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Traceability, validation and measurement uncertainty – 3 pillars for quality of measurement results

David MILDE

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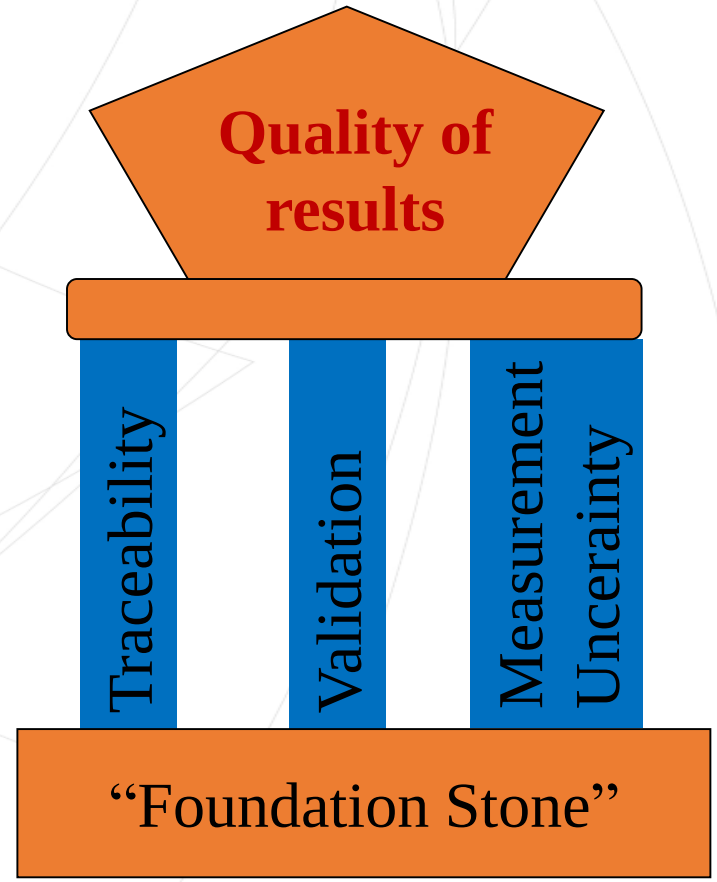
Outline

- Introduction to 3 pillars
- Recommended guidance
- Ex: elemental impurity determination
- Pillars in context
- Conclusion



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Metrological Traceability

Metrological Traceability (VIM 3, Entry 2.41): is a property of a measurement result whereby the result can be related to a stated reference through a documented unbroken chain of calibrations each contributing to the measurement uncertainty.

Traceability to ... stated reference:

- certified value of a reference material
- definition/realisation of an SI unit
- measurement standard

Types of CRMs:

- Pure substances (with stated purity)
- Standard solutions and gas mixtures (prepared gravimetrically)
- Matrix CRMs (Pb in blood)

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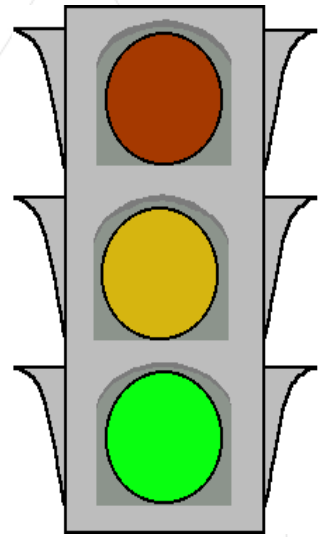
Influence of input quantities



- Based on SOP!
- GREEN – basic degree of control:
  - beakers, many buffers, at room temperature
- AMBER – significant degree of control:
  - calibrated equipment: volumetric flasks, balances, required purity of chemicals
- RED – significant degree of control - stated references:
  - pure substances, calibration solutions, CRM, …

Traceability in ISO/IEC 17025:2017

- Annex A (informative) – Metrological traceability
  - Establishing metrological traceability
  - Demonstrating metrological traceability

A 3.1 Laboratories are responsible for establishing metrological traceability in accordance with this document. Calibration results from laboratories conforming to this document provide metrological traceability. Certified values of certified reference materials from reference material producers conforming to ISO 17034 provide metrological traceability. There are various ways to demonstrate conformity with this document: third party recognition (such as an accreditation body), external assessment by customers or self-assessment.

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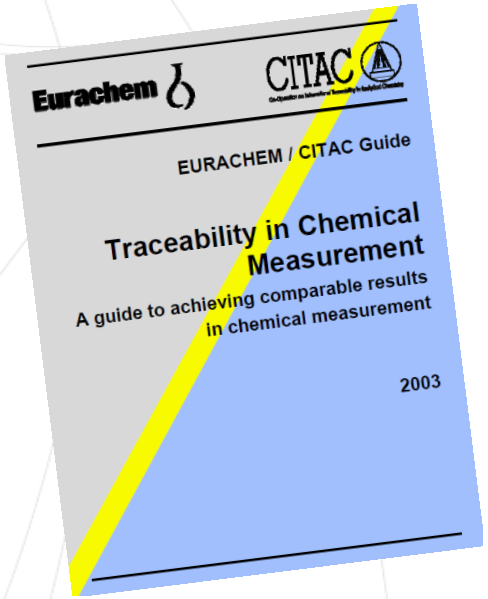
Traceability Guidance



- EURACHEM / CITAC Guide; Traceability in Chemical Measurement (2003): www.eurachem.org;
  - **UNDER REVISION**
- Barwick V., Wood S.: Meeting the Traceability Requirements of ISO 17025: An Analyst's Guide. LGC, 2005. (ISBN 0 948926 236)

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Method Validation

Validation (VIM 3, Entry 2.45): verification, where the specified requirements are adequate for an intended use

Verification (VIM 3, Entry 2.44): provision of objective evidence that a given item fulfills specified requirements

The Validation Checklist

Performance parameters

- ☐ **Selectivity**
- ☐ **Linearity, measuring interval**
- ☐ **LOD, LOQ**
- ☐ **Precision**
- ☐ **Trueness**
  - ☐ **Recovery**
- ☐ **Ruggedness (robustness)**

Parameter	Type of analysis		
	Qualitative	Major component	Trace analysis
Selectivity	+	+	+
Precision		+	+
Trueness		+	+
LOD	+		+
LOQ			+
Measuring interval		+	+
Ruggedness	+	+	+

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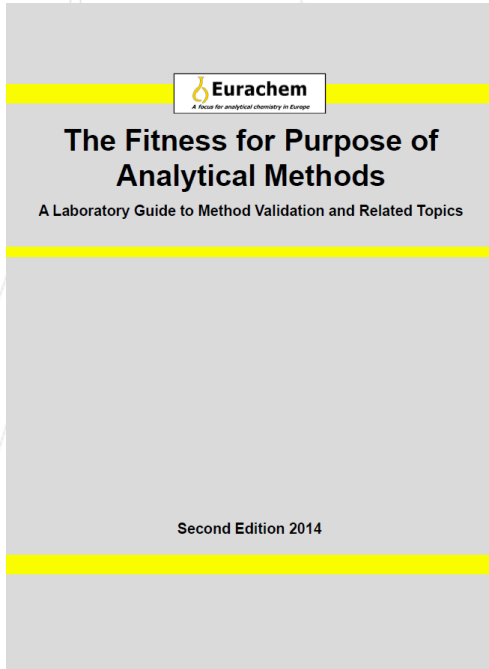
Validation Guidance

- Eurachem Guide: The Fitness for Purpose of Analytical Methods – A Laboratory Guide to Method Validation and Related Topics, (2nd ed. 2014). ISBN 978-91-87461-59-0. www.eurachem.org
- Filed specific guidance:
  - Ex: ICH Q2(R1) – Validation of Analytical Procedures: Text and Methodology
  - …



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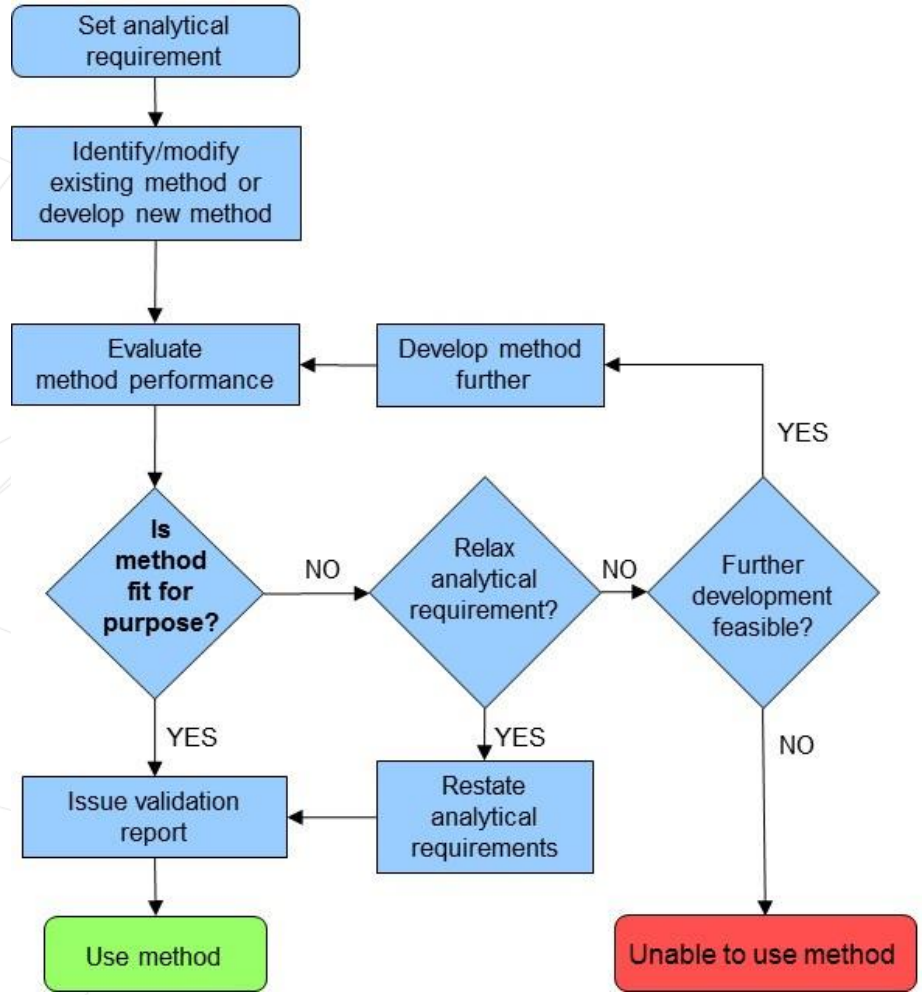
Eurachem "Validation Guide"

- The 2nd edition includes guidance on:
  - The concept of method validation;
  - The background and rationale for method validation;
  - How a method validation study should be performed and how much should be done (validation/verification);
  - A thorough explanation of the various validation parameters (performance characteristics);
  - Follow-up on the validation study (reporting, use of performance data in Internal Quality Control);
  - Documentation of analytical methods.



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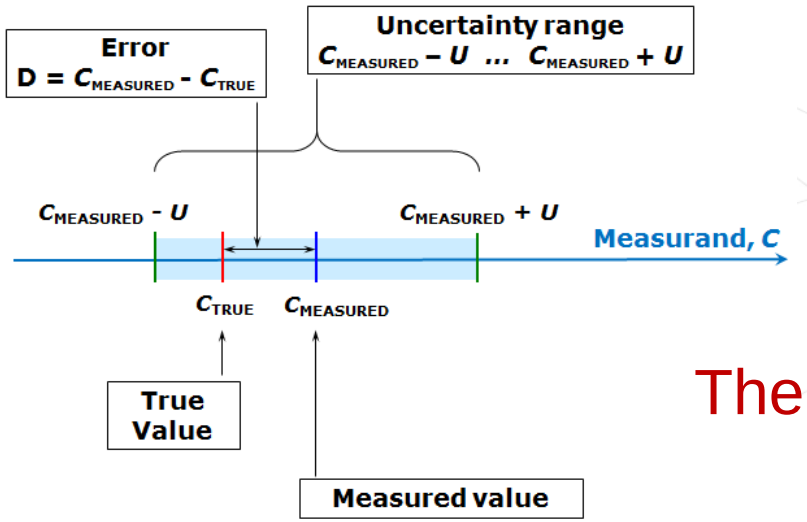
Measurement Uncertainty

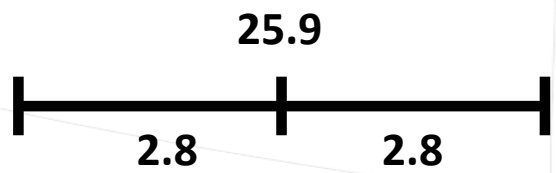
Measurement Uncertainty (Entry 2.26): Non-negative parameter characterizing the dispersion of the quantity values being attributed to a measurand, based on the information used.

VIM3: JCGM 200:2008; International vocabulary of metrology — Basic and general concepts and associated terms (VIM) (2008).



Mass concentration of a substance is
25.9 ± 2.8 mg/kg

The part of the result after the **±**



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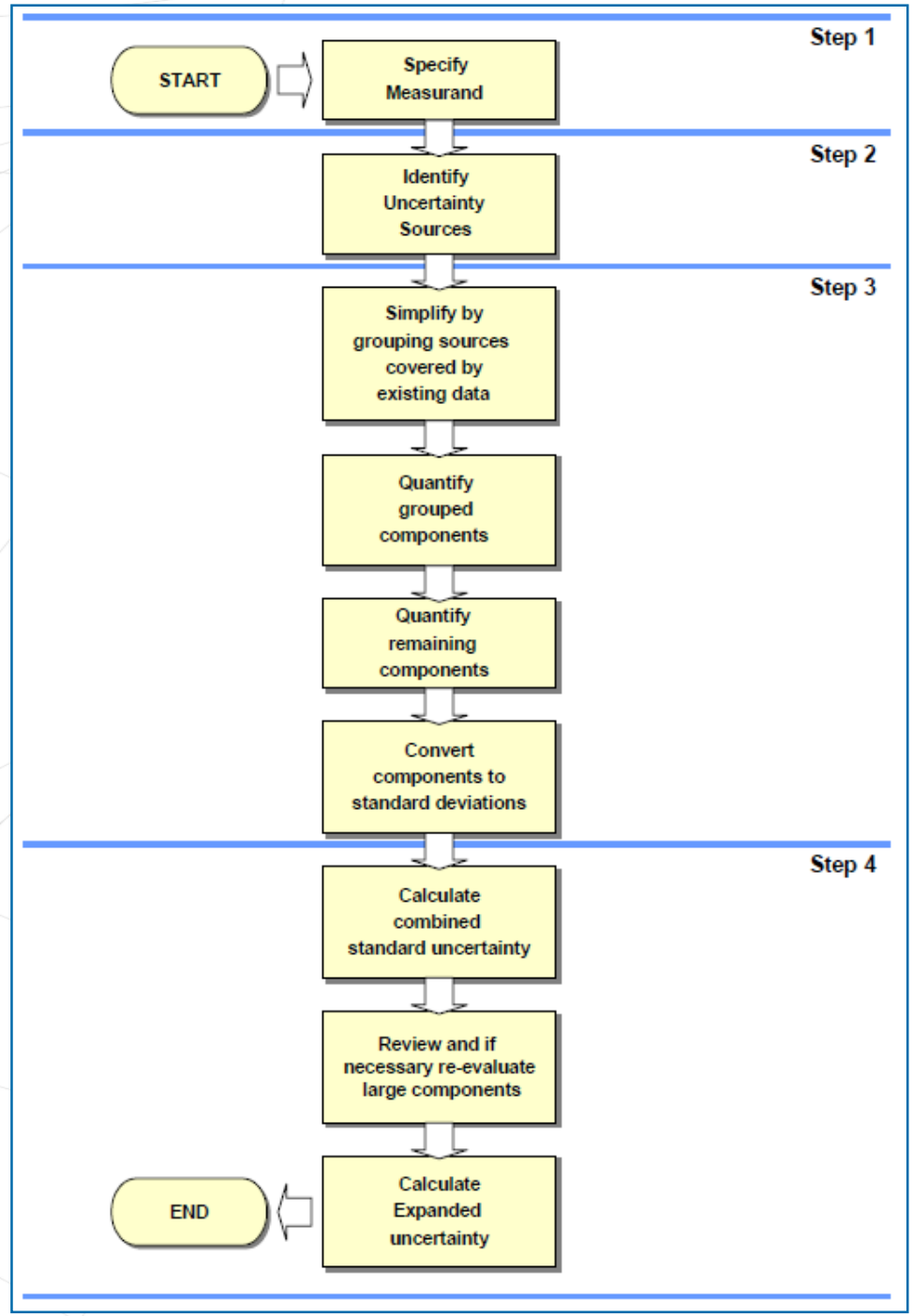
Uncertainty Estimation Process

- **Standard uncertainty u_x**
  - Find uncertainty for each component
  - Type A: from the statistical distribution
  - Type B: other information
- **Combined standard uncertainty $u_c(y)$**
  - Law of propagation of uncertainty (GUM)
  - Modifications: Kragten approach, …
  - Monte-Carlo simulation
- **Expanded uncertainty U**



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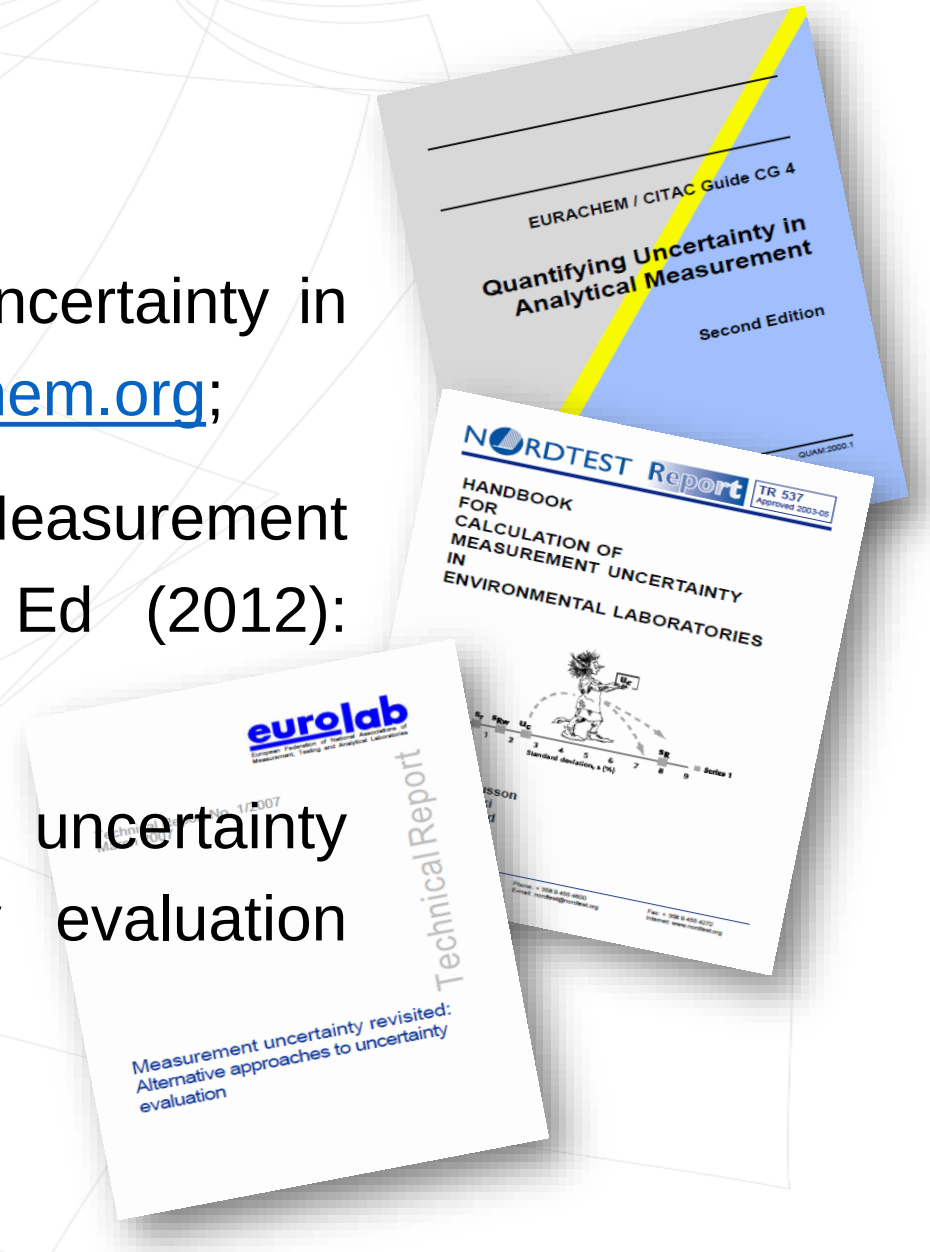
MU Guidance

- EURACHEM / CITAC Guide CG 4; Quantifying Uncertainty in Analytical Measurement; 3rd Ed (2012): www.eurachem.org;
- Nortdtest TR537; Handbook for Calculation of Measurement Uncertainty in Environmental Laboratories; 3rd Ed (2012): www.nordtest.info;
- Technical Report No. 1/2007; Measurement uncertainty revisited: Alternative approaches to uncertainty evaluation (2007): www.eurolab.org.



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Elemental Impurities in pharmaceuticals

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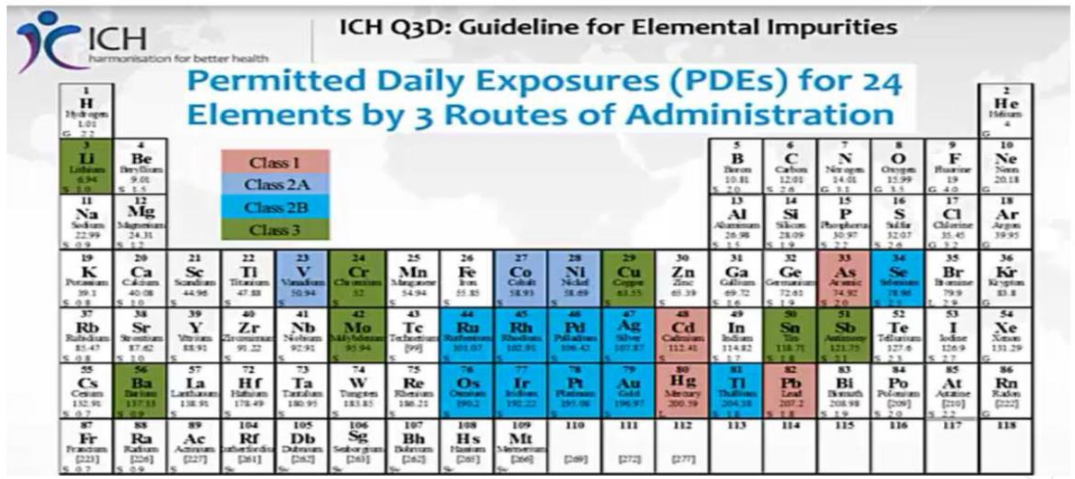
New “legislation”

- **US Pharmacopeia**
  - Chapter <232> ELEMENTAL IMPURITIES – LIMITS
    - Specifies limits for the amounts of elemental impurities in drug products.
    - A risk based strategy when analysts determine how to assure compliance with the standard.
  - Chapter <233> ELEMENTAL IMPURITIES – PROCEDURES
    - Procedures: ICP-OES, ICP-MS
    - Alternative procedures – must be validated and show to be acceptable.
- **ICH (International Conference on Harmonization …)**
  - ICH Q3D ELEMENTAL IMPURITIES – Guidance for Industry



Decock G.: Eurofins Pharma Presentation 17/11/2015

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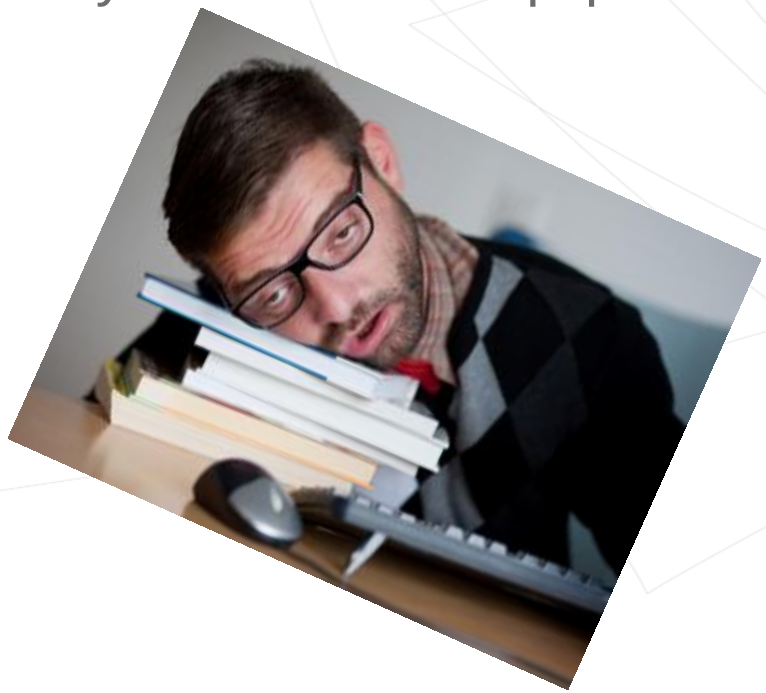
Good Manufacturing Practice (GMP, GLP)

- General management documentation
- Standard operation procedures (SOP)
- Written instructions for *everything*
- Daily control of all equipment in the lab



SÚKL **State Institute for Drug Control**

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Web: www.sukl.cz

Certifikát spisová zn.: / Certificate Ref. No.: sukls152628/2014

CERTIFIKÁT SVP PRO VÝROBCE
Část 1

Vydaný po inspekci v souladu s článkem 111(5) Směrnice 2001/83/ES a s §13, odst. 2, písm. a bod 3 zákona č. 378/2007 Sb., o léčivech a o změnách některých souvisejících zákonů (zákon o léčivech), ve znění pozdějších předpisů.

Příslušný orgán České republiky potvrzuje následující:

Kontrolní laboratoř:
Univerzita Palackého v Olomouci
Křížkovského 511/8
771 47 Olomouc

Adresa místa kontroly jakosti:
Univerzita Palackého v Olomouci
Přírodovědecká fakulta, Katedra analytické chemie, budova

CERTIFICATE OF GMP COMPLIANCE OF A MANUFACTURER
Part 1

Issued following an inspection in accordance with Art. 111(5) of Directive 2001/83/EC and Section 13, paragraph 2, letter a, point 3 of the Act No 378/2007 Coll., on Pharmaceuticals and on Amendments to Some Related Acts (the Act on Pharmaceuticals), as amended.

The competent authority of the Czech Republic confirms the following:

The control laboratory:
Univerzita Palackého v Olomouci
Křížkovského 511/8
771 47 Olomouc

Site address:
Univerzita Palackého v Olomouci
Přírodovědecká fakulta, Katedra analytické chemie, budova

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Elemental impurities

- Sample preparation:
  - Closed vessel digestion: MW with mixture of acids (HNO_3, HCl, $HClO_4$, H_2O_2)
- ICP-MS determination (quad, collision cell)
- Risk assessment on 3 batches for each API:
  - Blanks ⇒ LOD, LOQ
  - Precision – repeatability conditions
  - Accuracy – recovery
  - Linearity
  - Screening of elemental impurities in APIs / final products.

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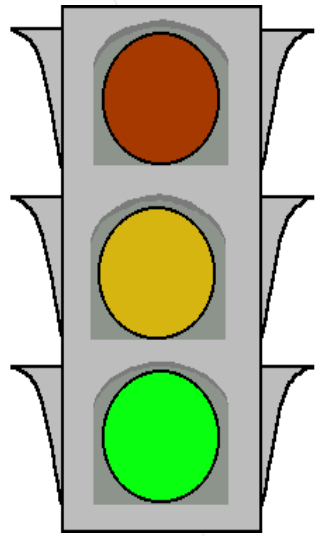
Metrological Traceability

- Demonstration of traceability in our lab:
  - CRM solutions for calibration – certificate of the CRM;
    - Expiration (shelf life)
  - Mass of a sample – calibration certificate of the balance;
  - Volume of volumetric flasks – calibration certificate of the manufacturer;
  - Microwave digestion unit – regular service – protocol;
  - ICP-MS – regular service & qualification (IQ/OQ) – protocols;
    - Performance check on daily basis



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Method Validation

- Every procedure used under GMP shall be validated!
  - We have a SOP dealing with validation & acceptance criteria.
  - It is based on **ICH Q2(R1) – Validation of Analytical Procedures: Text and Methodology.**
  - More rigorous approach – parameters, minimum of repeated measurements.

Type of analytical procedure characteristics	IDENTIFICATION	TESTING FOR IMPURITIES quantitat.	 limit	ASSAY - dissolution (measurement only) - content/potency
Accuracy	-	+	-	+
Precision				
Repeatability	-	+	-	+
Interm.Precision	-	+ (1)	-	+ (1)
Specificity (2)	+	+	+	+
Detection Limit	-	- (3)	+	-
Quantitation Limit	-	+	-	-
Linearity	-	+	-	+
Range	-	+	-	+

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Přírodovědecká fakulta

R-lab

Method Validation

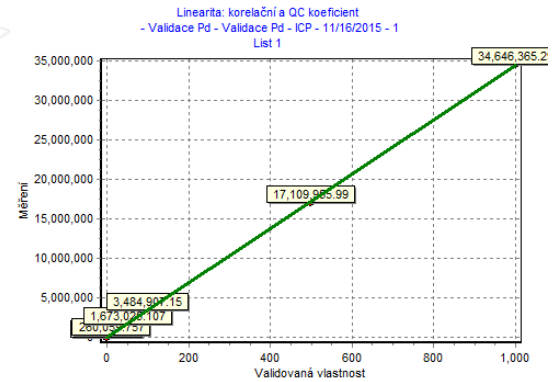
- **PROCEDURE:**
  1. **Validation protocol:** validation experiments, acceptance criteria
  2. Perform **validation experiments**
  3. **Validation report:** evaluation, compliance with criteria

Characteristic	Acceptance criteria	Experimental data
Linearity	R ≥ 0.99	R = 0.9998
Range	LOQ – 1000 µg.L^{-1}	1.17 – 1000 µg.L^{-1}
LOD	≤ 0.6 µg.L^{-1}	0.57 µg/L (n = 10)
LOQ	≤ 1.8 µg.L^{-1}	1.17 µg/L (n = 10)
Accuracy (recovery)	70 – 150 %	104.7 – 109.5 % (3 levels)
Precision (repeatability)	RSD < 20 %	< 5.2 % (n = 6)
Intermediate precision	RSD <25 %	< 7.9 (n = 2×6)
Specifity	recovery 70 – 150 %	92.9 – 115.3 % (^{105}Pd, ^{108}Pd)
Robustness	recovery 70 – 150 %	107.7 – 119.2 % (modifications in procedure)

VAZ-AS-001
Počet příloh: 5

Validační zpráva

Stanovení paladia jako nečistoty v aktivních farmaceutických substancích, meziproduktech a výchozích surovinách pomocí ICP-MS



Tab. 6: Přesnost - naměřená data

Měření	Spike 50 (µg/l)	Spike 500 (µg/l)	Spike 800 (µg/l)
1	51,20485347	508,7766914	811,9588187
2	53,01429983	525,2848819	836,6723320
3	54,37651572	527,7519614	836,8858552
4	54,08283967	539,0854652	847,8081330
5	56,76445689	518,6073688	838,9528434
6	59,18893703	539,6886986	851,0177846

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Ex: top down approach (MU)

- Trace metal analysis in coffee by AAS and ICP-MS:
  - Microwave digestion of roasted coffee beans (HNO_3 + H_2O_2)
  - CRM NSC ZC 73014 Tea
  - validation and subsequently MU evaluation

$$u_c(y) = \sqrt{S_{RW}^2 + u_{bias}^2} \qquad u_{bias} = \sqrt{\Delta^2 + u_{ref}^2}$$

$$U = 2 \times u_c(y)$$

	Relative uncertainty (%)	
	ICP-MS	AAS
Ca	6.22	7.20
Cu	6.87	11.37
Fe	7.91	24.78
Mg	5.51	8.73
Zn	6.11	10.03
Cd	17.01	25.67
Cr	13.82	33.70
Mn	6.28	13.15
Ni	15.64	28.50
Pb	16.53	34.07

Jarošová M., Milde D., Kuba M.: Czech J. Food Sci. **32**, 354-359 (2014).

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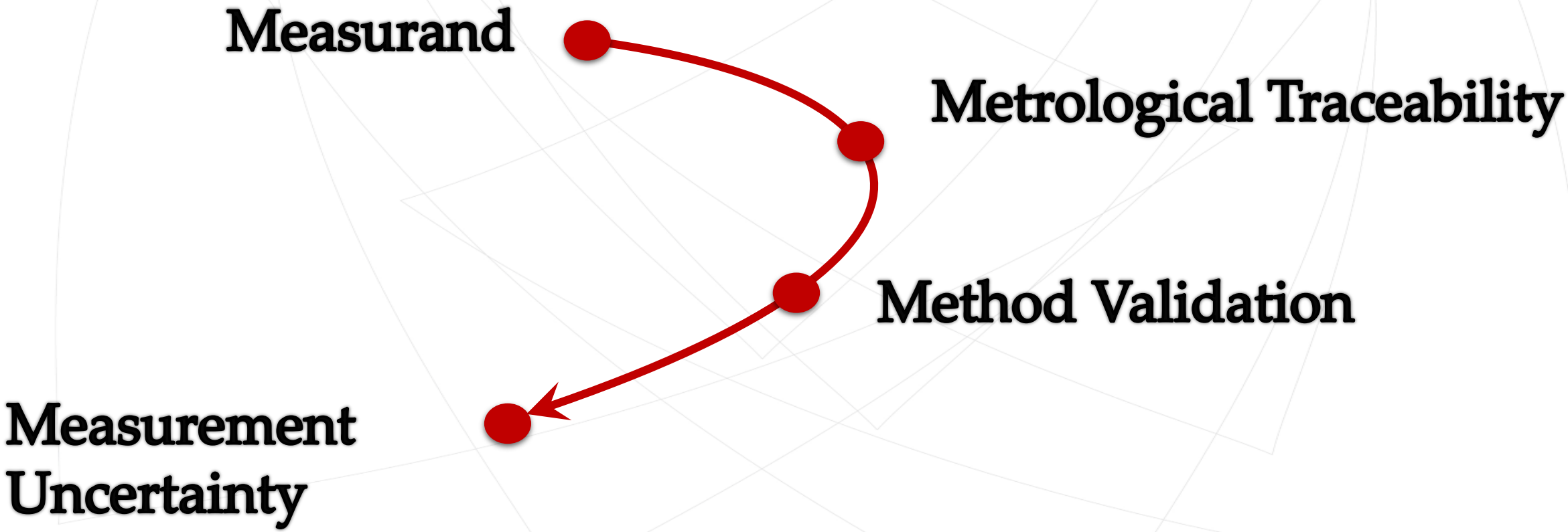
The chrono(logical) relation between concepts



Paul De Bièvre: ACQUAL (2010).

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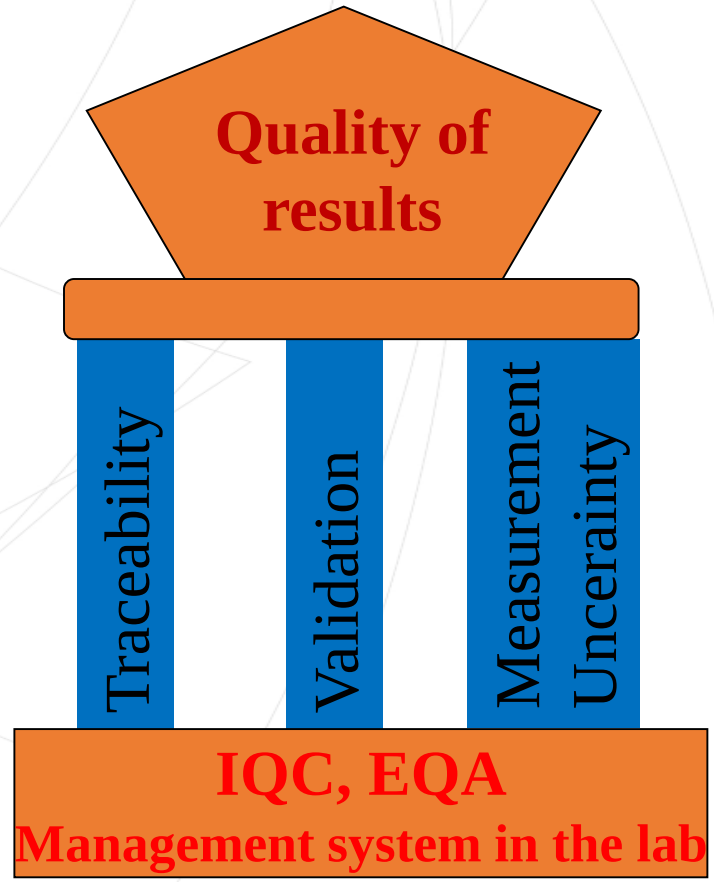
Conclusions

- 3 pillars are necessary for quality of results
- Mainly in development of a new method

- What does a foundation stone mean?
  - Internal quality control (IQC)
  - External quality assessment (EQA)
  - Management system in the lab



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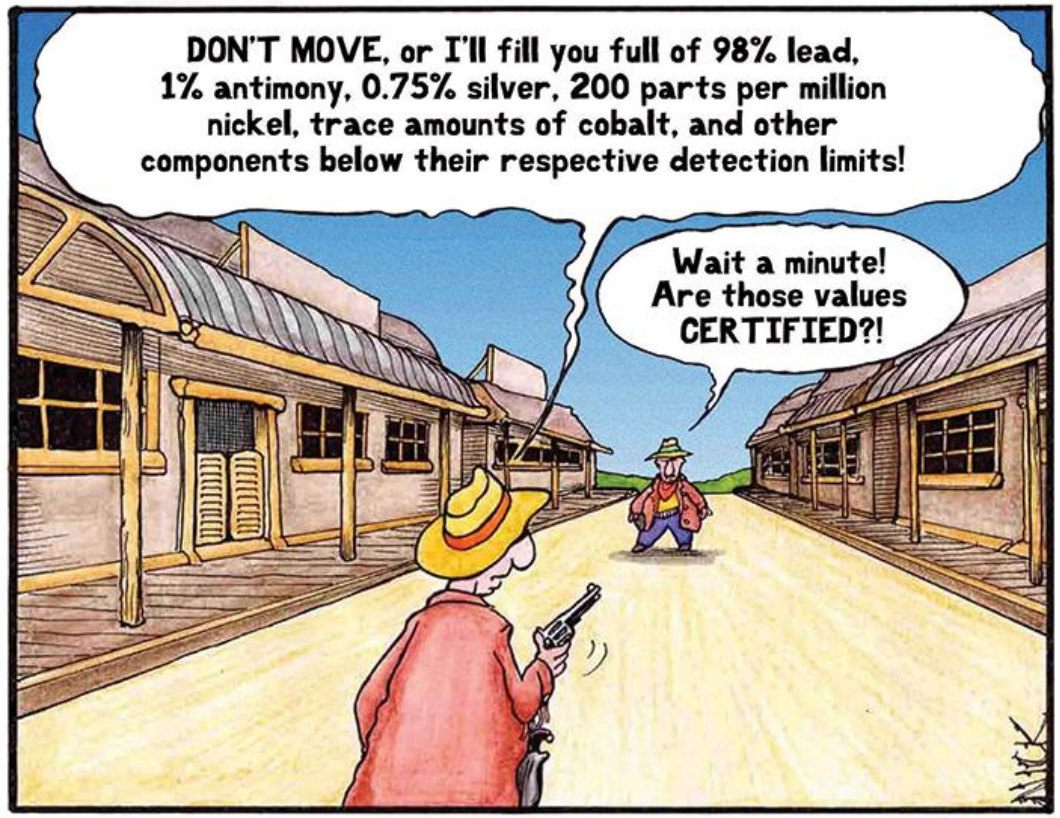
Acknowledgment



Analytical Chemists in the Wild West

Thank You for Your kind attention!

Financial support: Ministry of Education, youth and Sports (LTV 17015)