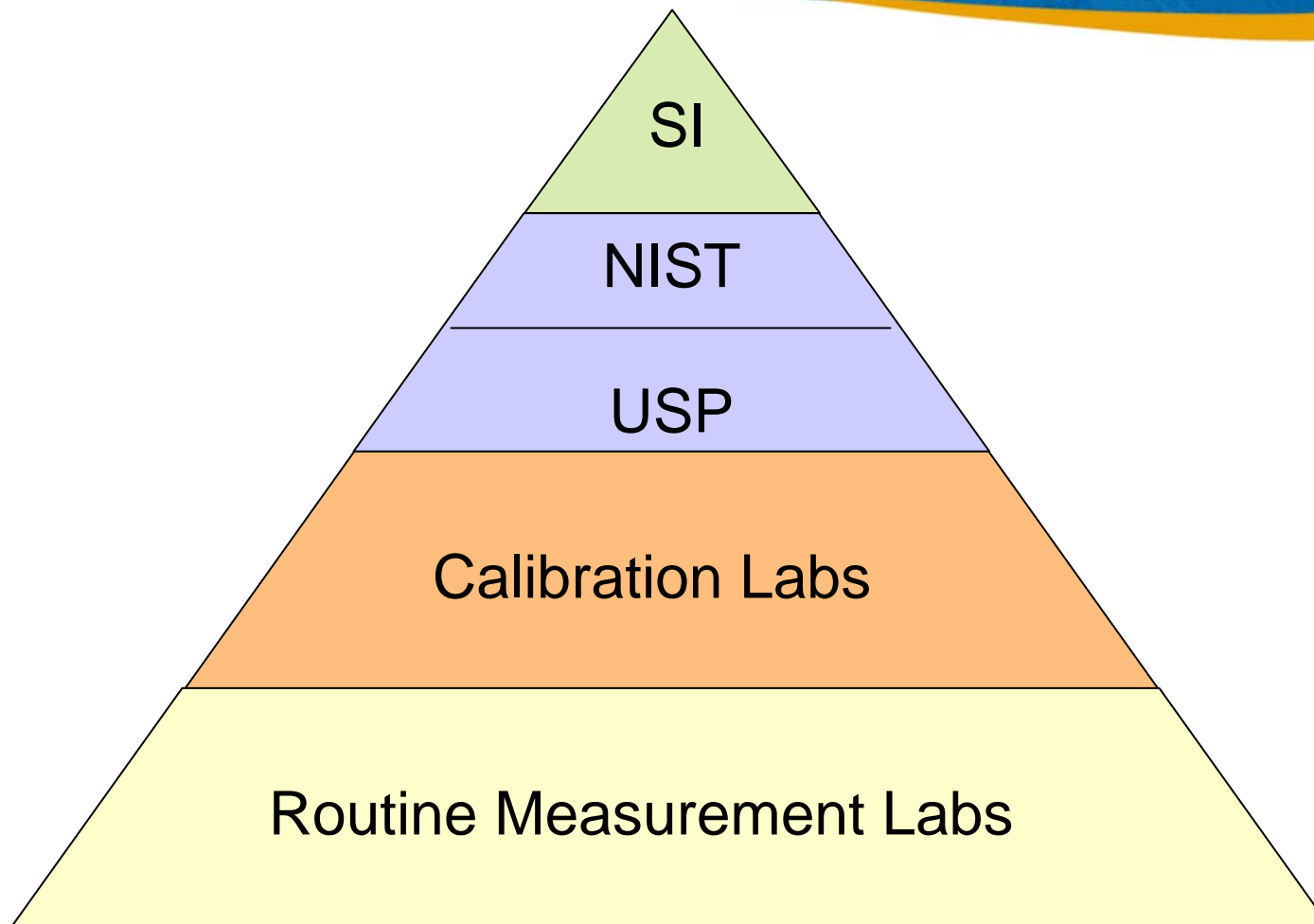


Metrology

- The **Science of Measurement** embraces both experimental and theoretical determinations at any level of uncertainty in any field of Science and Technology.
 - **Fundamental metrology** includes the establishment of measurement units, new measurement methods, realization of measurement standards and the transfer of traceability.
 - **Applied metrology** concerns the application of measurement science to manufacturing, ensuring the suitability of measurement instruments, their calibration and quality control of measurements.
 - **Legal metrology** concerns regulatory requirements of measurements and measuring instruments.



Hierarchy of Metrology





SI Base Units

The base units of the International System are listed below, which relates the base quantity to the unit name and unit symbol for each of the seven base units.

Base quantity	SI base unit	
Name	Name	Symbol
length	meter	m
mass	kilogram	kg
time, duration	second	s
electric current	ampere	A
thermodynamic temperature	kelvin	K
amount of substance	mole	mol
luminous intensity	candela	cd



Thermodynamics

vs.

Kinetics



Selected SI Coherent Derived Units

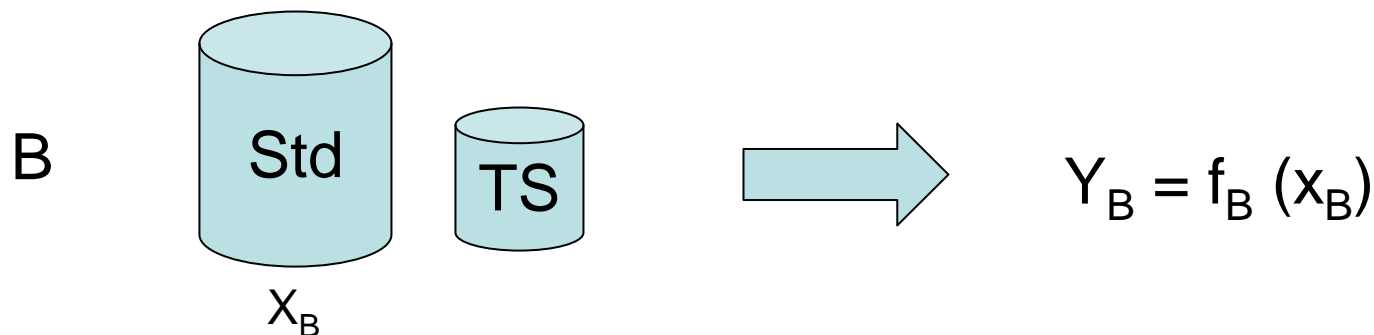
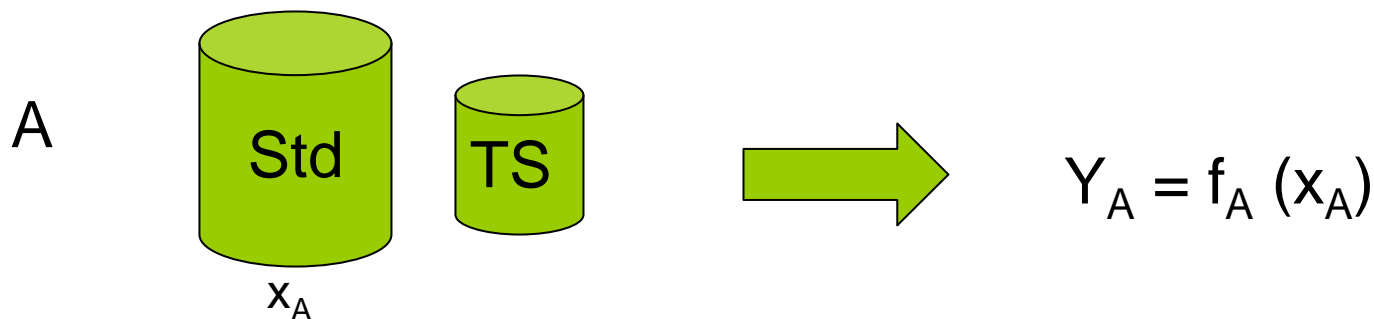
Derived quantity	SI coherent derived unit ^(a)			
	Name	Symbol	Expressed in terms of other SI units	Expressed in terms of SI base units
frequency	hertz ^(d)	Hz		s ⁻¹
force	newton	N		m kg s ⁻²
pressure, stress	pascal	Pa	N/m ²	m ⁻¹ kg s ⁻²
electromotive force	volt	V	W/A	m ² kg s ⁻³ A ⁻¹
electric conductance	siemens	S	A/V	m ⁻² kg ⁻¹ s ⁻³ A ²
Celsius temperature	degree Celsius ^(e)	°C		K
catalytic activity	katal	kat		s ⁻¹ mol

- (a): The SI prefixes may be used with any of the special names and symbols, but when this is done the resulting unit will no longer be coherent.
- (d): The hertz is used only for periodic phenomena, and the becquerel is used only for stochastic processes in activity referred to a radionuclide.
- (e): The degree Celsius is the special name for the kelvin used to express Celsius temperatures. The degree Celsius and the kelvin are equal in size, so that the numerical value of a temperature difference or temperature interval is the same when expressed in either degrees Celsius or in kelvins.



**All
Measurements
are
Comparisons**

Lab A and Lab B each make measurements of Property “Y” in a test sample using different standards.



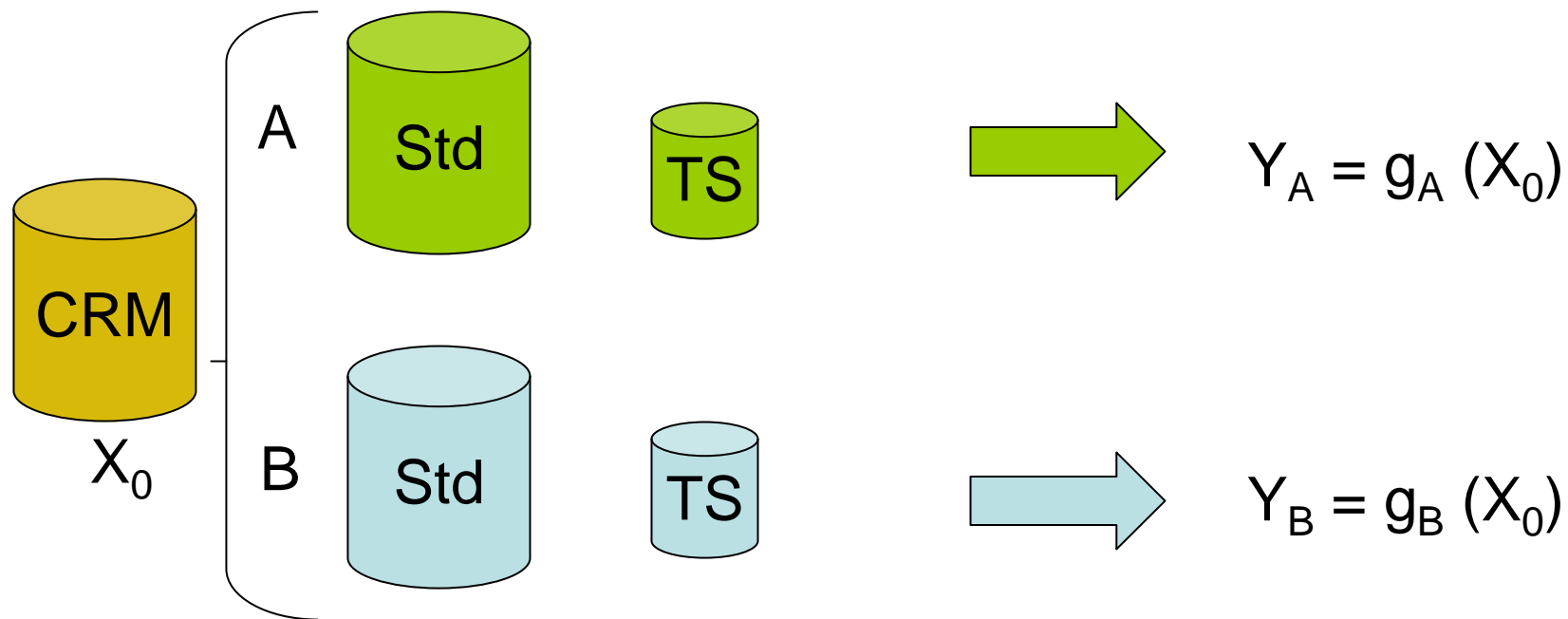
Where Std is a standard and TS is test sample

There is no basis to compare Y_A and Y_B

Traceability

Lab A and B make measurements

Y_A and Y_B are now traceable to the same reference, X_0



Where *Std* is a standard and *TS* is test sample



Traceability

Metrological Traceability

- **property of a measurement result whereby the result can be related to a reference through a documented unbroken chain of calibrations, each contributing to the measurement uncertainty**

(from International Vocabulary of Metrology - Basic and General Concepts and Associated Terms (VIM): 3rd Edition 2007)

- **thereby allowing/enabling consistency and comparability of measurement results across time, space, and technology.**



ISO 18153:2003 (E)

In vitro diagnostic medical devices –
Measurement of quantities of biological
samples – Metrological traceability of
values for catalytic concentration of
enzymes assigned to calibrators and
control materials



ISO 18153:2003 (E)

Scope

This International Standard specifies how to assure the metrological traceability of values assigned to calibrators and control materials are those provided by the manufacturers as part of , or to be used together with, in vitro diagnostic medical devices



ISO 18153:2003 (E)

Definitions

- **catalytic activity (Z_E):** property of a component corresponding to the catalysed substance rate of conversion of a specified chemical reaction, in a specified measurement system
- **catalytic-activity concentration / catalytic concentration (b_E):** catalytic activity of a component divided by volume of the original system
- **commutability of a material:** closeness of agreement between the mathematical relationship of the measurement results obtained by two measurement procedures for a stated quantity in a given material, and the mathematical relationship obtained for the quantity in routine samples

Structure

- The coherent derived SI/ unit of measurement “katal per cubic metre” or “mole per second cubic metre”, symbolized kat m^{-3} ($= \text{mol s}^{-1} \text{m}^{-3}$) shall be the top of any calibration hierarchy for catalytic concentration of an enzyme when a primary reference measurement procedure is available.



ISO 18153:2003 (E)

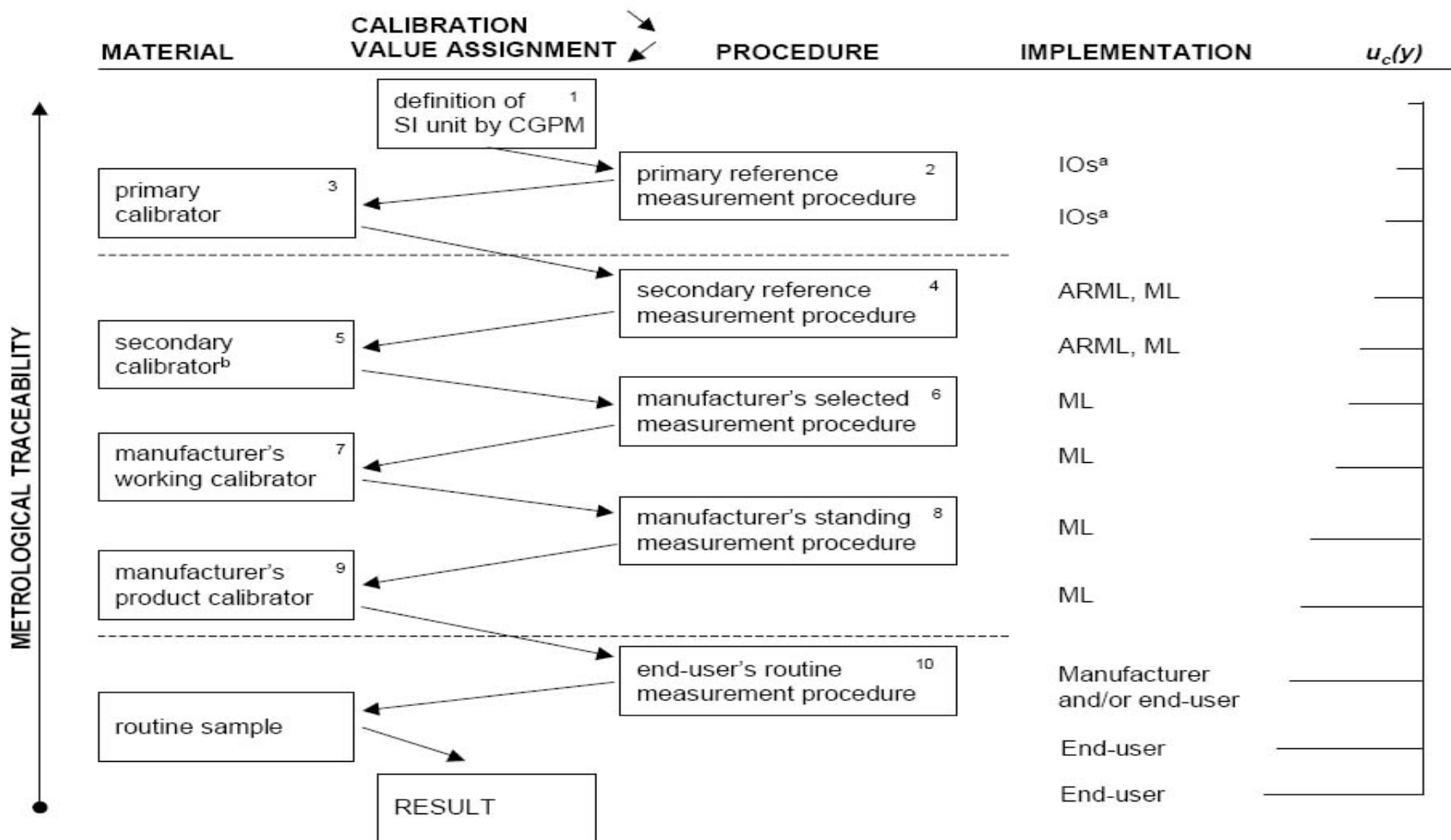
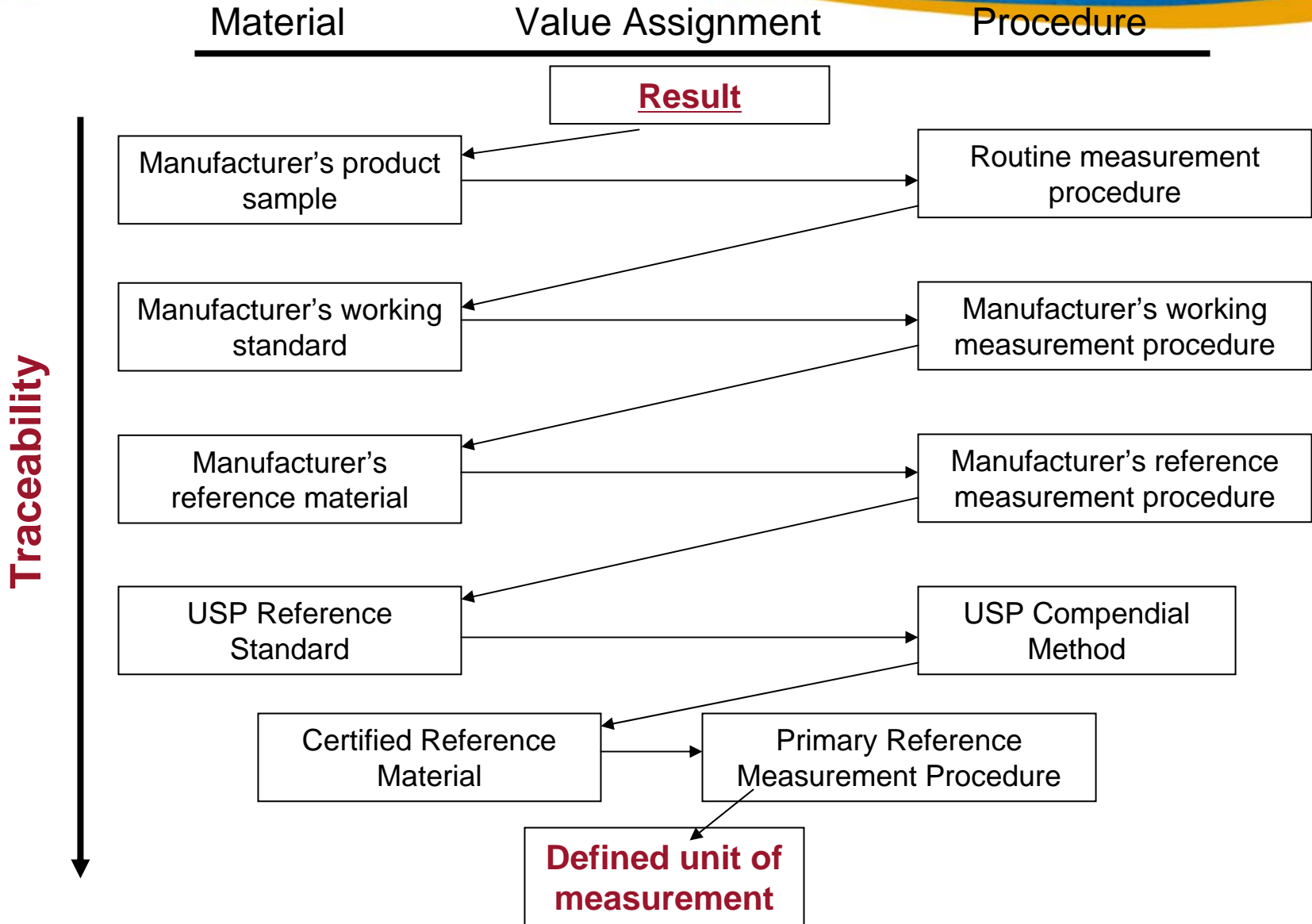


Figure – Extensive calibration hierarchy and metrological traceability to *S*/



Metrology: Applied to Pharmaceuticals





Uncertainty

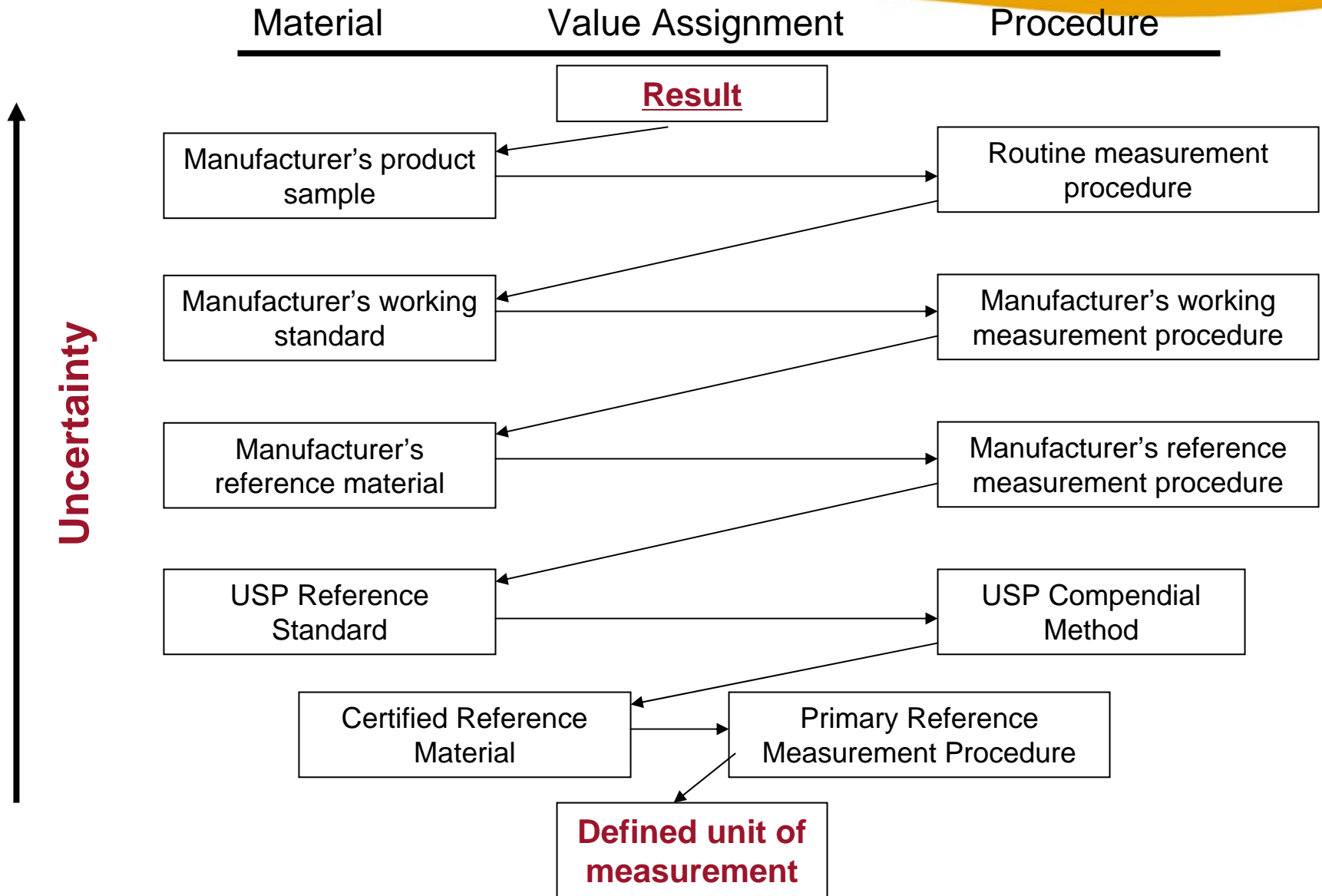
Measurement Uncertainty

Non-negative parameter characterizing the dispersion of the quantity values being attributed to a measurand, based on the information used.

(from International Vocabulary of Metrology - Basic and General Concepts and Associated Terms (VIM): 3rd Edition 2007)



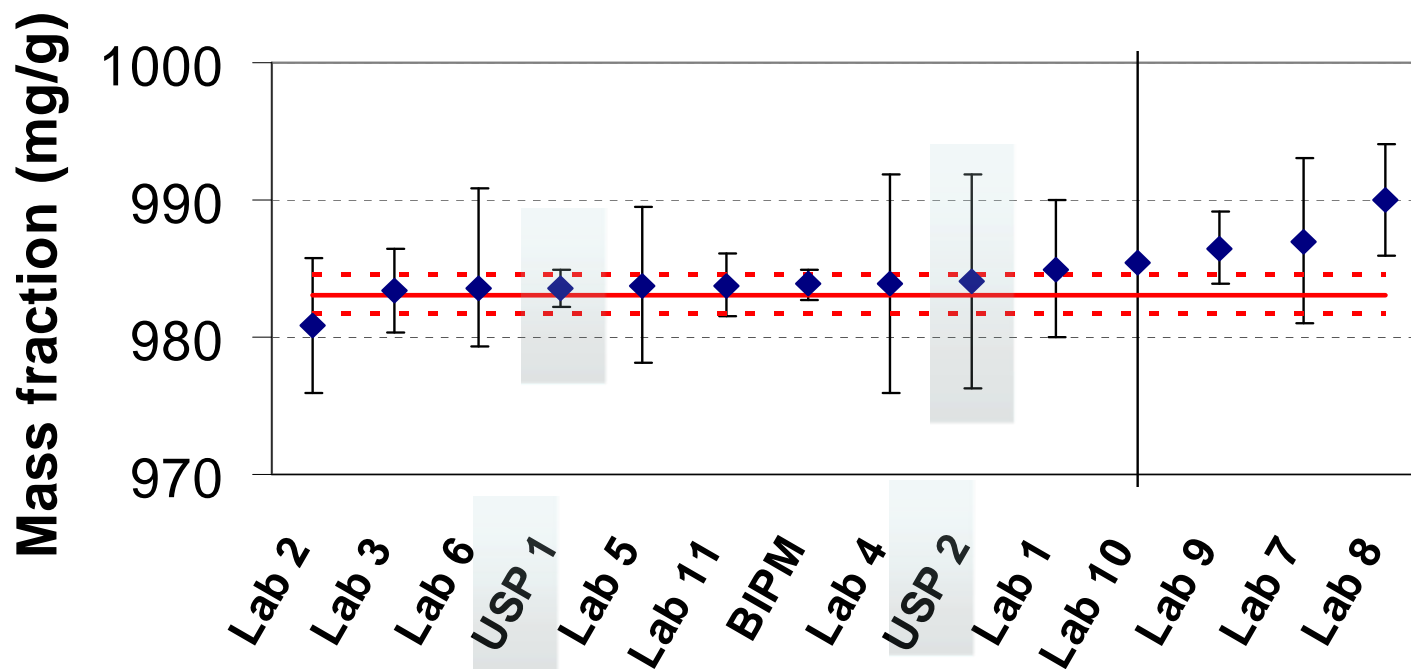
Metrology: Applied to Pharmaceuticals





Results - CCQM-P20.e.2

Theophylline content of CCQM-P20.e.2



Gravimetric Reference Value = 983.1 ± 1.5 mg/g



USP's Standards Program

USP establishes **documentary and reference standards** for medicines, food ingredients, and other health care products.

These standards are used by regulatory agencies and manufacturers of pharmaceuticals, over-the-counter drugs, dietary supplements, and food ingredients,

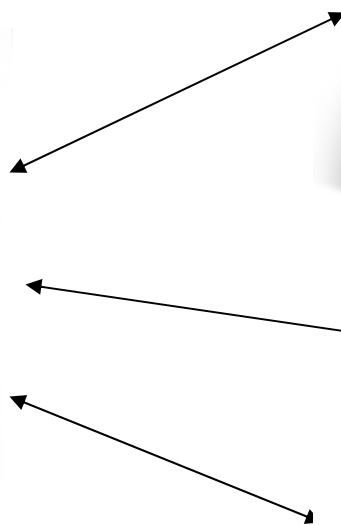
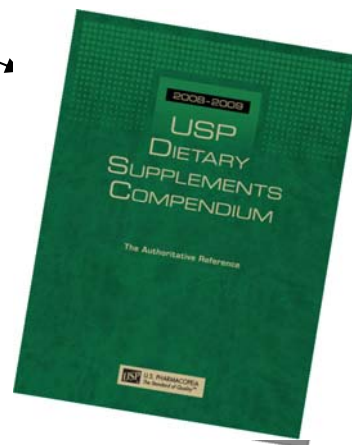
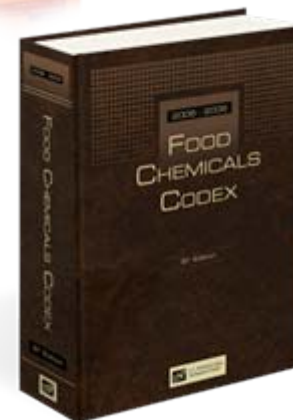
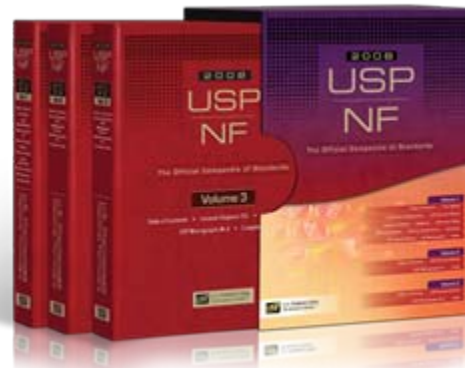
to ensure that these products are of the appropriate **identity, strength, quality, and purity.**



Articles of Metrology

Materials

Procedures





The Metrological Challenge for USP

- **Changing Types and Matrices**
 - Impurities and Degradants
 - Adulterants and Contaminants
 - Biologics and bio-pharmaceuticals
 - Generic biologics: Increased need for biologics reference standards
 - Calibrators, performance standards (dissolution reference standards tablets), others
 - Foods: dietary supplements, food additives
 - Bio and enzymatic assays
- **Changing Science**
 - Measurement science is advancing
 - Measurement technologies are advancing
 - QbD, PAT (On-line, In-line, At-line)
 - Demands for higher accuracy and lower uncertainty



The Challenges for Pharmaceutical and Biopharmaceutical Measurements

- **Establish a metrologically-sound and internationally recognized traceability system**
- **Develop Certified Reference Materials and Performance-Based Methods**
- **Replace the myriad of bio-assay units with an SI-based system**



The Challenge for Bio-Measurements

"In physical science, the first essential step in the direction of learning any subject is to find principles of numerical reckoning and practicable methods for measuring some quality connected with it.

Lord Kelvin (1883)

Thank you