JCTLM

Accurate results
for patient care

Traceability and harmonization; powerful tools for trueness of laboratory results

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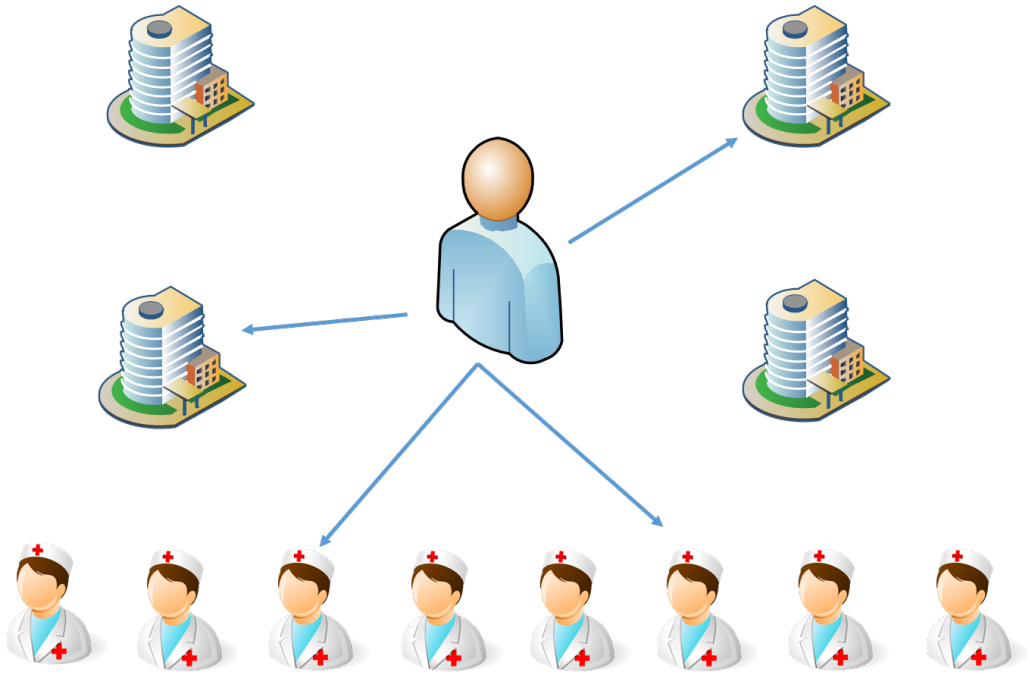
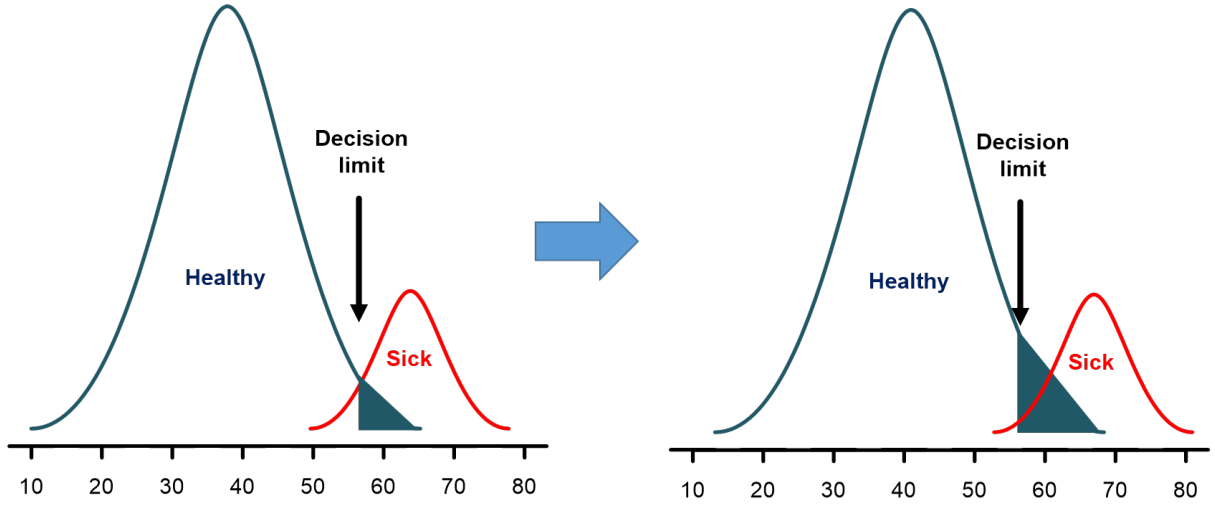
JCTLM Working Group for Traceability: Education and Promotion (WG-TEP)

Importance of consistent results measured in the same sample geographically and over time

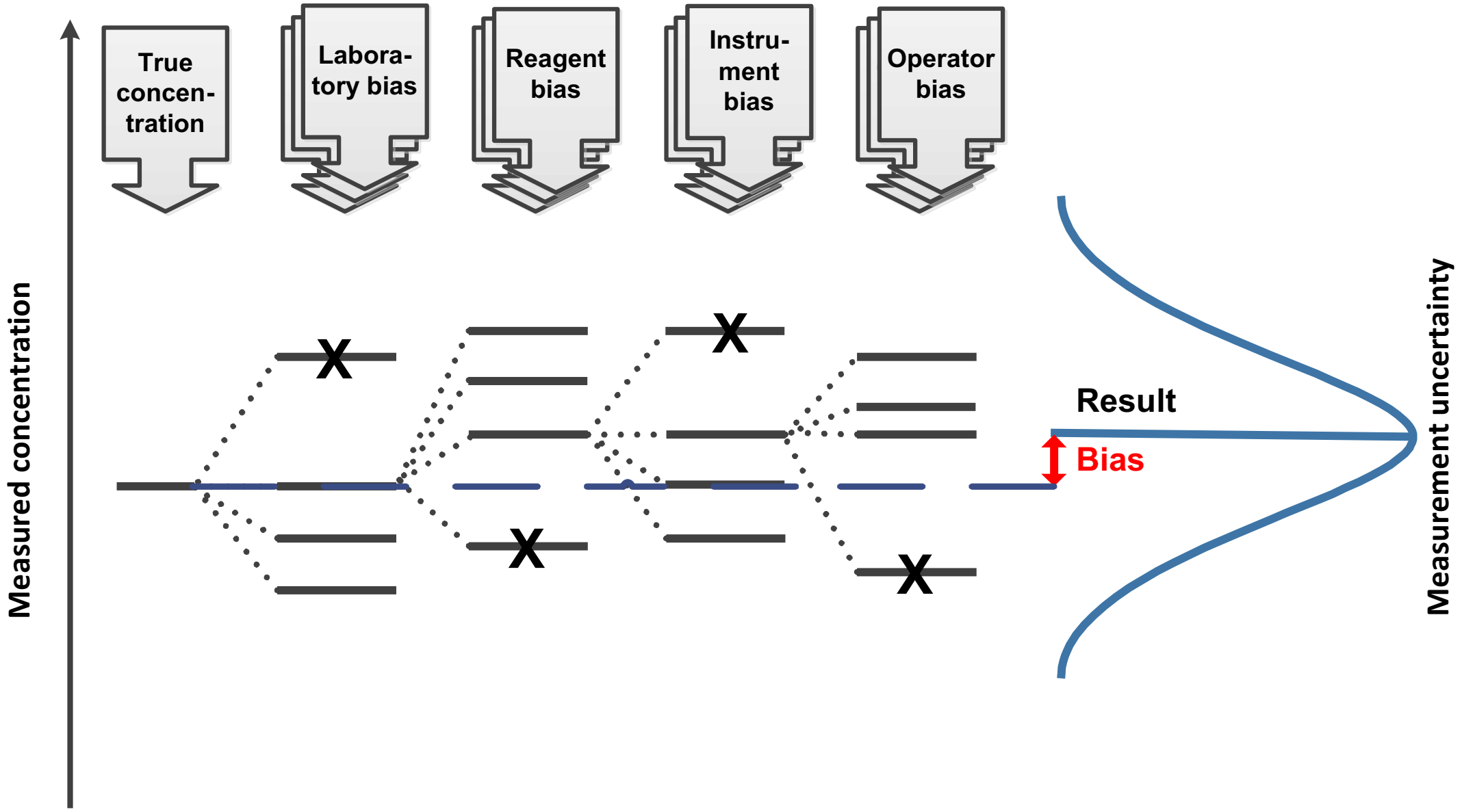


Patient perspective



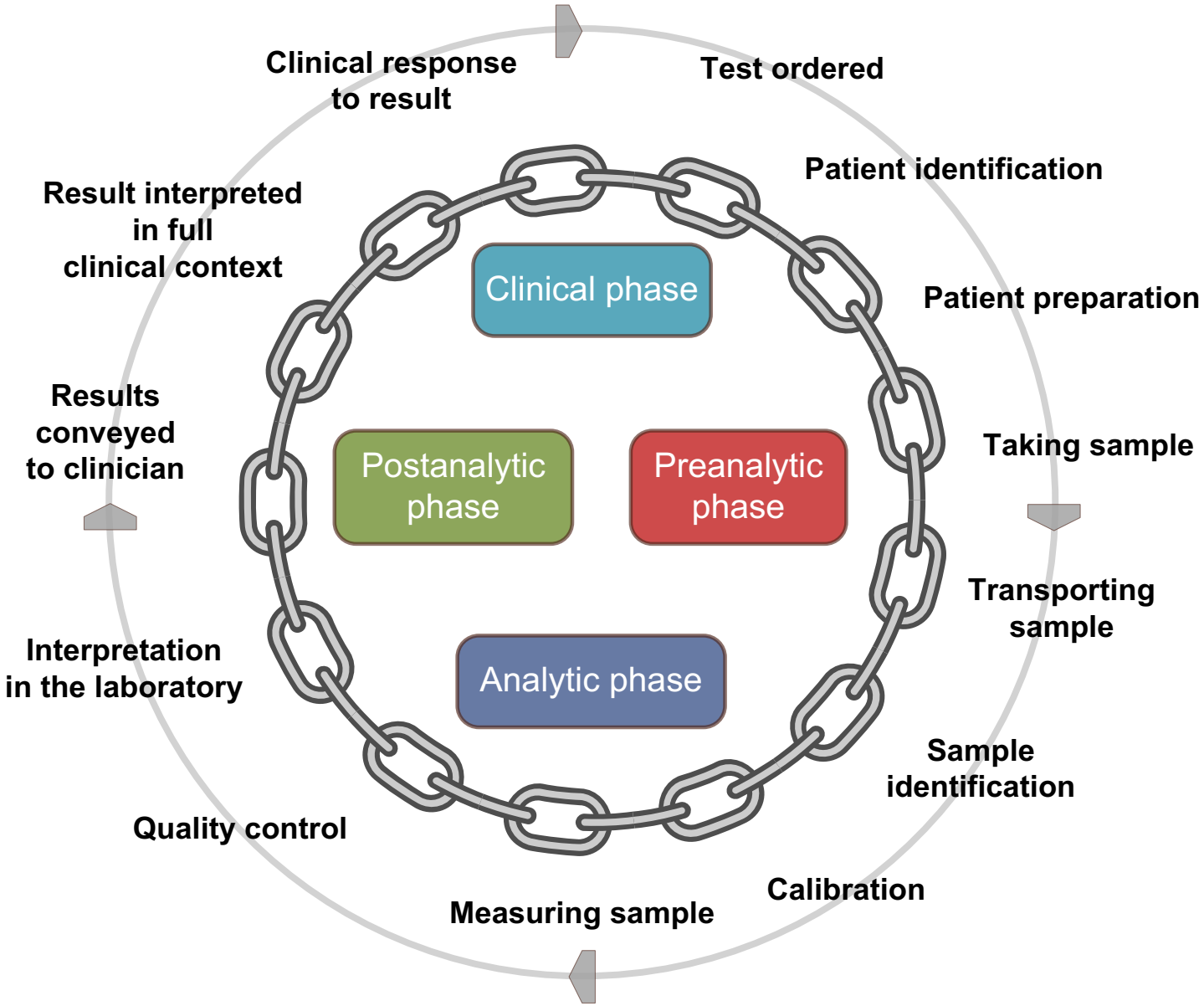
A bias of + 5 units means that healthy persons are diagnosed sick

From the perspectives of healthcare-, research-, reference intervals-, decision limits and guidelines


True concen-tration
Labora-tory bias
Reagent bias
Instru-ment bias
Operator bias
Measured concentration
Result
Bias
Measurement uncertainty

If different measurements systems result in different results for the same patient sample

- Physicians and patients will become confused
- Clinical guidelines will become less useful
- Suboptimal treatments and monitoring practices may be implemented



The total testing chain

- Several standards and guidelines are available for the preanalytic, postanalytic and clinical phases
- Their increased implementation is in the process of substantially improving the medical value of measurement results in laboratory medicine

Standardization

Metrological standardization

- Implementing and developing measurement **standards** and **reference measurement procedures** in order to achieve comparability and interchangeability of laboratory results amongst a multitude of measurement systems

Standardization in general

- Quality systems
- Concepts, terms and codes for information exchange
- Preanalytical procedures
- Postanalytical procedures

Traceability

- If something is traceable, you can find out where it came from, where it has gone, when it began or what its cause was
- Metrological traceability is **the property of a measurement result** which allows measurements made under different conditions (e.g. at different times, by different people, in different locations, using different measurement procedures) to be compared in a meaningful way

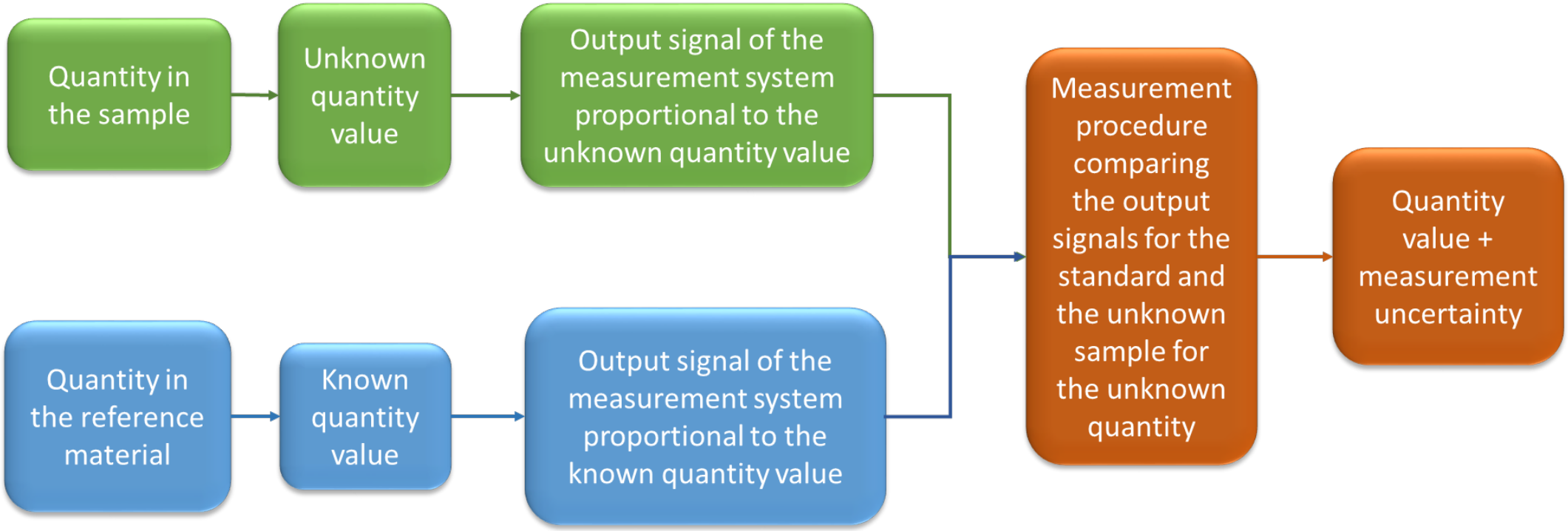
Types of traceability

- Traceability to SI
- Traceability agreed by convention
  - International conventional calibrator (e.g. WHO)
    - Calibrator with a value that is not traceable to SI
    - The assigned value of the calibrator is based on international agreement
  - International conventional reference measurement procedures
    - Yields values that are not traceable to SI, but the values obtained are agreed as reference values by international agreement

Kind of quantity

- **We do not directly measure the molecule of interest** but rather rely on a physiochemical property, “kind of quantity”, that sufficiently characterizes the molecule for the intended purpose of measurement, for example, absorbance of light at a certain wavelength, elution time from a chromatographic column, immunologic reactivity etc.

Measuring means comparing



Measurand – quantity inteded to be measured

Output signal - quantity subject to measurement

Ratio measurement

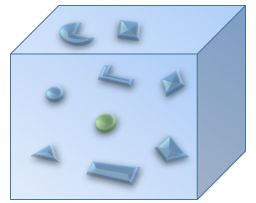
Measurement result

Comparing in chemistry

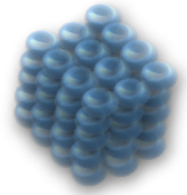
- Based on physical properties
- Prone to “influence quantities”

Influence quantities 1(2)

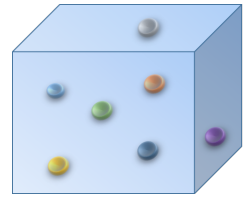
- The presence of “matrix factors”



- Inability to produce the substance in a pure form that can be weighed



- Molecular heterogeneity, e.g. transferrin, LH, FSH, TSH

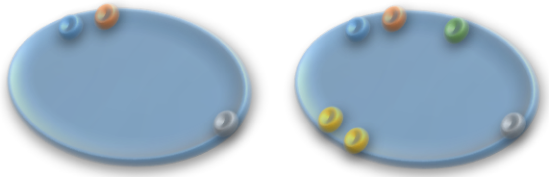


- Detection of different epitopes

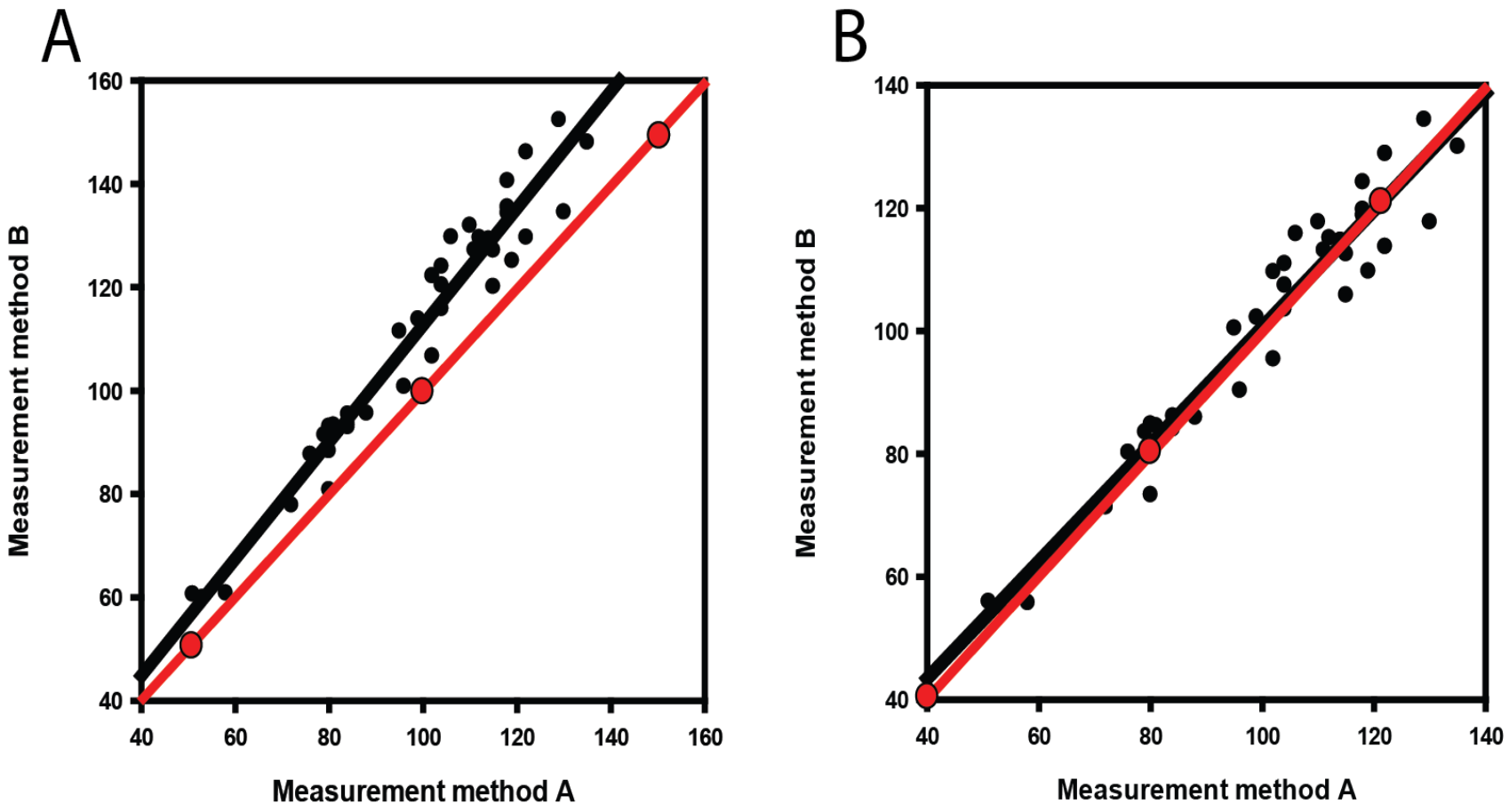
Influence quantities 2(2)

- Lack of knowledge of which epitopes of molecules are medically most relevant, e.g. most substantial biological activity or best diagnostic properties

- Changes in posttranslational modification of molecules e.g. LH and FSH during the ovarial cycle

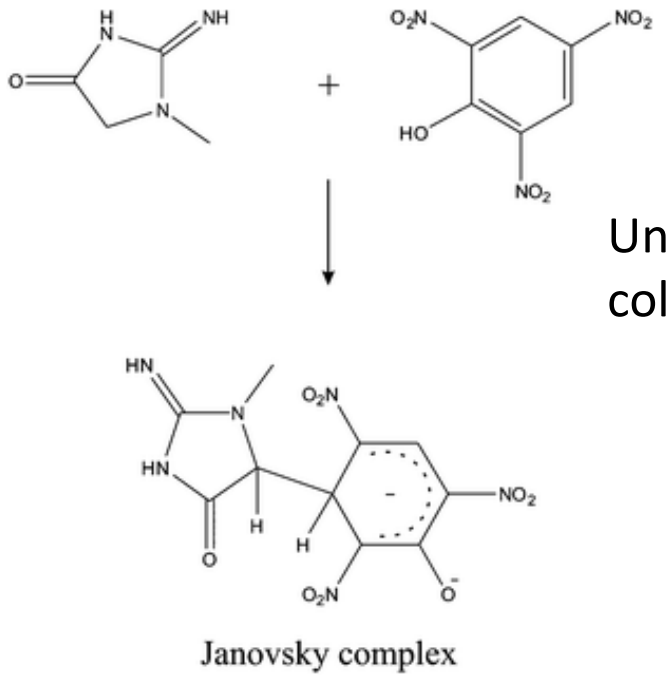


Commutability

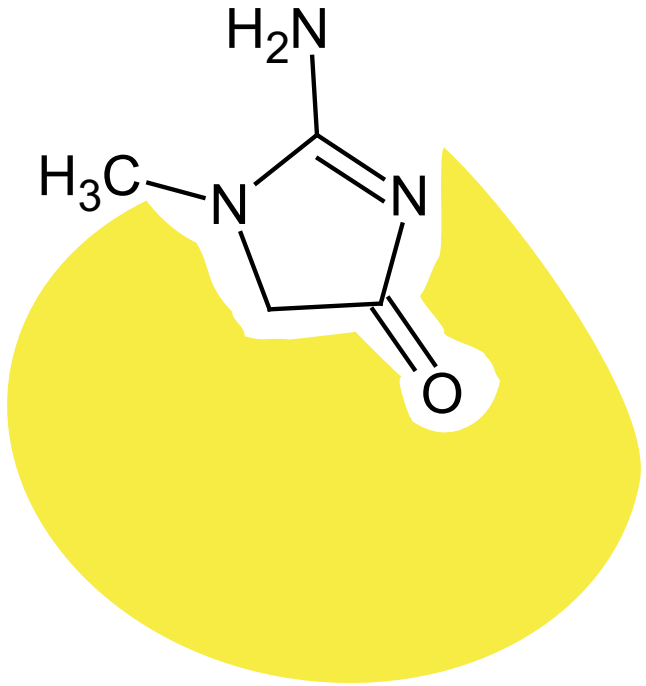


Selectivity VIM 3 - 4.13

”Property of a measuring system used with a measurement procedure, whereby it provides measured quantity value for one or more such that the values of each measurand are independent of other measurands or other quantities in the phenomenon, body, or substance being investigated.”



Unselective color reaction

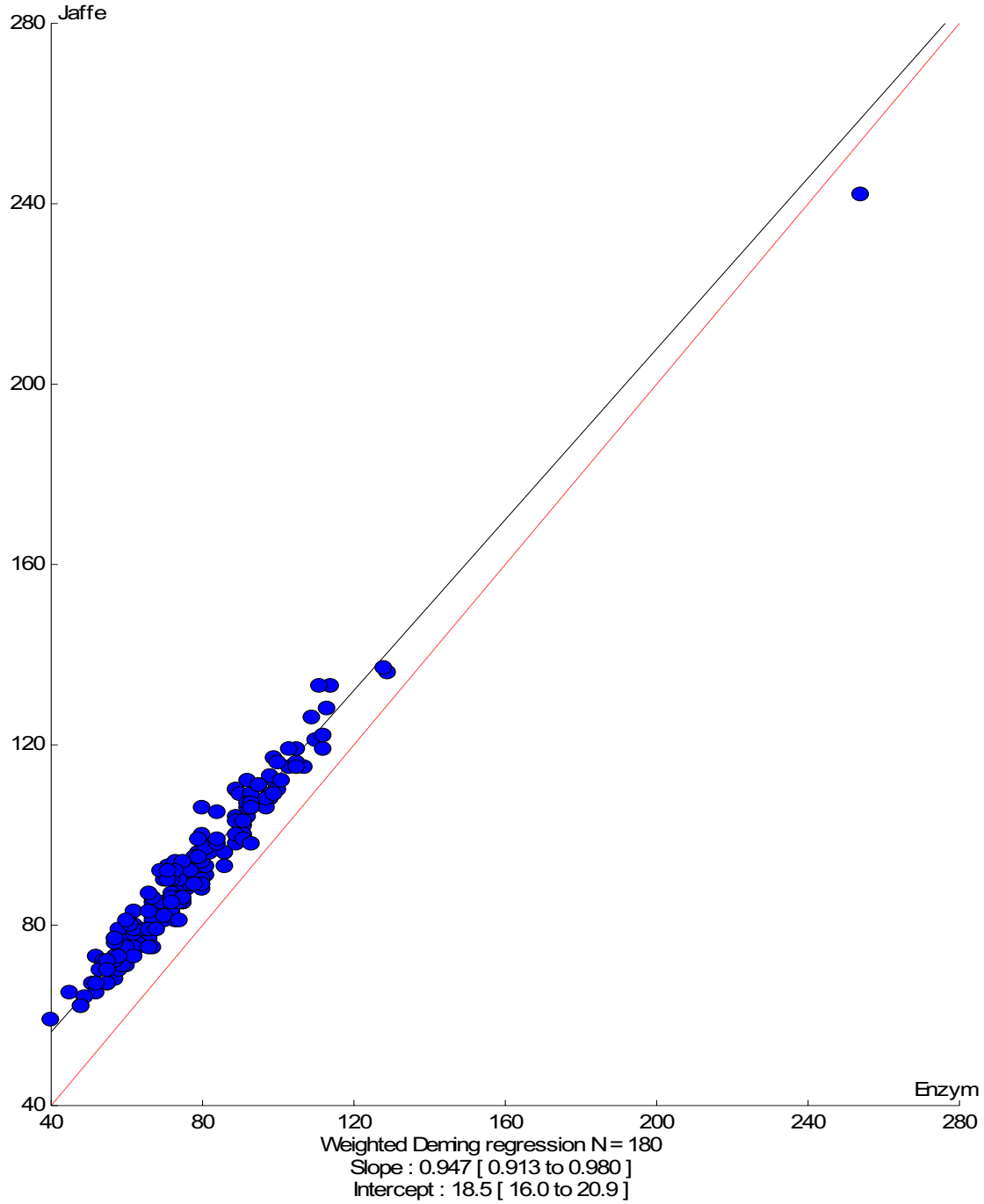


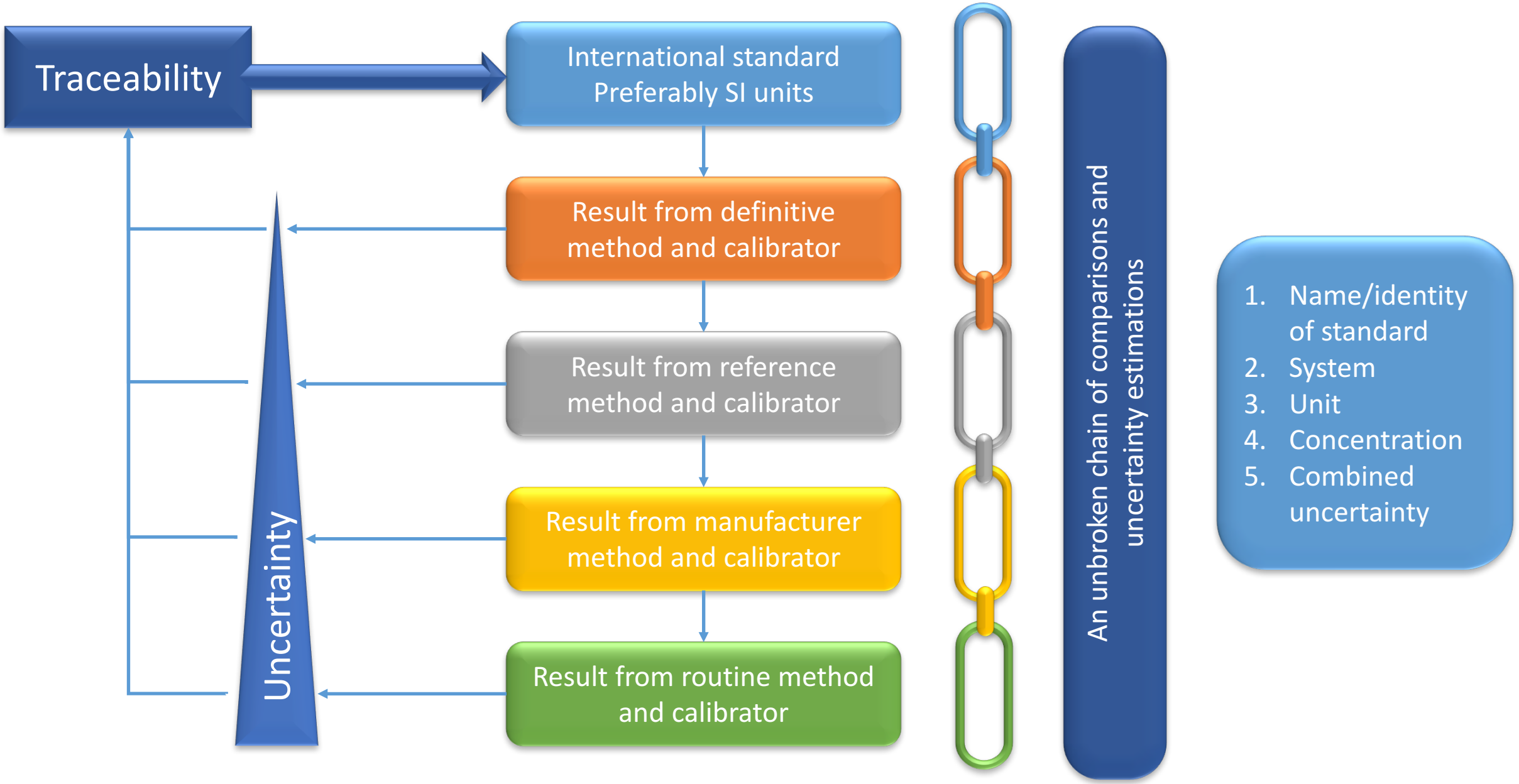
Selective enzymatic reaction

Comparison of the concentration of creatinine in 180 plasma samples measured using Jaffe and enzymatic methods

Jaffe = 0.947 * Enzymatic + 18.5

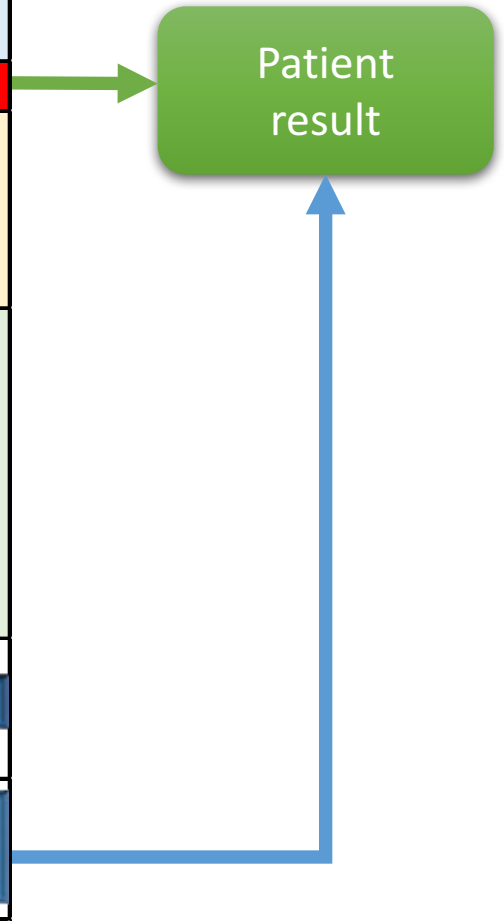
Enzymatic = Jaffe/0.947 – 18.5




Traceability
International standard
Preferably SI units
Result from definitive method and calibrator
Result from reference method and calibrator
Result from manufacturer method and calibrator
Result from routine method and calibrator
Uncertainty
An unbroken chain of comparisons and uncertainty estimations
1. Name/identity of standard
2. System
3. Unit
4. Concentration
5. Combined uncertainty

Commutability of the materials

Material	Primary reference	Secondary reference	Working calibrator	Product calibrator	Patient sample
	Commutable?	Commutable?	Commutable?	Commutable?	Commutable!
Measurement procedure	Primary reference measurement	Secondary reference measurement	Manufacturers measurement		Routine measurement in a clinical laboratory
Provider	BIPM, National metrology institutes, accredited reference laboratories	National metrology institutes, accredited reference laboratories	Manufacturers laboratory		End user
Uncertainty for commutable material					
Uncertainty for noncommutable material					



Success stories in standardization in laboratory medicine

- Molecules with simple molecular structures, LC/GC MS, ion-selective electrodes
- Standardization of methods for measuring enzymatic activity
- Enzymatic methods for measuring substances earlier measured by non-specific colorimetric procedures (e.g. creatinine)
- Cholesterol
- Glycated hemoglobin
- Carbohydrate-deficient transferrin

Harmonization

- Equivalence of measurement results among different routine measurement procedures over time and space according to defined analytical and clinical performance goals
- Any process that enables the establishment of equivalence of reported values produced by different measurement procedures for the same measurand

Standardization and harmonization

- Harmonization encompasses standardization and also addresses those tests that can’t be calibrated by traceability to a reference measurement procedure
- Standardization is preferable to harmonization, but it is not always an option even when an internationally accepted calibrator is available. It is preferable due to its traceability to primary reference materials and primary reference measurement procedures

Harmonization has a broader scope than standardization

- Quality systems, e.g. ISO standards
- Concepts, terms, unit of measurement and coding systems
- Preanalytical procedures
  - Patient preparation
  - Specimen collection and handling
- Harmonizing measurement results
- Interpretation of results in medical contexts
- Reference intervals

Comparability and interchangeability of medical laboratory results

- Medical laboratory results should be comparable in time and space across the globe enabling unequivocal diagnosis and monitoring of treatment results
- Multitude of guidelines, standards (ISO), directives (EU IVD directive) and authorities (FDA) govern measurement systems and practices in medical laboratories. These are unfortunately only partially harmonized or unequivocal
  - The EU IVD directive e.g. does not clarify which reference measurement system should be used to fulfil its requirements
  - Organizations at the pinnacle of metrology, lack legal authority

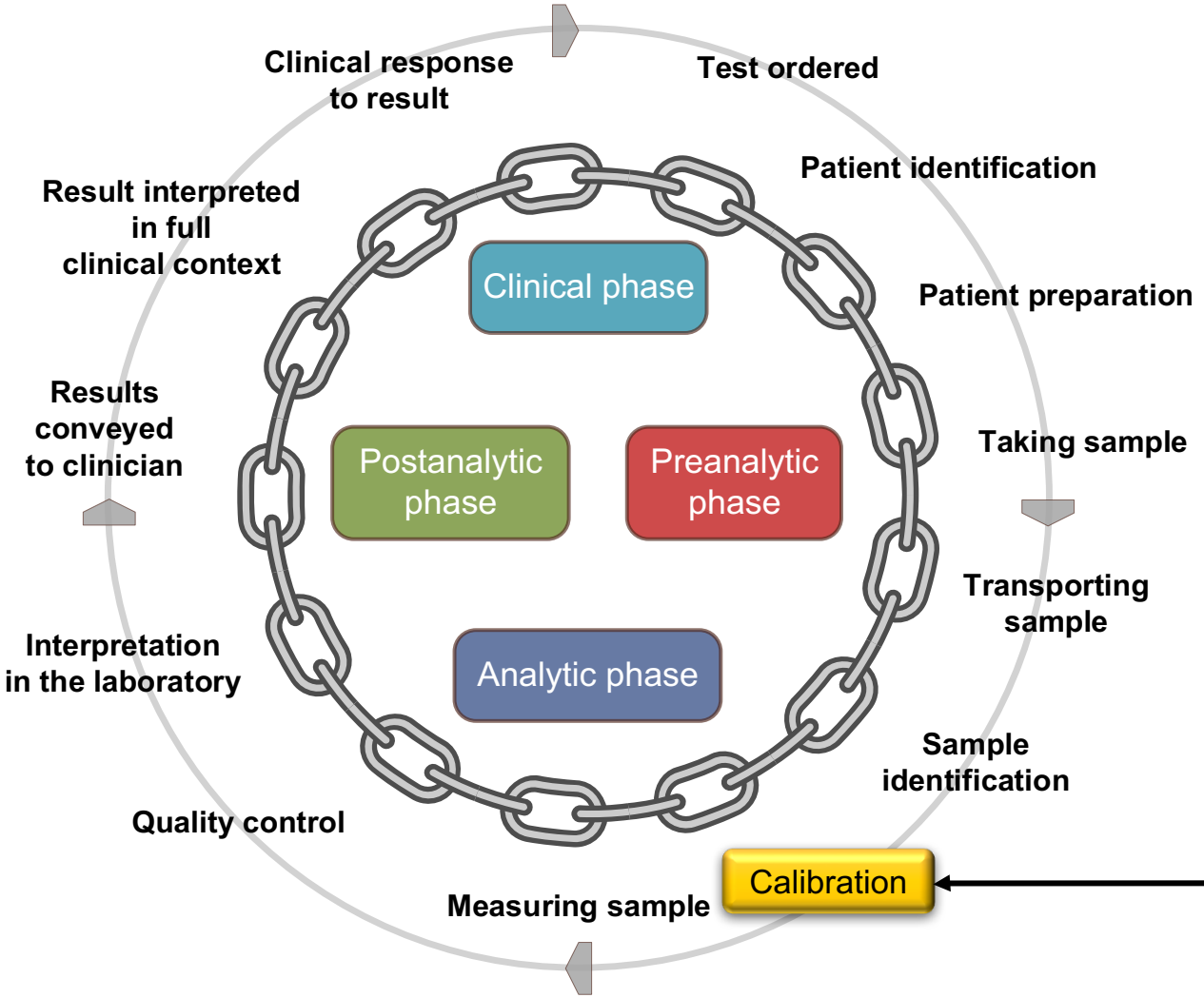
Harmonization strategies 1(2) (Greenberg)

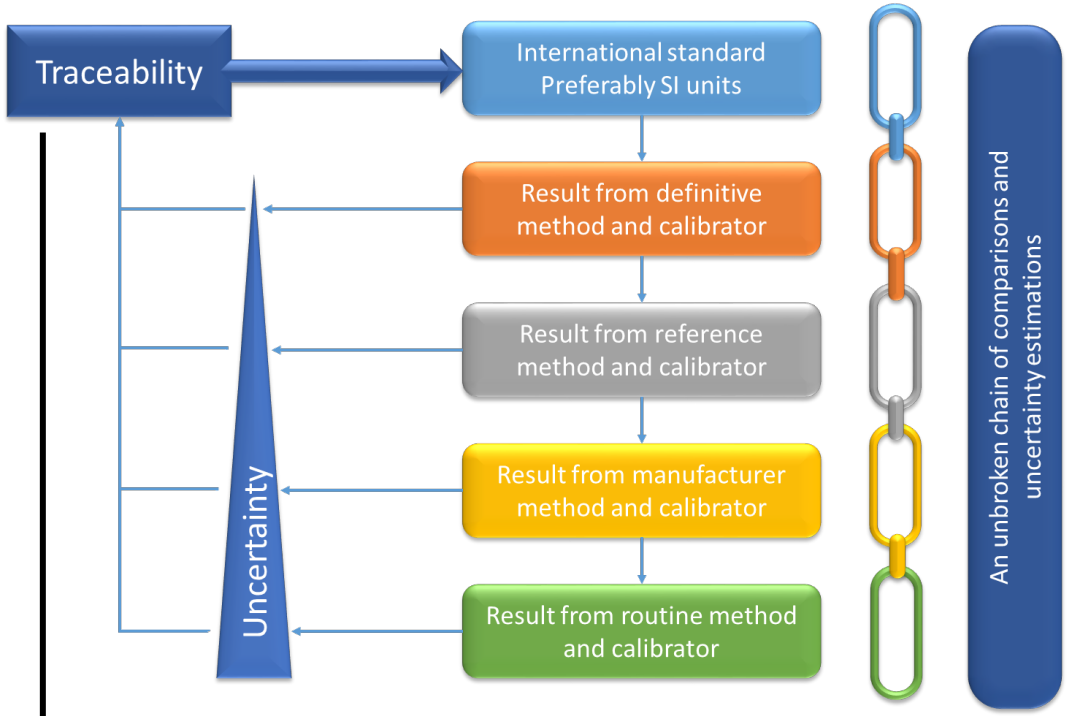
Attribute	Method 1	Method 2
Scheme	Hierarchical standardization per **ISO17511:2003**. **Top down** approach passing 'trueness' to lower order measurement procedures and calibrators.	Inter-method comparison as described by International Consortium for Harmonization of Clinical Laboratory Results (ICHCLR) (www.harmonization.net). **Bottom up** approach among routine (commercial) measurement procedures, with no SI traceability.
Reference measurement procedures	One or more **higher order reference measurement procedures available**, preferably fulfilling requirements of ISO 15193:2009	None available.
Reference materials	Certified purified reference materials and/or **commutable secondary reference materials**.	No higher order reference materials available. Panel(s) of **commutable human samples** assigned consensus values through harmonization studies. Some International Conventional Calibrators may be available (e.g. WHO materials), but usually not commutable.

Harmonization strategies 2(2) (Greenberg)

Attribute	Method 1	Method 2
Calibration traceability	Commercial calibrators and reported results for routine measurement procedures traceable to SI unit via a metrological reference system.	Commercial calibrators and reported results of routine measurement procedures not traceable to SI. **Traceability linked via inter-method comparison studies** of available commercial measurement procedures coupled with **mathematical recalibration** for removal of systematic differences among reported values.
Sustainability	**Inbuilt sustainability** through hierarchy of well-characterized and reproducible higher order and lower order reference measurement procedures and reference materials	**Risk for non-sustainability** of harmonized calibrations over time as routine methods and commercial calibrator lots change. Panels of patient samples used as “calibrators” in harmonization studies to be renewed over time (consumption and/or stability concerns.) Second and subsequent patient sample panels with values traceable to initial sample panel; presumes well-defined specifications for panel member selection.

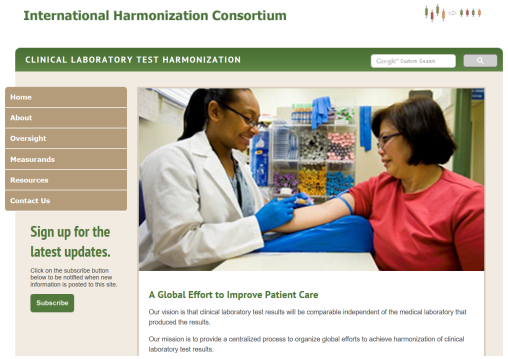
The total testing chain



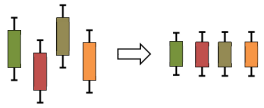


International Consortium for Harmonization of Clinical Laboratory Results (AACC)

- http://www.harmonization.net/Pages/default.html



- http://www.harmonization.net/Resource/Documents/Harmonization-Consortium-Operating-Procedures-11Feb2014.pdf

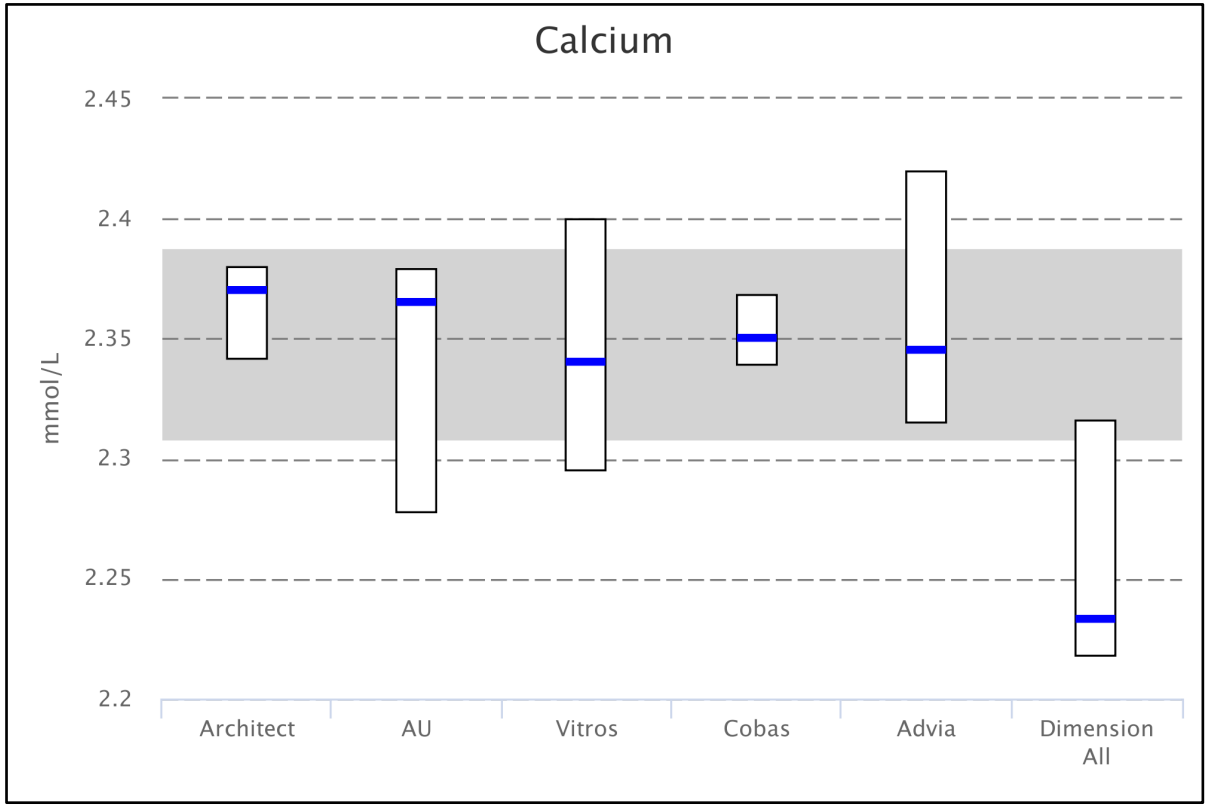


International Consortium for Harmonization of Clinical Laboratory Results

Operating Procedures

Dietmar Stöckl & Linda Thienpont

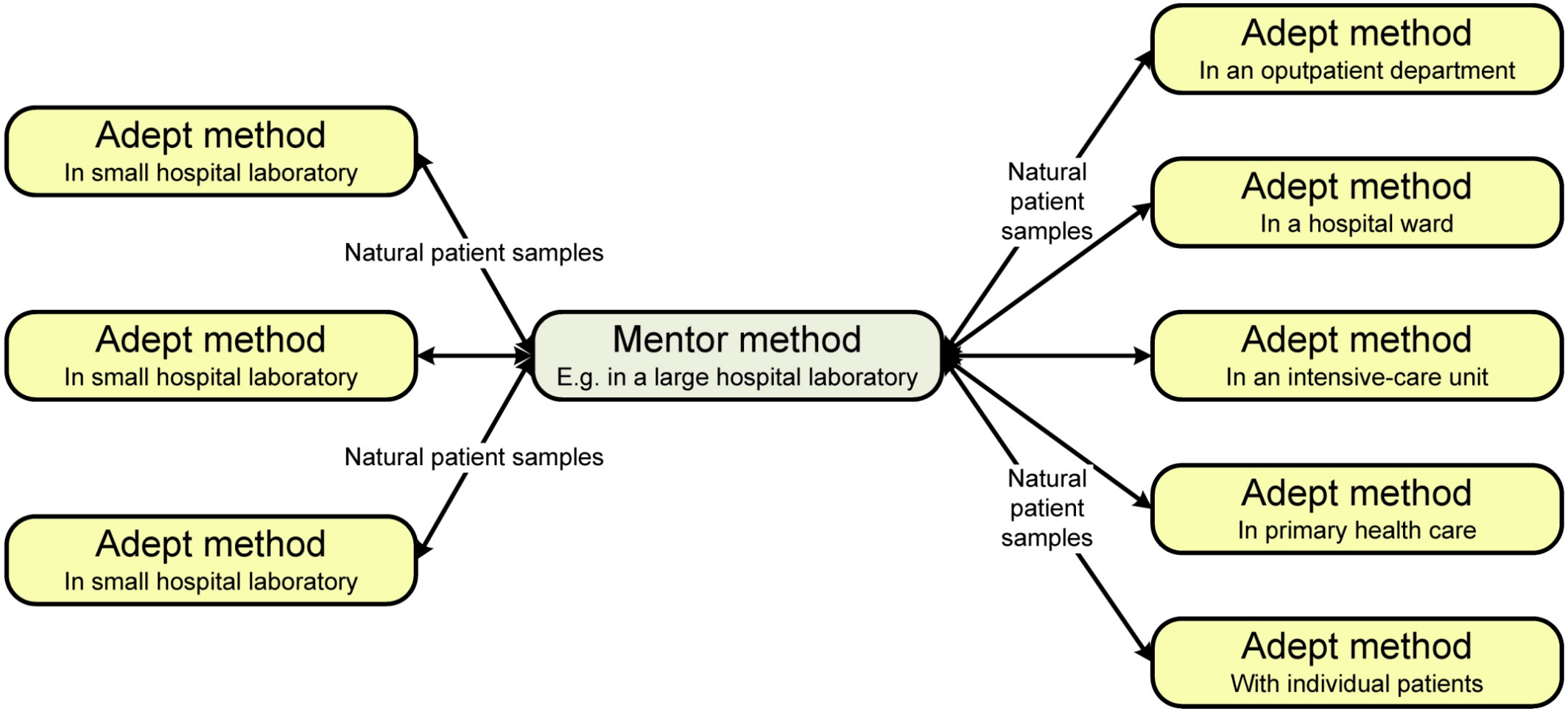
- The **Empower project** using the percentiler and flagger applications for retrieving medians of stratified measurement results of the measurement of patient samples
- dietmar@stt-consulting.com
- linda.thienpont@ugent.be



IFCC – harmonization projects

TSH

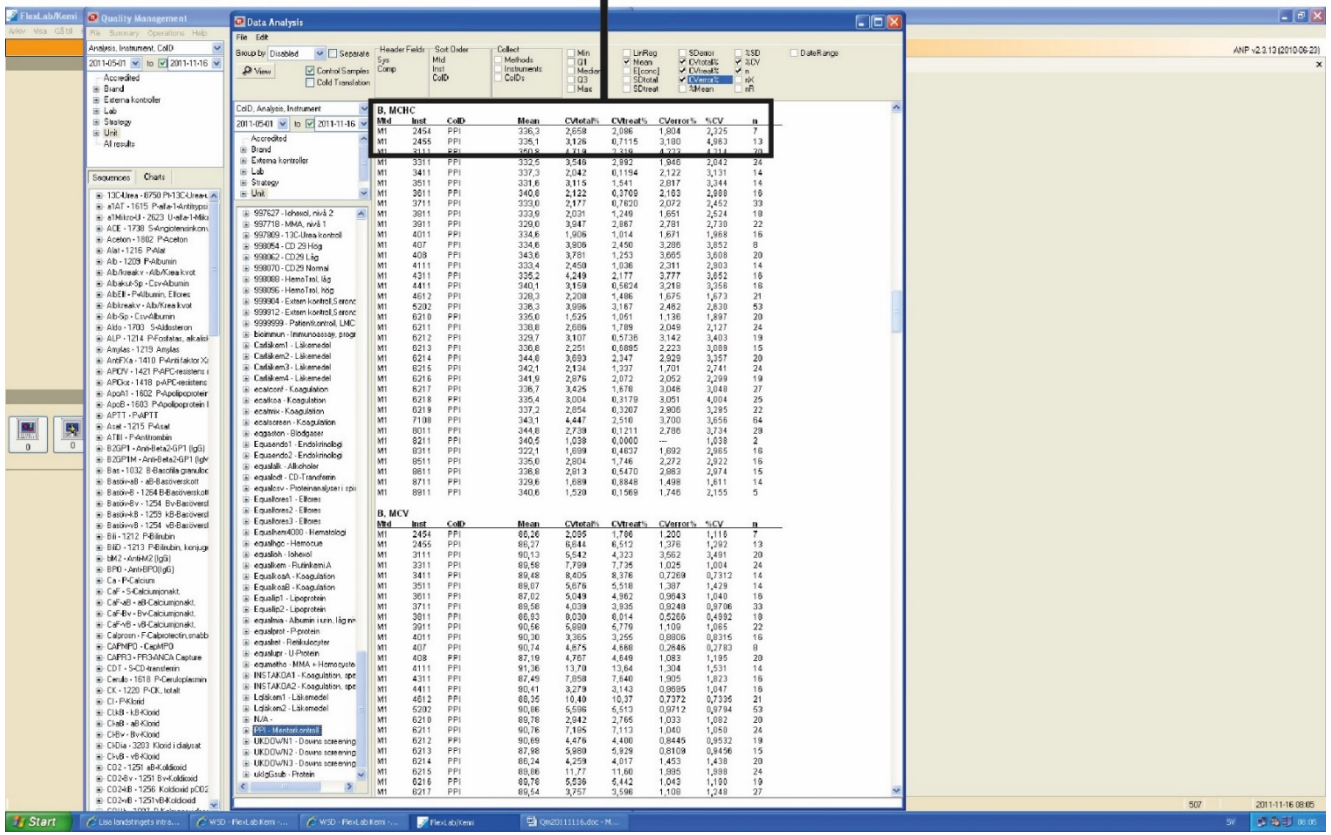
Regional harmonization



Variance component analysis

B, MCHC

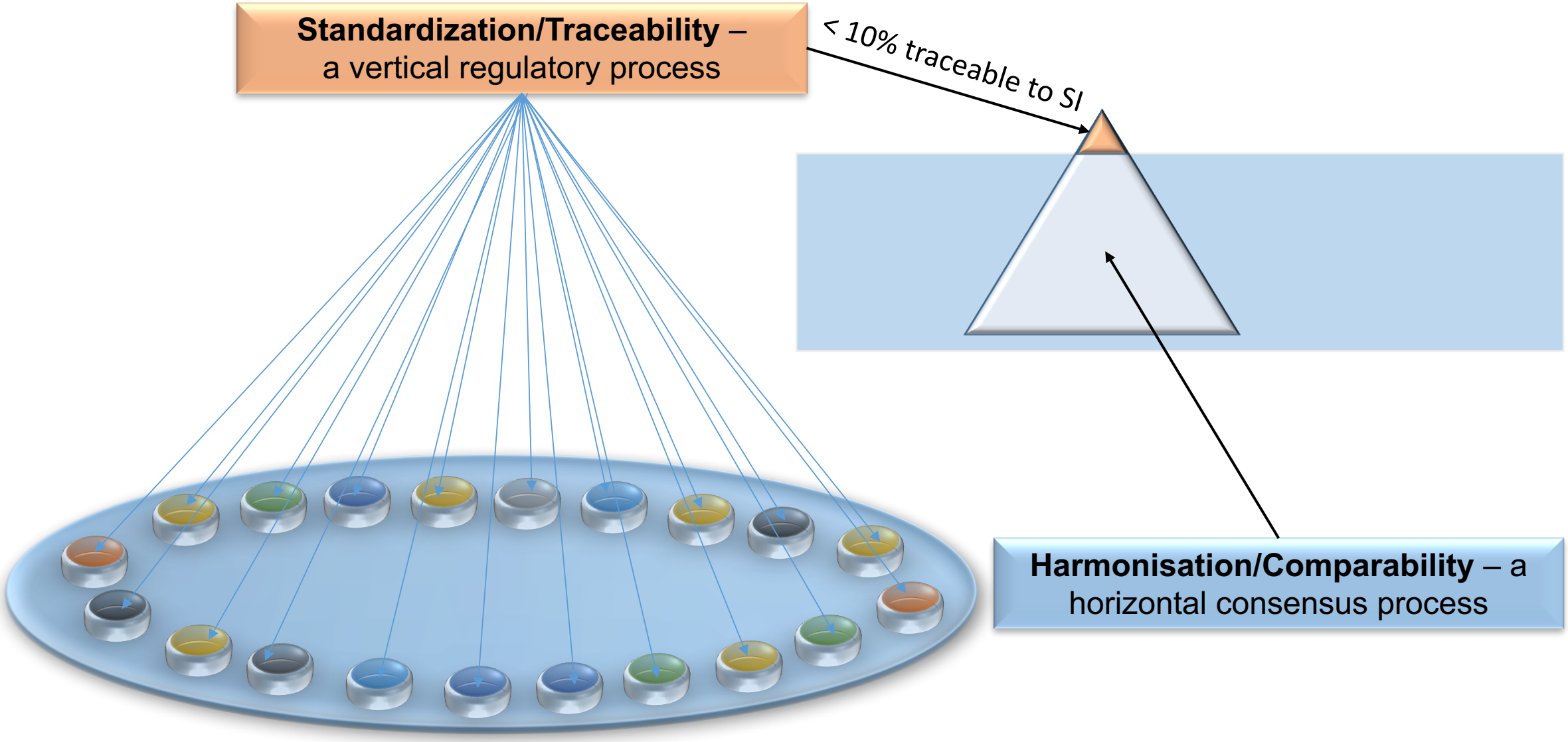
Mtd	Inst	ColD	Mean	CVtotal%	CVtreat%	CVerror%	%CV	n
M1	2454	PPI	336,3	2,658	2,086	1,804	2,325	7
M1	2455	PPI	335,1	3,126	0,7115	3,180	4,963	13
M1	3111	PPI	350,8	4,719	2,319	4,222	4,214	20
M1	3311	PPI	332,5	3,546	2,992	1,946	2,042	24



Investigating which of the following

- Measuring system
- Reagents
- Laboratory
- Operator

Contributes most to the overall diagnostic uncertainty


Standardization/Traceability –
a vertical regulatory process
< 10% traceable to SI
Harmonisation/Comparability – a
horizontal consensus process

Benefits of Clinical Laboratory Test Traceability and Harmonization

- **Improved clinical guidelines**: When clinical practice guidelines that inform diagnosis and treatment are based on specific values for laboratory test results, the broad success of those guidelines depends on harmonized test results. Significant differences in values from lab to lab or over time limit the applicability of guidelines.
- **Better-quality healthcare**: Standardized and/or harmonized clinical laboratory tests help ensure reliable screening and diagnosis so that appropriate treatments are provided. Physicians can be confident in their diagnosis and treatment decisions only if they can rely on the values reported by the lab.
- **Fewer medical errors**: Standardized and/or harmonized laboratory tests allow more accurate decision making by physicians, reducing diagnostic and treatment errors that result from too much variation in test results.
- **Lower healthcare costs**: False-positive or false-negative results from non-standardized/harmonized clinical laboratory tests can lead to unnecessary follow-up diagnostic procedures and treatments, adding unnecessary costs to patient care
- Possible to compare measurement results in different locations and over extended periods of time improving clinical research, future guidelines and decision limits

Accurate results
for patient care