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Eurachem
A focus for analytical chemistry in Europe

Method validation
- overview of accreditation requirements

Presentation at
Eurachem Workshop

Quality Assurance Challenges of Measurements from Field to Laboratory with a Focus on ISO/IEC 17025:2017 Requirements

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(Online event)

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What's on my agenda?

- ✓ A little historical background
- ✓ What is meant by validity, validation – and verification?
- ✓ ISO/IEC 17025:2017 requirements for validation and verification
- ✓ Ways to interprete and deal with requirements
  - Extent of validation efforts
  - The Eurachem guidelines
- ✓ Some new challenges

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Talk about method validation in the 90'es

- ✓ The concept introduced up through the 90'es – e.g.
  - The Valid Analytical Measurements (VAM) principles (UK, 1992)
  - First version of the Eurachem Fitness for Purpose Guide (1998)
- ✓ No formal (formulated!) requirement in the standards used as **basis for accreditation** in that period
- ✓ ISO Guide 25, "*General requirements for the competence of calibration and testing laboratories*" (1985 ?)

The testing shall have adequate documented instructions [..] on standard testing techniques, where the absence of such instructions could jeopardize the efficacity of the testing process

ISO Guide 25, Sect. 10.1

  - Not mentioning the concepts of validity or validation at all
  - Mentioning in the introduction that the guide "..can be used" by ABs as basis for approval of laboratories' competence

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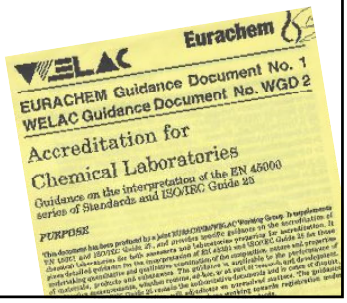
Accreditation practices in the 90'es

- ✓ EN 45001 (1989)
  - Part of the CEN/CENELEC system in Europe
  - More or less "copy/paste" from the ISO Guide 25 …but adding extra point:

"The testing laboratory shall reject requests to perform tests according to test methods that may endanger an objective result or have a low validity"

EN 45001, Sect. 5.4.1

  - I.e mentioning the "validity" concept!
- ✓ Some ABs started requiring MV as a precondition for accreditation (e.g. DANAK)
- ✓ The "Yellow Danger" from EA – eg. EAL-G4:
  - "*Accreditation for Chemical Laboratories. Guidance on the interpretation of theEN 45000 series of Standards and the ISO/IEC Guide 25*" (1993; ≈ Eurachem Guidance Document No. 1)
  - A specific chapter (15) on "Validation"



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Method validation and accreditation

- Included in the first version of ISO/IEC 17025, "*General requirements for the competence of testing and calibration laboratories*" (May 2000)
  - A conformity assessment standard
  - Section on "*Validation of methods*" (5.4.5)
- Remember: ISO/IEC 17025 is the laboratories' standard
  – which can also be used as basis for accreditation
  – and which is basis for many interpretations
- Establishing a QMS (based on ISO/IEC 17025) is not only about **proving competence technically**, but also about assuring the quality of the laboratory's **services towards its customers**, regarding both the **reliability of results** as well as **their fitness for the actual purpose**
- **AND** this is exactly why use of valid methods is so important

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Validity vs. Validation

- Change from talk about **validity** (before ISO/IEC 17025) to focus on **validation**
- Validity = **"Fitness for Purpose"** of a method is obtained through the validation process – fulfilling three purposes:
  1. The purpose of the method being **appropriate for solving the task** in question
  2. The purpose of **giving reliable results** as needed for the decision to be taken by the client
  3. The validation (or verification) process also serves the purpose of making the **laboratory well acquainted with the performance of the method** before start of using it routinely
- BUT maybe too much focus on the process of **validation** instead on the result of the process: **validity**
  - Validity of a method applied in the laboratory must be ensured
    - through validation if the method is not already valid (documented)
    - through verification if the method is already valid (e.g. a standtard met.) confirming it is still valid when applied in the laboratory

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Some definitions

Validity	[no formal definition in relation to metrology] The quality of being well-grounded, sound, or correct Note/example: Other researchers have questioned the validity of the test results. Source: Merriam Webster Dictionary (2022)
Valid	[no formal definition in relation to metrology] Appropriate to the end in view (effective) Source: Merriam Webster Dictionary (2022)

✓ In our context normally: **Validity** =

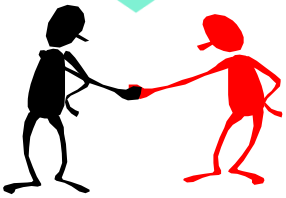
Fitness for Purpose

Some central terms

✓ **Validation**	1) Verification [see below], where the specified requirements are adequate for an intended use Source: VIM 3 (2012)
	2) Confirmation of plausibility for a specific intended use or application through the provision of objective evidence [see above] that specified requirements [see above] have been fulfilled. Source: ISO/IEC 17000 (2020)
Verification	1) Provision of objective evidence that a given item fulfils specified requirements [see above] Source: VIM 3 (2012)
	2) Confirmation of truthfulness through the provision of objective evidence [see above] that specified requirements [see above] have been fulfilled Source: ISO/IEC 17000 (2020)

Method Validation

- ✓ **….. the process of proving that an analytical method is acceptable for its intended purpose**
- ✓ **…and gives results which are valid for decision making**



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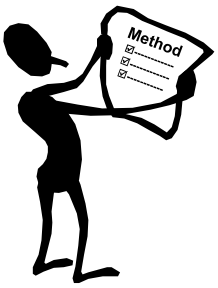
Different categories of methods

1) Standard method
- Already validated
- Requiring **verification** in the laboratory
- Description in place (⇨ SOPs on performance?)

2) Modified standard method
- Requiring **additional validation**
- Description supplemented with internal SOP

3) In-house developed method
- Requiring **full validation**
- Method description/SOP to be elaborated



- ✓ The 2017 version of the ISO/IEC 17025 standard stating option 1) as the primary option !
  - 7.2.1 ***Selection and verification of methods***
  - 7.2.2 ***Validation of methods***

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ISO/IEC 17025:2017
Selection and verification of methods

- Some requirement of use of methods – e.g.

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

ISO/IEC 17025;2017, Sect. 7.2.1.1

- and

The laboratory shall ensure that it uses the latest valid version 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

ISO/IEC 17025;2017, Sect. 7.2.1.3

- The standard does not use the term "standard method" directly! - but latest valid version of a method (= standard method?)
- Appropriate procedures of MU estimation – and use of statistics
- Supplementary SOPs may be relevant (based on experiences from verification studies)

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ISO/IEC 17025:2017
Verification of methods

The laboratory shall verify that it can properly perform methods before introducing them by ensuring that it can achieve the required performance

ISO/IEC 17025;2017, Sect. 7.2.1.5

- No specific requirements on how verification must be done - but must ensure proper performance!
  - I.e. objective evidence that the performance fulfils specified requirements for the valid method must be provided (acc. to definition)
- Furthermore, build up experience with performance of the method (Re. 7.1.2.3)
  - Identify any difficult (risky!) parts of the process, which might endanger a consistent routine performance
  - Possibly elaborate supplementary SOP

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ISO/IEC 17025:2017
Validation of methods

The laboratory shall validate non-standard methods, laboratory-developed methods and standard methods used outside their intended scope or otherwise modified.
The validation shall be as extensive as is necessary to meet the needs of the given application or field of application.

ISO/IEC 17025;2017, Sect. 7.2.2.1

- ✓ Can include **sampling** and **sample handling**
- ✓ The standard is suggesting (in a note) some possible techniques for **validation through comparison** and **in-house validation**

The performance characteristics of validated methods, as assessed for the intended use, shall be relevant to the customers' needs and consistent with specified requirements.

ISO/IEC 17025;2017, Sect. 7.2.2.3

- ✓ **Fitness for Purpose**!

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Performance characteristics

Performance characteristics can include, but are not limited to, measurement range, accuracy, measurement uncertainty of the results, limit of detection, limit of quantification, selectivity of the method, linearity, repeatability or reproducibility, robustness against external influences or cross-sensitivity against interference from the matrix of the sample or test object, and bias.

ISO/IEC 17025;2017, Sect. 7.2.2.3, NOTE

- ✓ I.e. not stated as a general requirement
- ✓ The well-known characteristics
  Note:
  - **Measurement uncertainty** of laboratory results can be influenced by parameters others than the method performance (Coming Eurachem guideline!)
  - Cross-sensitivity against interference from the **matrix** of the sample or test object

⇨ Awareness of possible **Matrix Effects**

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Extent of validation studies

- It has to be decided by the laboratory which performance characteristics need to be investigated as part of a validation study
  - AND how detailed the investigation of a single performance characteristic should be
- Should "in principle" be specified by the customer/user!
- A careful consideration of the analytical specification given in the scope of the documented procedure provides a good start for planning of the validation process.
  (may sometimes also be sector-specific; E.g. pharm. Sector)
- ISO/IEC 17025:2005 (clause 5.4.5.3):
  - ***Validation is always a balance between costs, risks and technical possibilities.***

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WHAT? – and HOW MUCH? (Some risks !)

- Decision on extent of method validation/verification needed in various situations to ensure that the method applied is valid
  - A question about **WHAT**, and **HOW MUCH**, must be done.
- The "**what**", it is a question about which of the typical performance characteristics should be subject to some studies in the laboratory.
  - The decision on this may involve some **risks**
- The "**how much**" relates to the proper number of experi-ments needed in the laboratory to take the best decision about the fitness for purpose of the analytical method.
  - Statistical estimations on the proper number of experiments
  - A **balance** between the risk of **accepting** a method not fit for the purpose and the risk of **rejecting** a method that is fit for the purpose

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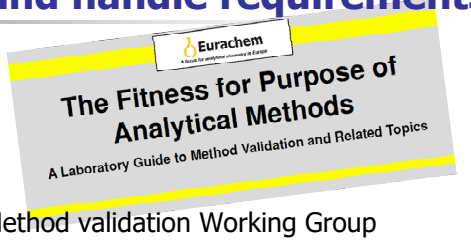
How to interprete and handle requirements



- ✓ Widely applied guidance on method validation:
  - Elaborated by the Eurachem Method validation Working Group
  - 1st version issued in 1998
  - 2nd revised edition, October 2014!
  - 3rd edition under preparation
- ✓ MVWG have issued two supplementary documents
  - ***Planning and Reporting Method Validation Studies***
  - ***Blanks in Method Validation***
  - Working on two new supplements
    "Extend of validation/verification studies" (incl. risk assessment)
    " Method Validation/Verification and assessment of response curves"

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All documents can be downloaded for free from www.eurachem.org

New challenges

- ✓ Looking into the validity of the **sampling process** preceding the testing in the laboratory
  - New Joint Task Group (in collaboration with EUROLAB)
  - Aiming at elaborating new guideline
  - Looking at sampling as an integrated part of the entire measurement process - or as a stand-alone activity
- ✓ Developments within analytical techniques and instrumentation
  - Fitness for Purpose of **Analytical Equipment**
    Possible new guideline
  - **Bioanalytical Methods**
    Supplementing/replacing microbiological test methods
    Requiring new ways of validating/verifying
  - **Non-Targeted Methods**
    Especially validation of data-handling and interpretation will be a challenge

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