JCTLM

Accurate results
for patient care

The pillars of standardization

JCTLM Working Group for Traceability: Education and Promotion (WG-TEP)
Area 2: Mini-presentations to explain scientific concepts

Standardization

- Standardization in general
  - The process of developing and implementing technical and de-facto standards in consensus for the purpose of improving quality
- Standardization in the metrology of chemistry
  - Developing and implementing *measurement standards* and *reference measurement* procedures in order to achieve comparability and interchangeability of laboratory results amongst a multitude of measurement systems
  - The achievement of *equivalent and consistent results* by different clinical laboratory tests conducted by different laboratories around the world using calibration that can be *traced* to a reference measurement procedure.
  - The results are consistent when this calibration is repeated at different times and in different places.

Amount of substance and its unit mole - 1971

- The “amount of substance”, mole, caters for common concepts in metrology – in physics and in chemistry
- The mole is currently defined as “the amount of substance of a system which contains as many elementary entities as there are atoms in 0.012 kilogram of carbon 12”.
- In the draft revised version of the SI brochure to be published in 2018 the Avogadro “constant” instead represents a conversion factor between the quantity amount of substance (with unit mole) and the quantity for counting entities (with unit one, symbol 1).

Base Quantity	Name	Symbol
Length	meter	m
Mass	kilogram	kg
Time	second	s
Electric Current	ampere	A
Thermodynamic Temperature	kelvin	K
Luminous Intensity	candela	Cd
Amount of Substance	mole	mol

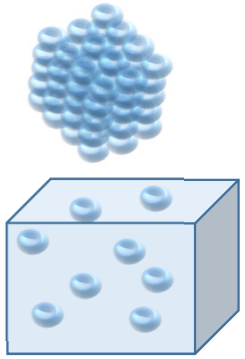
Bureau International des Poids et Mesures

The mole as a base unit in SI

- The mole is a convenient way to express amounts of reactants and products of chemical reactions
- The mole makes it possible to perform chemical measurements using the same principles as the ones used in other disciplines of metrology, e.g. physics
- The mole requires an exact knowledge of the chemical entity being measured
- When amount-of- substance are not feasible the SI units of mass and length/volume are used

Fundamentals of measurements

- Pure substance
- Substance concentration



- Concentration
  - Molar concentration
  - Mass concentration
    - Mass of a constituent divided by the volume of the mixture. The constituent does not need to be a pure substance. It can be a heterogenous mixture of molecules e.g. extract of a hormonal gland

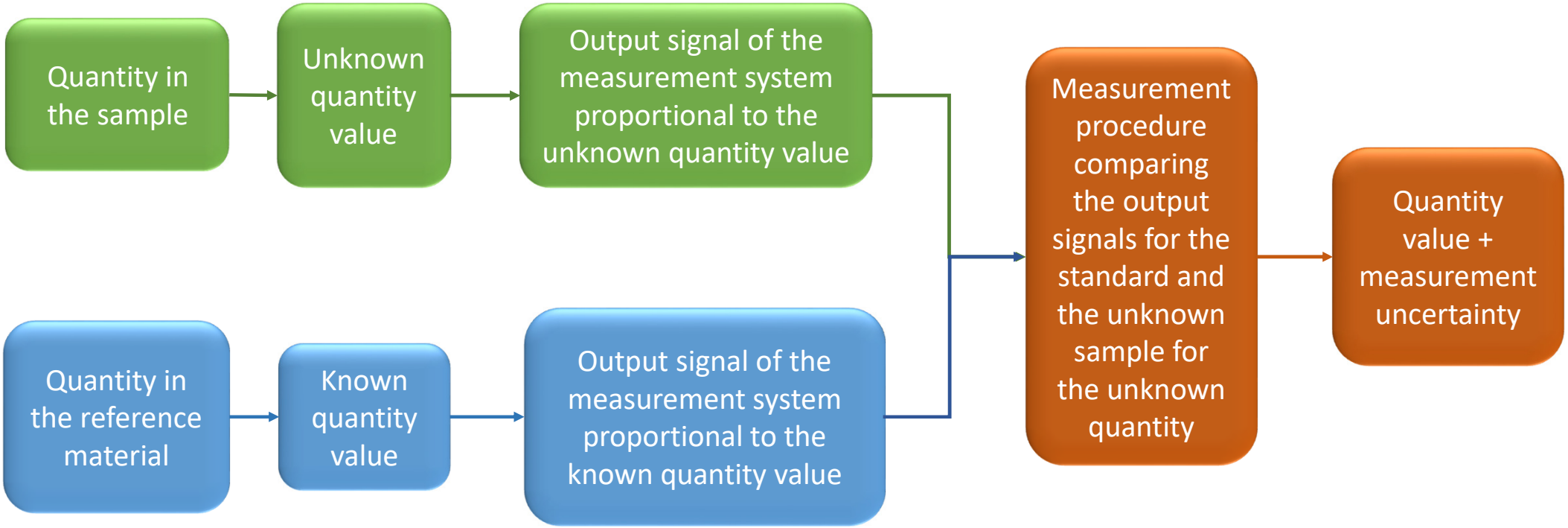
Measurand

- 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, molecular mass, immunologic reactivity etc.
- This is the reason that the term used for what we in fact measure is “measurand”; it is the “quantity intended to be measured”.
- The more truly the quantification of the measurand reflects the amount of substance intended to be measured the more selective is the measurement method, e.g. less matrix effects, interferences .

Measurand vs analyte

- The VIM 3 definition of the measurand “quantity intended to be measured” contrasts with a longstanding tradition in laboratory medicine of using the word “analyte” for this concept.
- The use of the term “analyte” or the name of a substance or a compound as synonym for “measurand” is wrong because these terms do not refer to quantities. We measure quantities in chemistry.
- The term “component” is used in the in the IUPAC/IFCC NPU clinical laboratory terminology with the basic structure System-component; kind of property in order to avoid the ambiguity of the term “analyte”

Measuring means comparing



Measurand – quantity inteded to be measured

Output signal - quantity subject to measurement

Ratio measurement

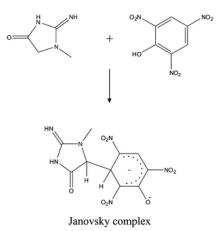
Measurement result

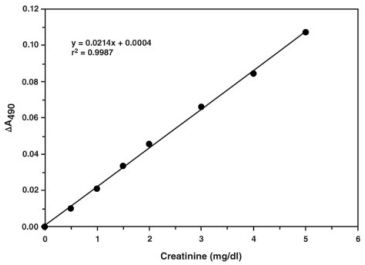
Traceability is the property of the measurement result and NOT of the reference material

- We can compare a value to another value but not a reference material with another material
- The role of the reference material is to carry the value and its uncertainty
- Traceability means carrying the values and their uncertainties through an unbroken chain of comparisons/measurements of reference materials

Example: Measuring creatinin

- We wish to measure creatinine, which is possible by measuring one of its numerous physiochemical properties - measurands
  - One of them is the orange dye complex between creatinine+picrate

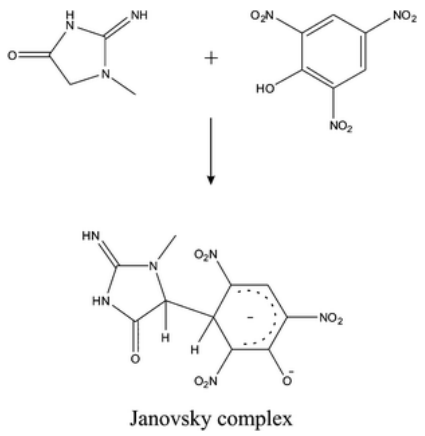

Janovsky complex



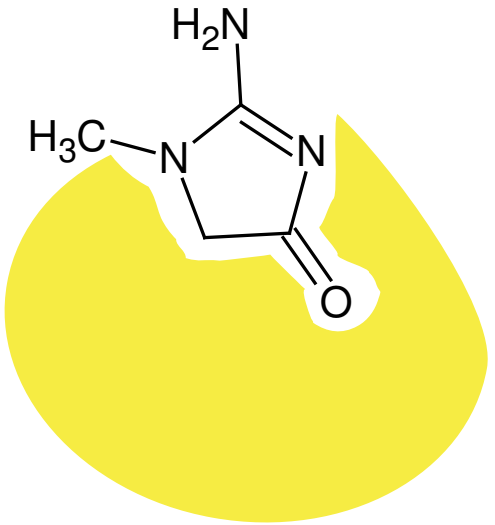
  - The orange dye complex is the measurand detectable by spectrophotometry
  - That measurand is not entirely specific for creatinine
  - The specificity can be substantially increased using enzymatic methods

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

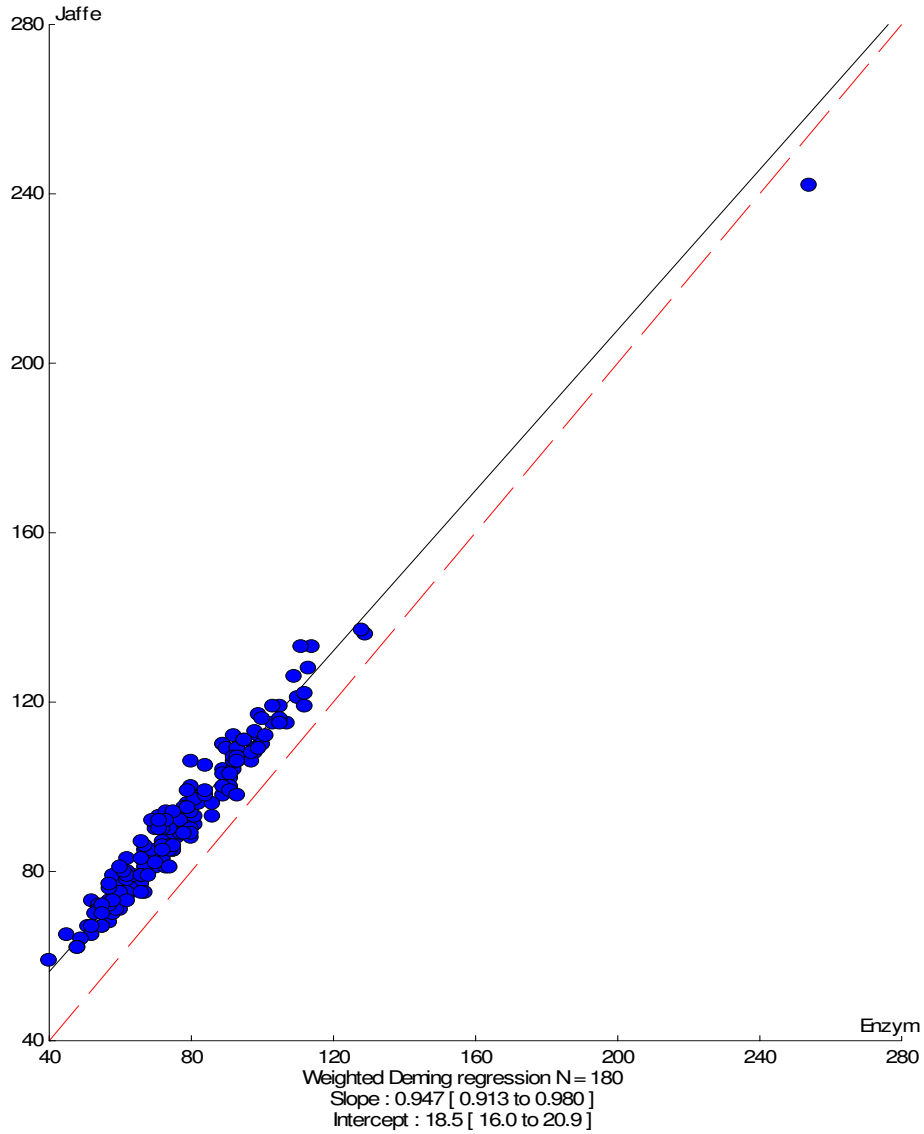


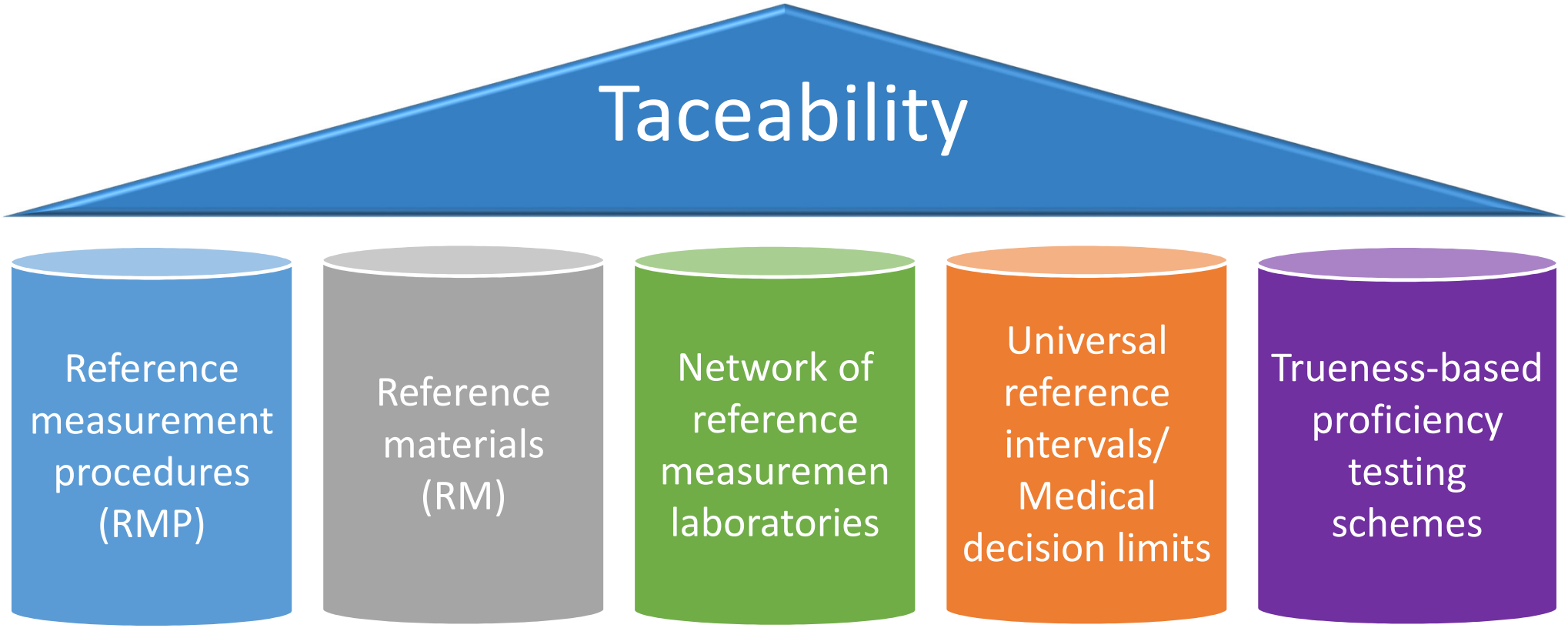
Selective enzymatic reaction

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

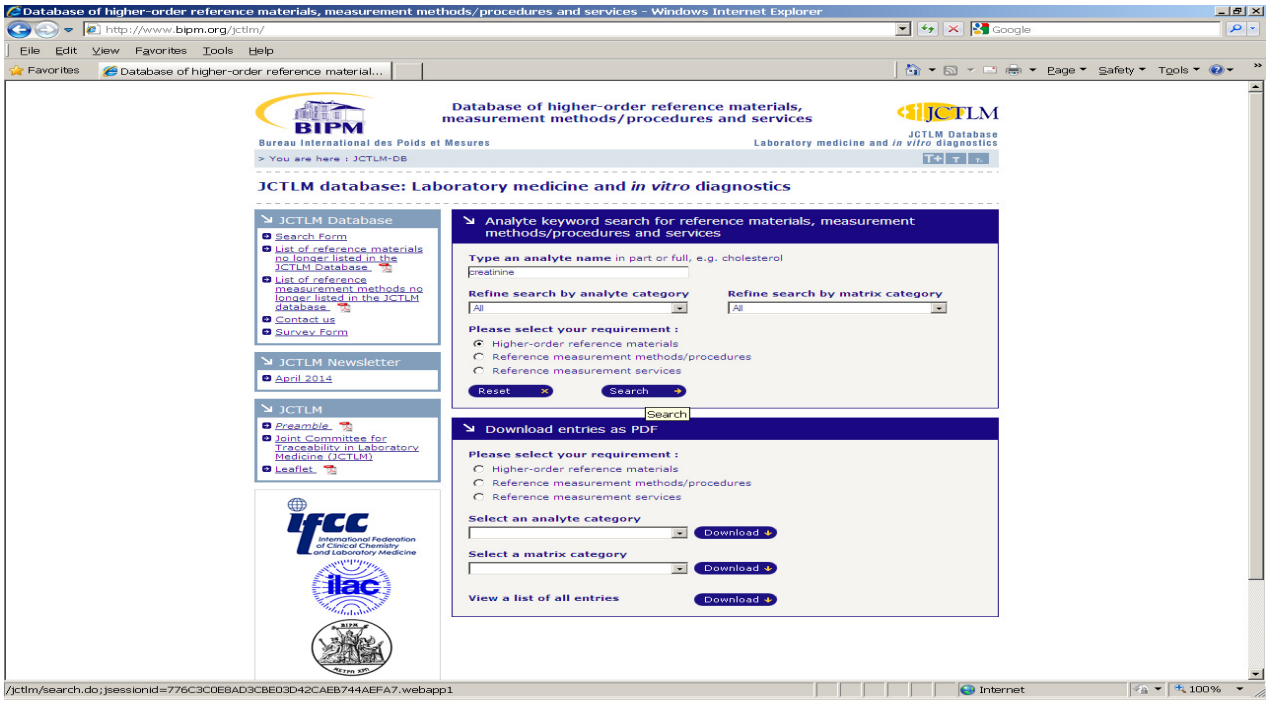
Jaffe = 0.947 * Enzymatic + 18.5

Enzymatic = Jaffe/0.947 – 18.5




Taceability
Reference measurement procedures (RMP)
Reference materials (RM)
Network of reference measuremen laboratories
Universal reference intervals/ Medical decision limits
Trueness-based proficiency testing schemes

Sources of Certified Reference Materials and Methods



JCTLM website hosted by BIPM (http://www.bipm.org/jctlm/)

1. Reference Materials
2. Reference Measurement Methods
3. Reference Measurement Services

World Health Organization

Institute for Reference Materials and Measurements

National Institute of Advanced Industrial Science and Technology
National Metrology Institute of Japan

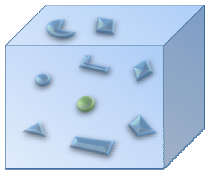
National Institute of Standards and Technology

National Institute of Standards and Technology
U.S. Department of Commerce

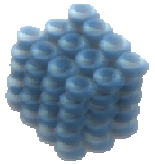
Australian Government
National Measurement Institute

Confounding factors in measurements 1(2)

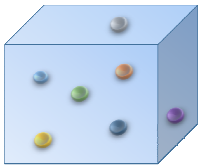
1. The presence of “matrix factors”



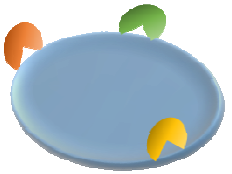
2. Inability to produce the substance in a pure form that can be weighed



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

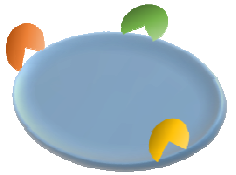


4. Detection of different epitopes

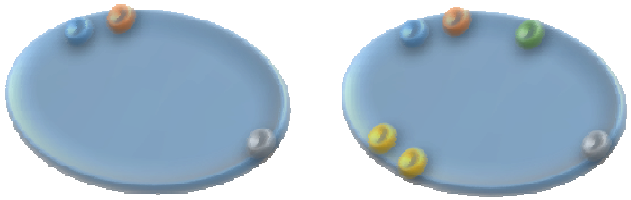


Confounding factors in measurements 2(2)

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



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

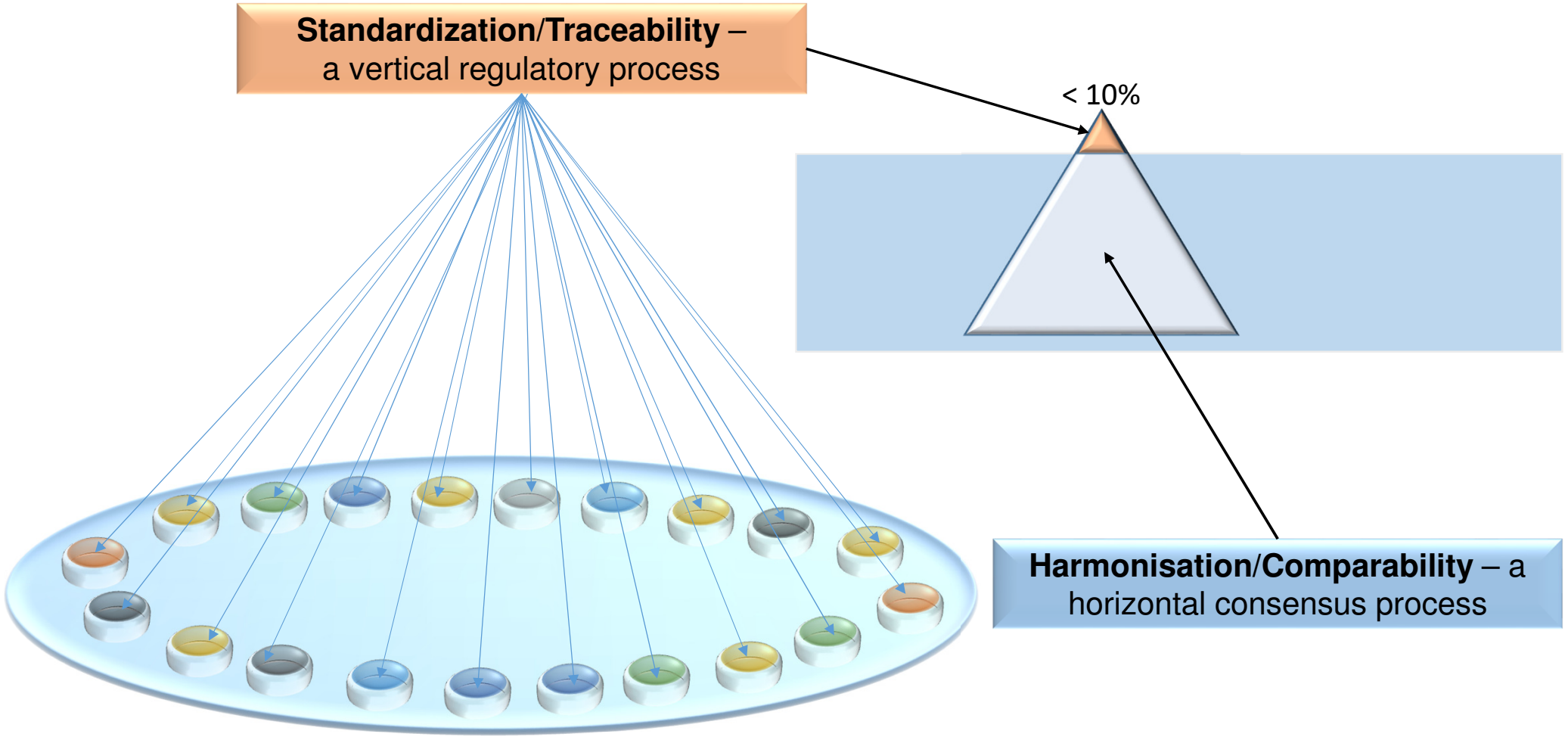


Sucess stories in standardization in laboratory medicine

- 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 measurements
- Glycated hemoglobin
- Carbohydrate-deficient transferrin

Classes of measurands

- **Class A** measurands: whose measurement results that are *traceable* to SI units
- **Class B** measurands : whose measurement results are **not** *traceable* to SI units but to arbitrary units, e.g., mass units or WHO International Units


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

Accurate results
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