Hva kreves når man skal verifisere en akkreditert analyse?

Elvar Theodorsson

Most important regulatory documents

- **ISO 15189:2020** – accreditation
- **ISO 17025:2017** – normative standard for 15189
- **IVDR** - 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

IVDR – 9.3.

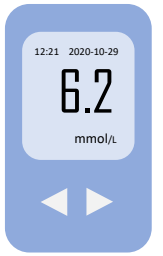
Traceability to suitable reference measurement procedures and/or to suitable reference materials of a higher metrological order

- “Where the performance of devices depends on the use of calibrators and/or control materials, the metrological traceability of values assigned to calibrators and/or control materials shall be assured through suitable reference measurement procedures and/or suitable reference materials of a higher metrological order. Where available, metrological traceability of values assigned to calibrators and control materials shall be assured to certified reference materials or reference measurement procedures.”

Traceability in Laboratory Medicine

- **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

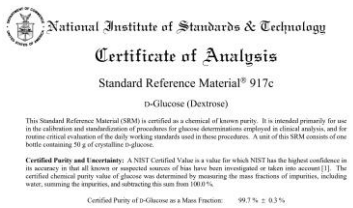
m. 2
Primary calibrator - prepared as solution of m. 1 in water

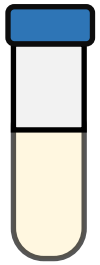
m. 3
Secondary, commutable certified reference materiial conforming to ISO 15193. Matrix is pooled human plasma

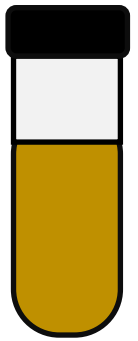
m. 4
Manufacturers working calibrator

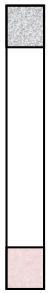
m. 5
Calibrator for the end-user measurement device

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 17511:2020 and ISO 21151:2020

The *reference* must be amongst the following:

1. The *definition of a SI unit*
2. A certified value of a *reference material*
3. The result of a *reference measuring system*
4. The value assigned to an *international conventional reference material*
5. The values assigned to *international harmonization reference materials*

IVDR – 9.3.

Verification of examination methods

- The laboratory shall verify that it can properly perform methods before introducing them by ensuring that it can achieve the required performance. Records of the verification shall be retained. If the method is revised by the issuing body, verification shall be repeated to the extent necessary. The laboratory should obtain information from the manufacturer/method developer for confirming the performance specifications of the method established when the measurement method was selected.
- The performance claims (and other specified requirements) for the examination method confirmed during the verification process shall be those relevant to the intended use of the examination results and at the medical decision levels of interest. The laboratory shall take a risk-based approach to ensure the extent of verification of examination methods meets clinical needs.
- The laboratory shall document the procedure required for verification and record the results obtained.
- Staff with the appropriate authority and competence shall review the verification results and record the review.”

ISO 15189:draft2020 §6.2

Personnel

6.2.1 Personnel who influence laboratory activities

All personnel of the laboratory, either internal or external, that could influence the laboratory activities shall act impartially, ethically, and be competent and work in accordance with the laboratory's management system.

6.2.2 Personnel qualifications

a) The laboratory shall have a process for managing competence of its personnel.

b) The laboratory management shall define and document the competence requirements for each position/function influencing the results of laboratory activities, including requirements for education, qualification, training, technical knowledge, skills, experience.

c) The laboratory shall have documented information demonstrating competence of its personnel.

ISO 15189:draft2020 §6.2

6.2.3 Communication of duties and responsibilities

The management of the laboratory shall communicate to personnel their duties, responsibilities, and authorities.

6.2.4 Personnel authorization

The laboratory management shall authorize personnel to perform specific laboratory activities, including but not limited to, the following:

a) development, modification, verification and validation of methods;

b) analysis of results, including statements of conformity, or opinions and interpretations;

c) report, review, and authorization of results.

d) use of laboratory information systems, in particular:

accessing patient data and information;
entering patient data and examination results;
changing patient data or examination results;
authorizing the release of examination results and reports

ISO 15189:draft 2020 §6.2

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ISO 15189:draft 2020
7.2.2 Verification of examination methods

The laboratory shall verify that it can properly perform methods before introducing them by ensuring that it can achieve the required performance. Records of the verification shall be retained. If the method is revised by the issuing body, verification shall be repeated to the extent necessary. The laboratory should obtain information from the manufacturer/method developer for confirming the performance specifications of the method established when the measurement method was selected.

The performance claims (and other specified requirements) for the examination method confirmed during the verification process shall be those relevant to the intended use of the examination results and at the medical decision levels of interest. The laboratory shall take a risk-based approach to ensure the extent of verification of examination methods meets clinical needs.

ISO 15189:draft 2020
7.2.2 Verification of examination methods

The laboratory shall document the procedure required for verification and record the results obtained.

Staff with the appropriate authority and competence shall review the verification results and record the review.

ISO 15189:draft 2020
7.2.3 Validation of examination methods

The laboratory shall validate examination methods derived from the following sources:

- non-standard methods;
- laboratory designed or developed methods;
- methods used outside their intended scope;
- validated methods subsequently modified;
- methods used outside the manufacturer’s instructions of use;
- validated methods at other clinical decision levels than the ones that are of interest.

ISO 15189:draft 2020
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ISO 15189:draft 2020
7.2.3 Validation of examination methods

The validation shall be as extensive as is necessary and confirm, through the provision of objective evidence (in the form of performance specifications), that the specific requirements for the intended use of the examination have been fulfilled. The laboratory shall take a risk-based approach to ensure the extent of validation of examination procedures meets clinical needs.

> NOTE Performance specifications of an examination method includes, but is not limited to: measurement trueness; measurement precision including measurement repeatability and measurement intermediate precision; , analytical specificity; including interfering substances; analytical sensitivity; detection limit and quantitation limit; measuring interval; clinical relevance; diagnostic specificity and diagnostic sensitivity.

The laboratory shall document the planned procedure used for the validation and record the results obtained. Staff with the appropriate authority and competence shall review the validation results and record the review.

The laboratory shall ensure the extent of revalidation and reverification of examination methods meets clinical needs.

When changes are made to a validated or verified examination methods the clinical impact of these should be reviewed.

The laboratory shall retain the following records of validation:

ISO 17025:2017

- 6.4.7 The laboratory shall establish a calibration program to ensure metrological traceability of the measurement results is maintained. The calibration program shall be reviewed and adjusted as necessary in order to maintain confidence in the status of calibration.
- 6.4.12 When calibration and reference material data include reference values or correction factors, the laboratory shall ensure the correction factors and reference values are updated and implemented, as appropriate, to meet specified requirements.
- 6.4.13 The laboratory shall ensure practicable measures are taken to prevent unintended adjustments of equipment which would invalidate results.
- 6.4.14 The laboratory shall select and use reference materials that are fit for the specific purpose in the measurement process.

ISO 17025:2017

- 6.5.1 The laboratory shall establish and maintain metrological traceability of its measurement results by means of a documented unbroken chain of calibrations each contributing to the measurement uncertainty, linking them to an appropriate reference.

ISO 17025:2017 7.2 Selection, verification and validation of methods

7.2.1.1 The laboratory shall use appropriate methods and procedures for all laboratory activities and, where appropriate, for evaluation of the measurement uncertainty as well as statistical techniques for analysis of data.

NOTE For calibration laboratories, “method” as used in this International Standard can be considered synonymous with the term “measurement procedure” as defined in the JCGM 200 : 2012.

7.2.1.2 All methods, procedures and supporting documentation, such as instructions, standards, manuals and reference data relevant to the laboratory activities, shall be kept up to date and shall be made readily available to personnel (see 8.3).

7.2.1.3 Deviation from methods and procedures for all laboratory activities shall occur only if the deviation has been documented, technically justified, authorized, and accepted by the customer.

ISO 17025:2017 7.2 Selection, verification and validation of methods

7.2.1.4 The laboratory shall use methods for laboratory activities which meet customer requirements and which are appropriate for the laboratory activities it undertakes. The laboratory shall ensure that it uses the latest valid edition of a method unless it is not appropriate or possible to do so. When necessary, the application of the method shall be supplemented with additional details to ensure consistent application.

7.2.1.5 When the customer does not specify the method to be used, the laboratory shall select an appropriate method and inform the customer of the method chosen.

ISO 17025:2017 7.2 Selection, verification and validation of methods

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ISO 17025:2017 7.2 Selection, verification and validation of methods

7.2.1.6 The laboratory shall verify that it can properly perform methods before introducing them by ensuring that it can achieve the required performance. Records of the verification shall be maintained. If the method is revised, verification shall be repeated to the extent necessary.

7.2.1.7 When method development is required, this shall be a planned activity and shall be assigned to qualified personnel equipped with adequate resources. As method development proceeds, periodic review shall be carried out to verify that the needs of the customer are still being fulfilled. Any change in requirements requiring modifications to the development plan shall be approved and authorized.

ISO 17025:2017 – Validation of methods 7.2.2

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 – Validation of methods 7.2.2

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.

7.2.2.4 The laboratory shall record the following as evidence of validation:

a) the validation procedure used;

b) specification of the requirements;

c) determination of the performance characteristics of the methods;

d) results obtained;

e) verification that the requirements can be fulfilled by using the method; and

f) a statement on the validity of the method, detailing its fitness for the intended use.

ISO 15189:2020

- ISO-15189 implicitly expects laboratories to create their own written standard operating procedures (SOP), including a SOP for validation

Crucial philosophical and practical matters

- Is your primary intent to minimize bias an imprecision within your laboratory organization or to other measurement systems from the different manufacturers you are purchasing from?
- Do you intend to compare your bias and imprecision using the same or very similar samples as the manufacturer?
  - Manufacturers usually do not provide such data or samples
- Do you intend to compare your bias and imprecision to the same comparison method that the manufacturer used?
  - Manufacturers usually do not provide information on comparison methods
- Do you intend to use certified reference materials or reference measurement methods?

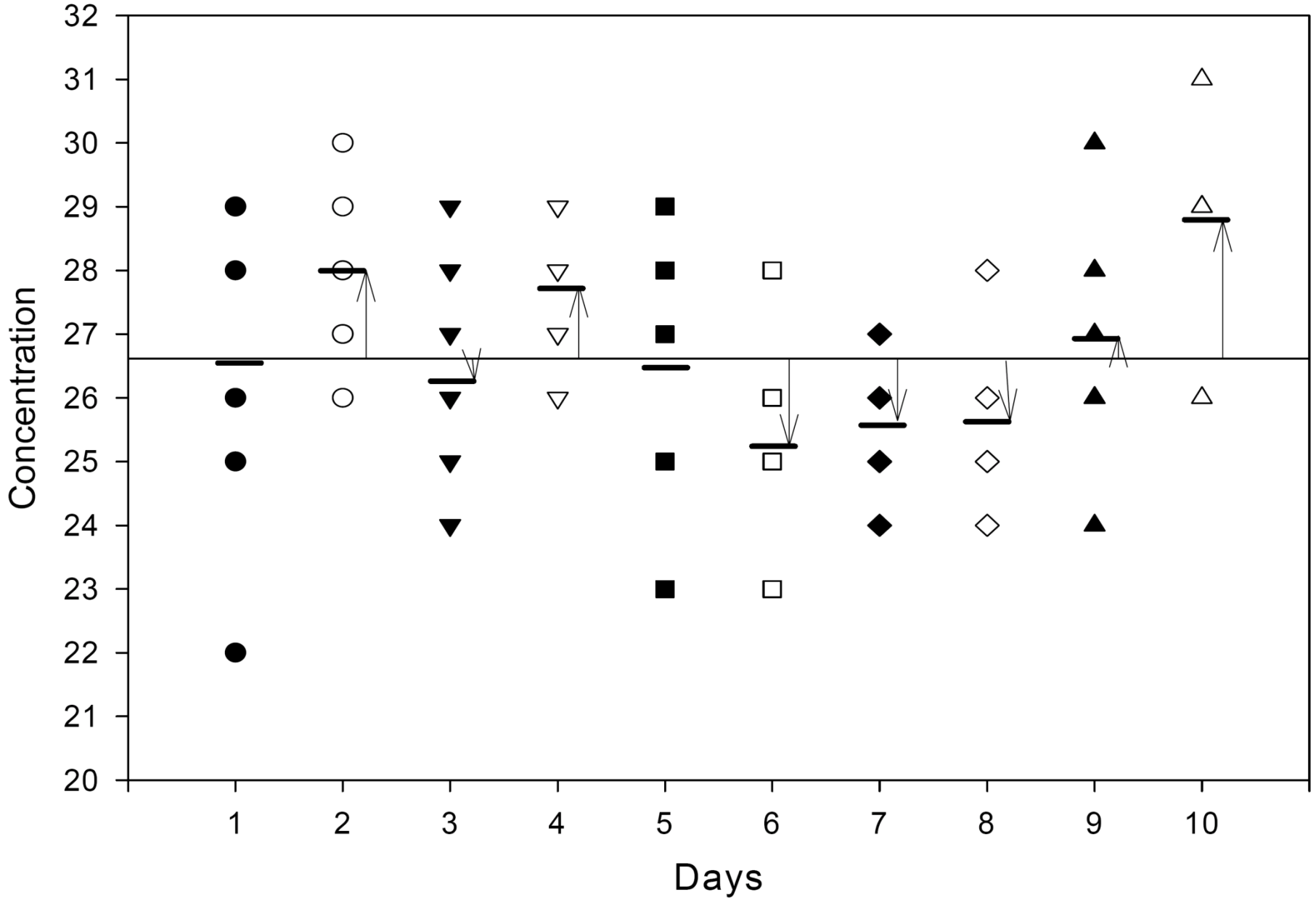
Verification

- 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
  1. bias
  2. reproducibility imprecision
  3. repeatability imprecision

Repeata
bility

and

Reprodu
cibility

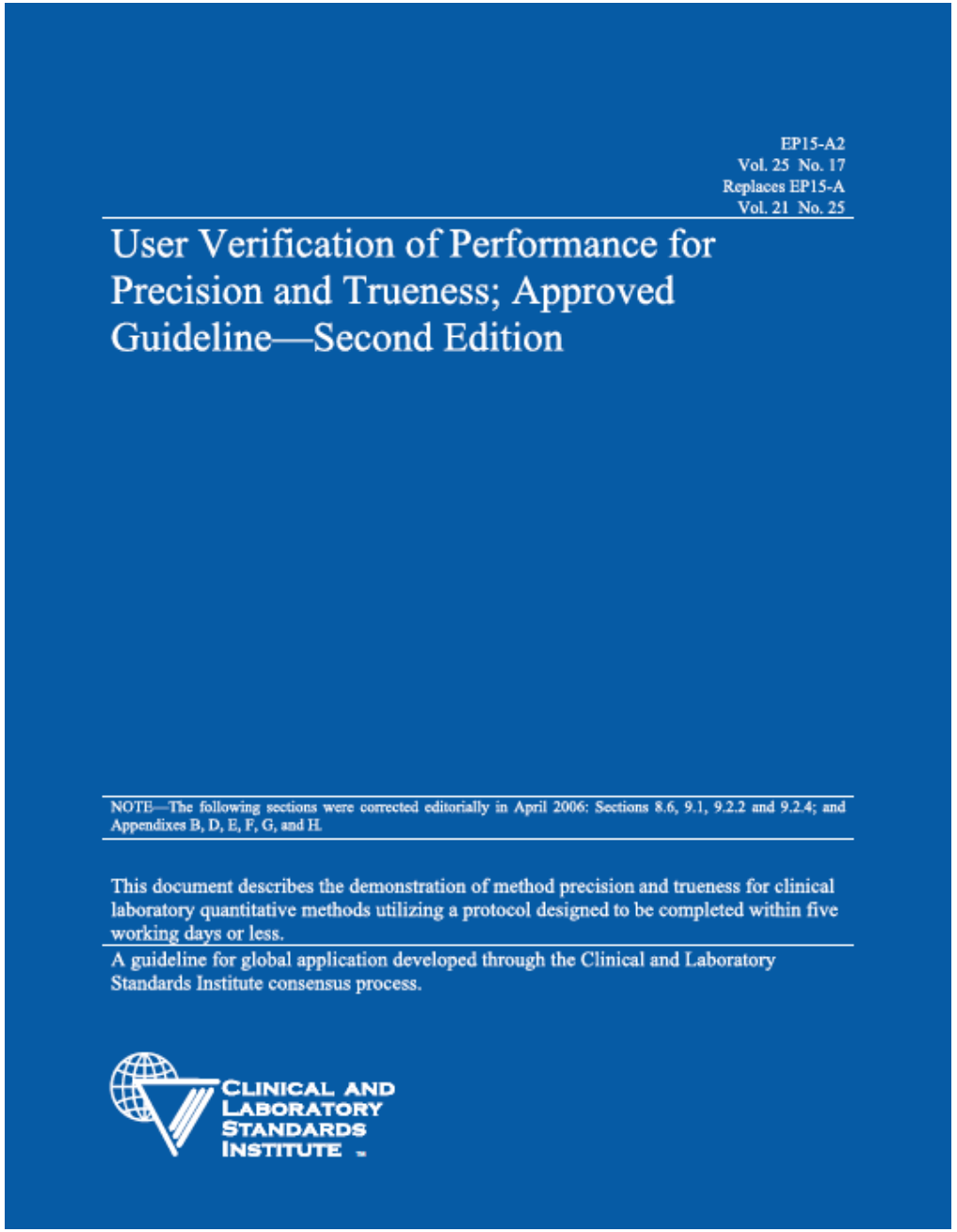


Statistical matters

- The repeatability imprecision influences the calculation of reproducibility imprecision
- Calculation models that compensate for this should therefore be used, e.g. from ISO 5725-2:2019 or from CLSI EP15 when calculating repeatability and reproducibility imprecision

Statistical matters

- The repeatability and/or reproducibility imprecisions may by pure chance exceed values from the manufacturers even though the the true imprecisions are less than the values provided by the manufacturer.
- If the true imprecisions were actually exactly equal to the ones claimed by the manufacturer the calculated imprecisions would exceed their published counterparts fifty percent of the time in verification experiments.
- The user therefore needs to calculate "verification limits" based on the data from the manufacturer and the number of replicates used in the verification experiment.
- Calculation methods and tables provided e.g. in CLSI EP15 or NIST special publication 829 https://www.nist.gov/system/files/documents/mml/csd/inorganic/NIST_SpecialPub829.pdf



CLSI EP15

Single coherent experiment taking five days to perform

Which version of the CLSI EP15?

- EP15-A2 includes bias test using natural patient materials
- EP15-A3 includes bias test using stabilized control materials which may or may not be higher order reference materials
  - The authors of EP15-A3 the comparison using natural patient samples had little value. Users that needed to perform a patient comparison experiment are referred to CLSI EP9-A3 "Measurement procedure comparison and bias estimation using patient samples."

Medical aspects

- The results from Laboratory Medicine are evidently used for diagnosis and for monitoring of treatment results. Decisions on which diagnostic methods and which analytic performance specifications are appropriate are therefore ultimately medical decision best made by the persons in the laboratory with the most extensive appropriate medical schooling.

Educational background

- Persons authorized to technically verify measuring systems can be of any relevant university background – which in my opinion – should be at least four years in total.

Verification guidelines – CLSI EP15

- Verify bias, repeatability precision and reproducibility precision using e.g. EP15-A2 and/or your own SOP based on equal or a bit more extensive principles.

Agree on your own criteria

- Create a working group where all persons responsible for making verification or validation decisions – medical and/or technical participate. Task them to write a SOP for verification.

Vertical revisions

- Establish a routine for vertical revisions twice a year, which also includes revisions of verification activities and possible revision of the verification SOP.

Verification of reference intervals, decision limits, detection limits, limits of quantification

- Verification of reference intervals, decision limits, detection limits, limits of quantification etc. etc. should in my opinion not be a part of standard verification. They should only be done when there is a well-grounded suspicion – e.g. from
  a) comments from clinically active personnel – that e.g. the reference intervals are not appropriate or
  b) from proficiency testing schemes.

Above “single laboratory verification”

- Verifications as of today are practically always “single laboratory verifications” since the manufacturers only have done “single laboratory validations”.
- Estimating and controlling the bias and between measuring system imprecision in a large laboratory organization is highly relevant and something the laboratory may wish to spend time and energy on as other routines mentioned earlier have been implemented.
- My belief is that both the patients and the quality system of the laboratory will benefit from such efforts.