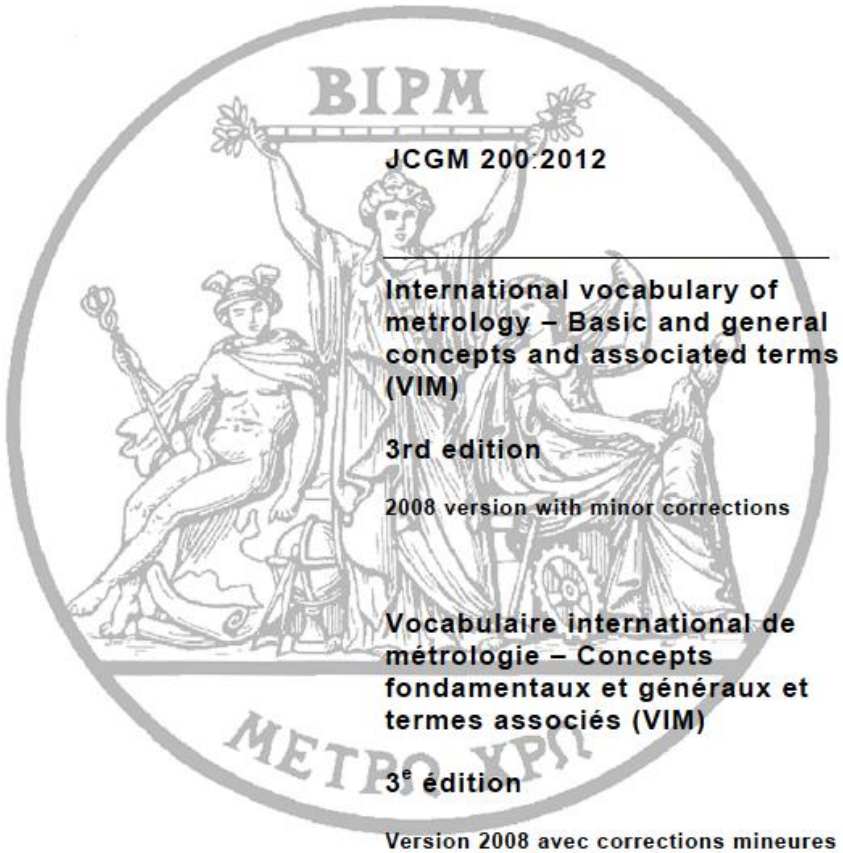
Metodeverifisering baseres på metodevalidering!

Elvar Theodorsson

Validation vs verification in Laboratory Medicine in common language

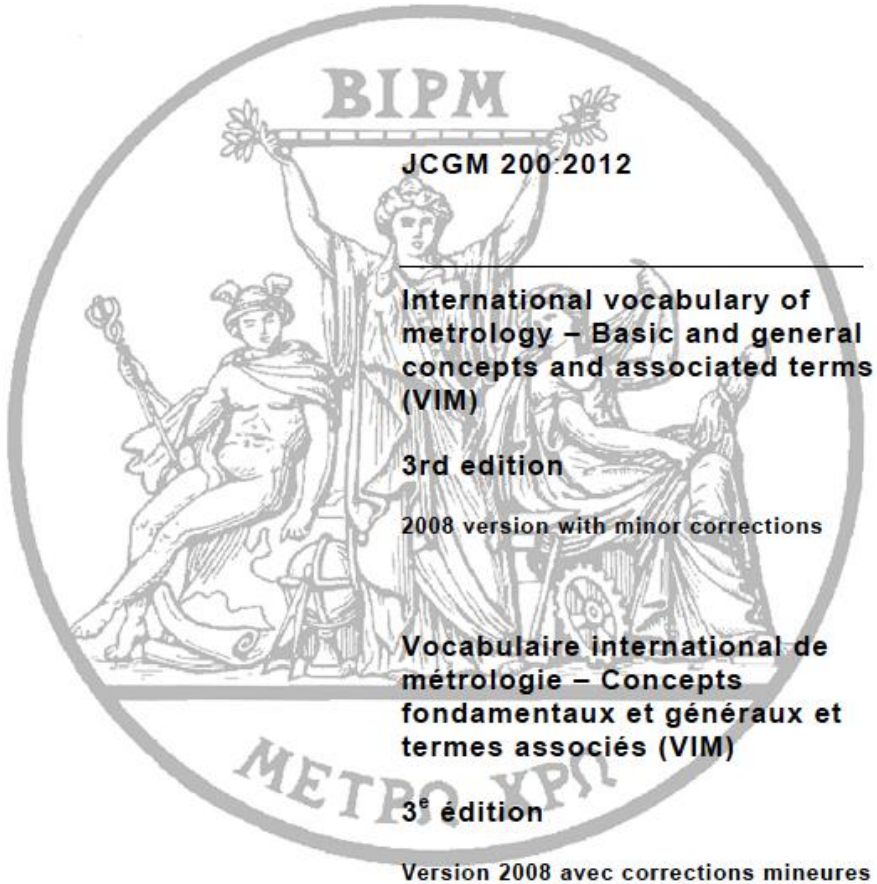
- **Validation**
  - Investigating whether a measuring system is fit for the intended use for diagnosing diseases, risks of diseas or for monitoring treatment effects in humans
- **Verification**
  - Acertaining whether the diagnostic properties of a measuring system validated by a manufacturer can be reproduced in the environment of a user laboratory – centralized of point-of-care
  - The most commonly verified properties are bias, reproducibility imprecision and repeatability imprecision



2.45
validation

verification, where the specified requirements are adequate for an intended use

EXAMPLE A **measurement procedure**, ordinarily used for the **measurement** of mass concentration of nitrogen in water, may be validated also for measurement of mass concentration of nitrogen in human serum.



2.44
verification

provision of objective evidence that a given item fulfils specified requirements

EXAMPLE 1 Confirmation that a given **reference material** as claimed is homogeneous for the **quantity value** and **measurement procedure** concerned, down to a measurement portion having a mass of 10 mg.

EXAMPLE 2 Confirmation that performance properties or legal requirements of a **measuring system** are achieved.

EXAMPLE 3 Confirmation that a **target measurement uncertainty** can be met.

IVDR

L 117/176 EN Official Journal of the European Union 5.5.2017

REGULATION (EU) 2017/746 OF THE EUROPEAN PARLIAMENT AND OF THE COUNCIL

of 5 April 2017

on *in vitro* diagnostic medical devices and repealing Directive 98/79/EC and Commission Decision 2010/227/EU

(Text with EEA relevance)

THE EUROPEAN PARLIAMENT AND THE COUNCIL OF THE EUROPEAN UNION,

Summary of safety and performance

- The identification of the device and the manufacturer, including the Basic UDI-DI and, if already issued, the SRN
- The intended purpose of the device and any indications, contra-indications and target populations
- A description of the device, including a reference to previous generation(s) or variants if such exist, and a description of the differences, as well as, where relevant, a description of any accessories, other devices and products, which are intended to be used in combination with the device
- Reference to any harmonised standards and CS applied
- The summary of the performance evaluation as referred to in Annex XIII, and relevant information on the PMPF
- The metrological traceability of assigned values
- Suggested profile and training for users
- Information on any residual risks and any undesirable effects, warnings and precautions.

Performance evaluation and studies – appendix XIII

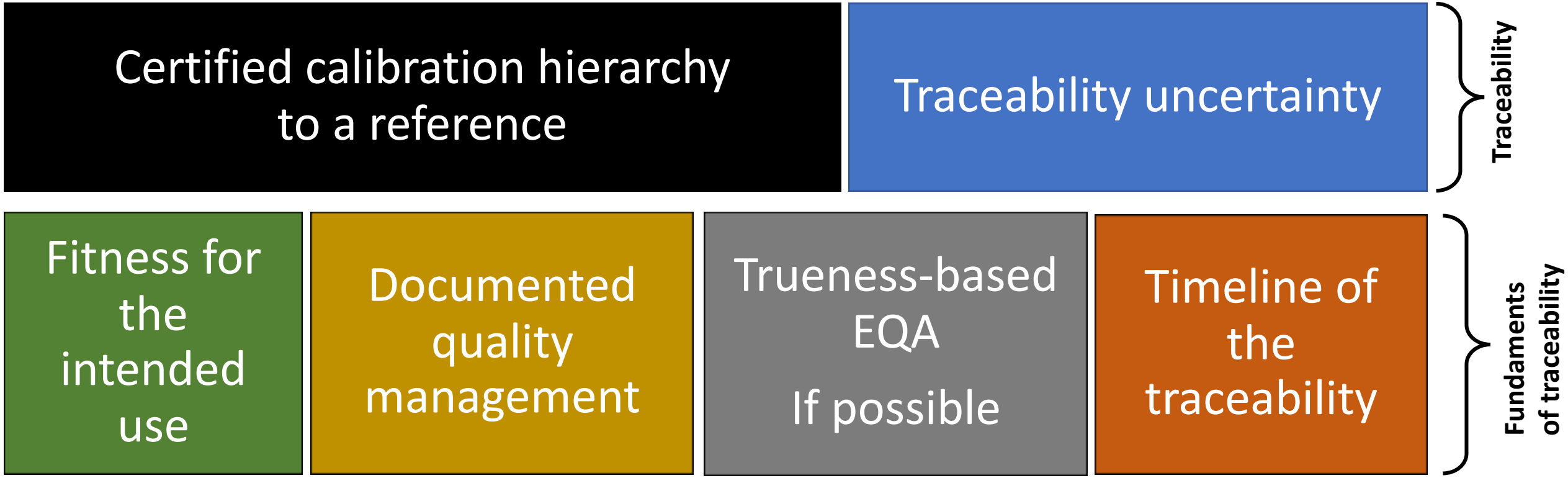
- “Performance evaluation of a device is a continuous process by which data are assessed and analysed to demonstrate the scientific validity, analytical performance and clinical performance of that device for its intended purpose as stated by the manufacturer”
- “Its depth and extent shall be proportionate and appropriate to the characteristics of the device including the risks, risk class, performance and its intended purpose”

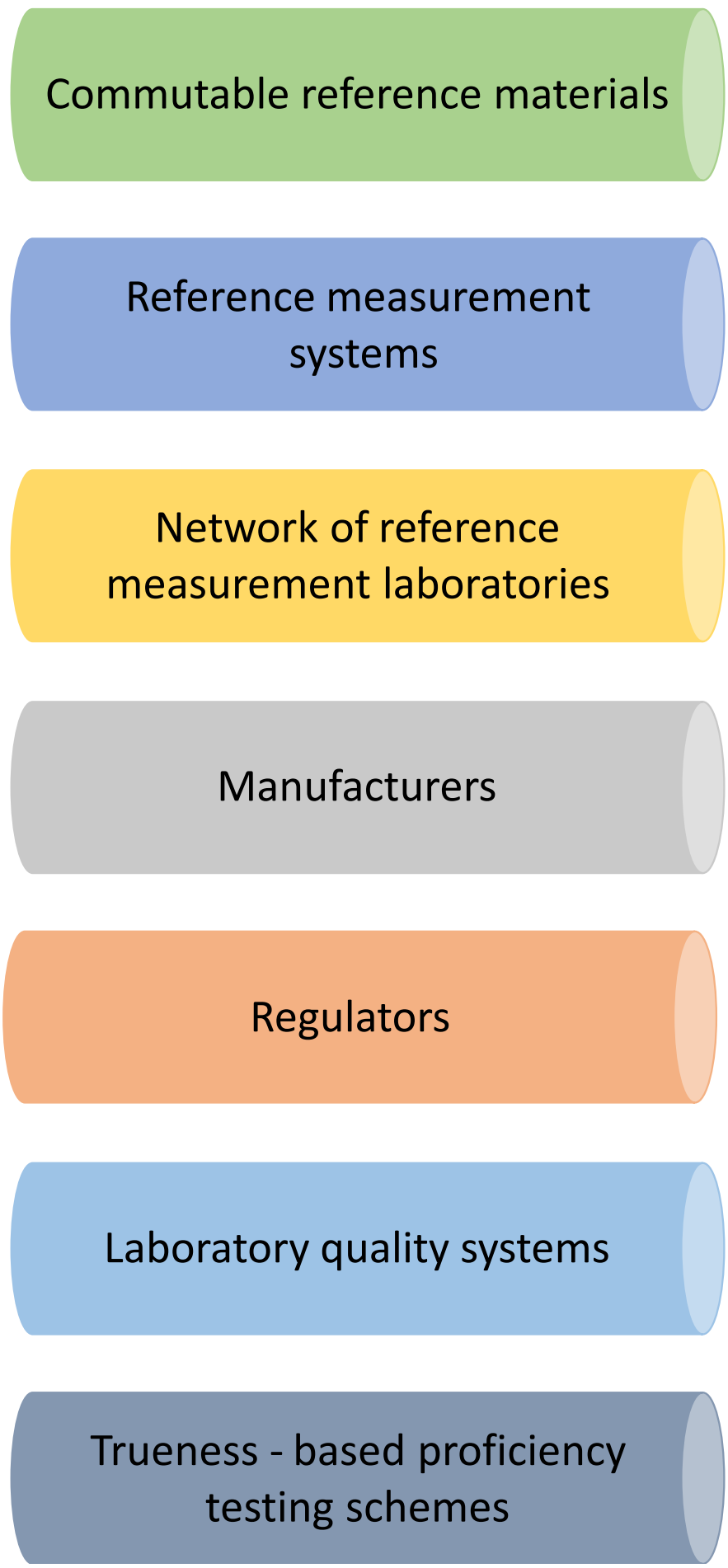
Performance evaluation and studies – appendix XIII

- Scientific validity
- Analytical performance
- Clinical performance
- Post-market performance follow-up

Metrological traceability

- “Comparability by being connected”
- Traceability **IS**
  - “A *property of a measurement result* that can be related to a *reference* through a documented unbroken chain of calibrations, each contributing to the *measurement uncertainty*”
- Traceability **IS NOT** “traceability” to:
  - the producers of the reference materials used for calibrating measuring systems
  - to the internal or external quality control samples used in the measurement
  - to the manufacturers of the reagents and measuring systems used.

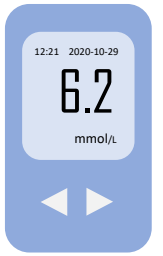

Certified calibration hierarchy to a reference
Traceability uncertainty
Traceability
Fitness for the intended use
Documented quality management
Trueness-based EQA
If possible
Timeline of the traceability
Fundaments of traceability


Commutable reference materials
Reference measurement systems
Network of reference measurement laboratories
Manufacturers
Regulators
Laboratory quality systems
Trueness - based proficiency testing schemes

Traceability standards

- **ISO-17511:2020**: In vitro diagnostic medical devices — Requirements for establishing metrological traceability of values assigned to calibrators, trueness control materials and human samples.
- **ISO-21151:2020** In vitro diagnostic medical devices – Requirements for international harmonization protocols establishing metrological traceability of values assigned to calibrators and human samples.

measurement procedure (ms.)



ms. 1
Quantitative Nuclear Magnetic Resonance (qNMR) procedure for purity and identity assessment

ms. 2
Primary reference measurement procedure for calibrator. Weighing of the certified primary reference material m. 1

ms. 3
Reference measurement procedure for the measurand. Isotope dilution mass spectrometry of the diluted certified primary reference material m. 2 conforming to ISO 15193

ms. 4
Manufacturers selected measurement procedure

ms. 5
Manufacturers standing measurement procedure

ms. 5
End-users measurement device

material (m.)

m. 1
Certified primary reference material conforming to ISO 15194

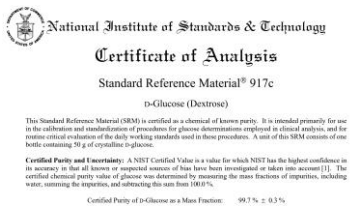
m. 2
Primary calibrator - prepared as solution of m. 1 in water

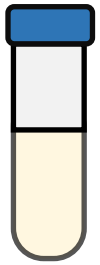
m. 3
Secondary, commutable certified reference materiial conforming to ISO 15193. Matrix is pooled human plasma

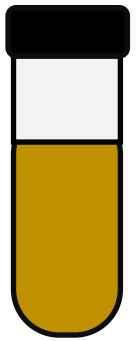
m. 4
Manufacturers working calibrator

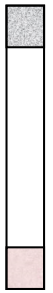
m. 5
Calibrator for the end-user measurement device

m. 6
Human sample with result


National Institute of Standards & Technology
Certificate of Analysis
Standard Reference Material® 917c
D-Glucose (Dextrose)



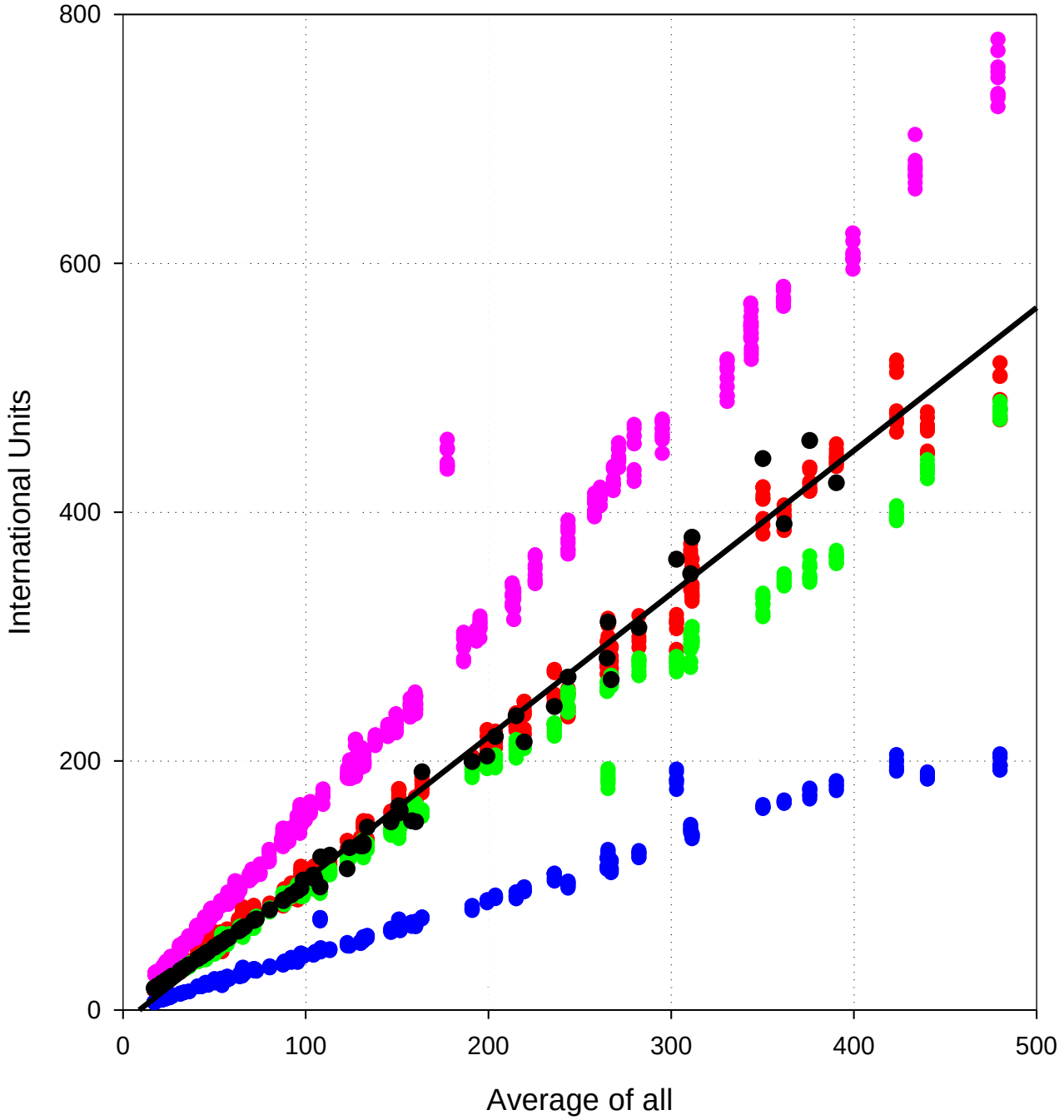




Metrology institutes

Manufacturers

End users



ISO-21151:2020 In vitro diagnostic medical devices – Requirements for international harmonization protocols establishing metrological traceability of values assigned to calibrators and human samples.

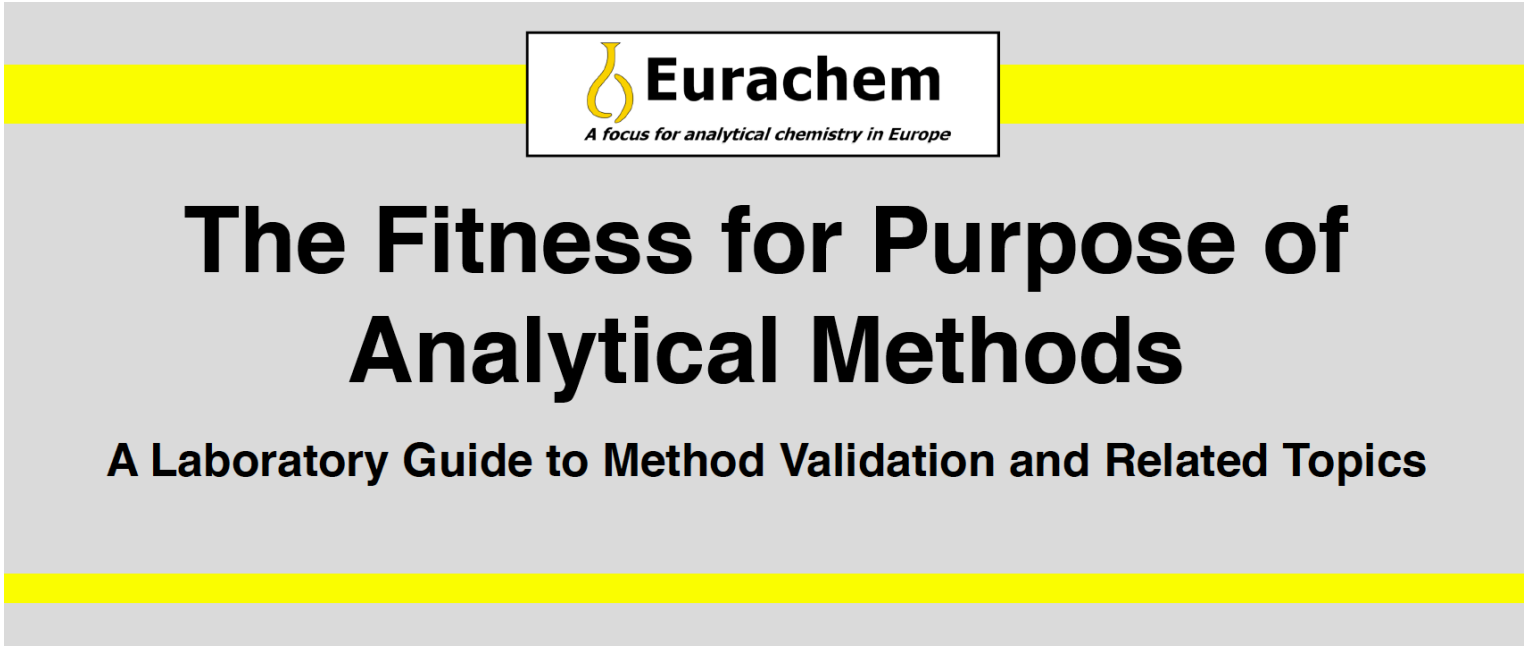
Traceability hierarchies

- Traceability to SI
- Availability of certified reference materials
- Availability reference measurement procedures
- Availability of harmonization protocols

Calibration hierarchies ISO-17511:2020

1. Both primary reference material and reference measurement procedure are available
2. A primary reference measurement procedure defines the measurand
3. Measurands defined by a reference measurement procedure calibrated with a particular primary calibrator
4. Measurand defined by value assignment protocol for international conventional calibrator (no SI traceability but conforming to ISO-15194:2009)
5. Measurand defined by an international harmonization protocol (not traceable to SI and certified reference material is not available)
6. Measurand defined by manufacturer's internal arbitrarily defined reference material (not traceable to SI, no certified reference material, no reference measurement procedure, and no harmonization protocol)

EuraChem



https://eurachem.org/images/stories/Guides/pdf/MV_guide_2nd_ed_EN.pdf

CLSI

- EP05-A3 Evaluation of Precision of Quantitative Measurement Procedures
- EP6-A Evaluation of Linearity of Quantitative Measurement Procedures: A Statistical Approach
- EP07-A2 Interference Testing in Clinical Chemistry
- EP09-A3 Measurement Procudure Comparison and Bias Estimation Using Patient Samples
- EP12 Evaluation of Qualitative, Binary Outpur Examination Performance
- EP15-A2 User verification of Performance for Precision and Trueness

ISO 17025:2017

7.2.2 Validation of methods

7.2.2.1 The laboratory shall validate non-standard methods, laboratory-developed methods and standard methods used outside their intended scope (modified standard methods). The validation shall be as extensive as is necessary to meet the needs of the given application or field of application. The laboratory shall record the results obtained, the procedure used for the validation, and a statement as to whether the method is fit for the intended use.

NOTE 1 Validation can include procedures for sampling, handling and transportation.

NOTE 2 The techniques used for method validation can be one of, or a combination of, the following:

a) calibration and/or evaluation of bias and precision using reference standards or reference materials;
b) systematic assessment of the factors influencing the result;
c) testing method robustness through variation of controlled parameters such as incubator temperature, volume dispensed, etc.;
d) comparison of results achieved with other validated methods;
e) interlaboratory comparisons;
f) evaluation of measurement uncertainty of the results based on scientific understanding of the theoretical principles of the method and practical experience.

ISO 17025:2017

7.2.2.2 When changes are made to any validated methods, the influence of such changes shall be documented and, if appropriate, a new validation shall be performed.

7.2.2.3 The range and accuracy of the values obtainable from validated methods as assessed for the intended use, shall be relevant to the customers' needs and consistent with specified requirements.

Validation

1. Single laboratory method validation
2. Full method validation
3. Full diagnostic method validation

DE GRUYTER

Clin Chem Lab Med 2021; 59(5): 823–835

Opinion Paper

Catharine Sturgeon, Stephen A. Butler, Fiona Gould, Sarah Johnson*, Sam Rowlands, Ulf-Håkan Stenman and David G. Grenache

Recommendations for validation testing of home pregnancy tests (HPTs) in Europe

https://doi.org/10.1515/cclm-2020-1523
Received October 13, 2020; accepted December 3, 2020; published online January 28, 2021

Keywords: European Directive; home pregnancy tests; human chorionic gonadotrophin; *in vitro* diagnostic regulation; validation testing.

Nomenclature of HPTs, description of hCG isoforms recognised and units for reporting

1. Achieving agreement on the broad descriptions of different types of device formats is a priority
2. Data regarding the relative recognition of hCG isoforms expressed in molar units should be included in technical data sheets
3. hCG results should be expressed using the same units

Analytical requirements for validation of HPTs

1. Pre-analytical requirements for urine collection and storage prior to validation studies should be clearly defined
2. The minimum number of urine specimens containing added hCG and the appropriate concentration range for validation of analytical accuracy should be defined
3. Lower limit of detection should be expressed as the lowest concentration of hCG that the HPT detects ≥99% of the time
4. Analytical precision should be assessed by: (a) repeating the test at least 20 times per condition, across standards which include hCG concentrations near the detection limit of the method and the “50:50” point; and (b) repeating the testing series on at least three separate days spaced across a minimum five-day time frame, and with a minimum of three different operators and three different lot numbers
5. Cross-reactions with LH, hCGβcf and other potential clinically relevant interferences should be assessed in HPT validation studies and results documented in technical data sheets

Clinical requirements for validation of HPTs

- Data supporting claims for “early pregnancy testing” should be provided and how studies were conducted described in full in the technical data sheet
- Potential drawbacks of highly sensitive HPTs should be assessed, and relevant information included in technical data sheets and package inserts
- Statements that any HPT is 100% accurate should not be permitted in data sheets or other promotional material

Requirements for validation of HPTs by lay users

1. Sensitivity, specificity, PPV and NPV should be calculated
2. A study where the HPT is used by women representative of the lay user and the volunteer results are compared to clinical pregnancy status should be conducted. The study should also consider ease of use, with results presented in the technical data sheet.
3. Clear and detailed instructions about urine collection and timing between steps in the testing process must be provided in the instructions for use. The clarity of these instructions should be assessed in practice by an appropriately constituted panel of lay users during validation of the HPT
4. Clear information about limitations of the HPT should be included in the instructions for use. The clarity of the information provided should be assessed during validation through questionnaires provided to lay users participating in the analytical validation studies