My desk 3 months before an ISO 17025 audit

An auditor's perspective on

Method Validation

A (hopefully) comprehensive guide on how to handle method validation, drafted for convincing everyone of the importance of validating all analytical methods and keep such validation reports up-to-date

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Tanaka Kikinzoku & Metalor Technologies

LBMA Assaying & Refining Conference

March 2023

Definition of Method Validation

- Validation is [ISO 9000:2015]

  the confirmation, through the provision of objective evidence, that the requirements for a specific intended use or application have been fulfilled

In English…

- Validation confirms that

  an analytical method is fit for its intended purpose

  and provides accurate results

When & How to Validate ?

When to Validate ?

- One simple rule: not just before an auditor visit…

- Before applying a new method
- After any significant change of analytical conditions
  (such as change in concentration range or matrix)
- After any change of instrument or environment (infrastructure, location…)

How to Validate ?

- Depends on the purpose (ISO 17025 accreditation, customer request…)
- This presentation proposes *one approach to method validation*,
  specifically optimised for our precious metal industry

Define Method Purpose

Before any validation, the following have to be clearly defined:

- What shall the method quantify ?
- What is the desired range of measurement ?
- What is the matrix ?
- What precision is required ?
- Which uncertainty is acceptable ?

6 Phases in Physico-Chemical Analyses

- Sample taking
- Storage / Transportation
- Pre-treatment (homogeneisation…)

} Pre-analytical phases

- Preparation (mineralization…)
- Analysis
- Result evaluation

} Analytical phases

This presentation focuses only on the analytical phases.
But the pre-analytical phases should not be neglected!

A General Canvas – in 7 Steps

- ❶ Identification — What is being measured ?
- ❷ Working range — What is a valid range for the result ?
- ❸ Precision — How repeated results compare to each other ?
- ❹ Accuracy — How far off the true value is the result ?
- ❺ Uncertainty — How far off the true value could the result be ?
- ❻ Stability — Do the results degrade over time ?
- ❼ Robustness — What could become a problem ?

❶ Identification

- Specificity

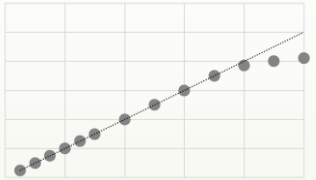
Ability to measure an analyte of interest in a sample without interferences generated by other components of the sample

SPARK-OES : list wavelengths used for each element and check for interferences

Cupellation : determine if Pt, Pd, Ir, Ru, Rh can be present in the final gold cornet

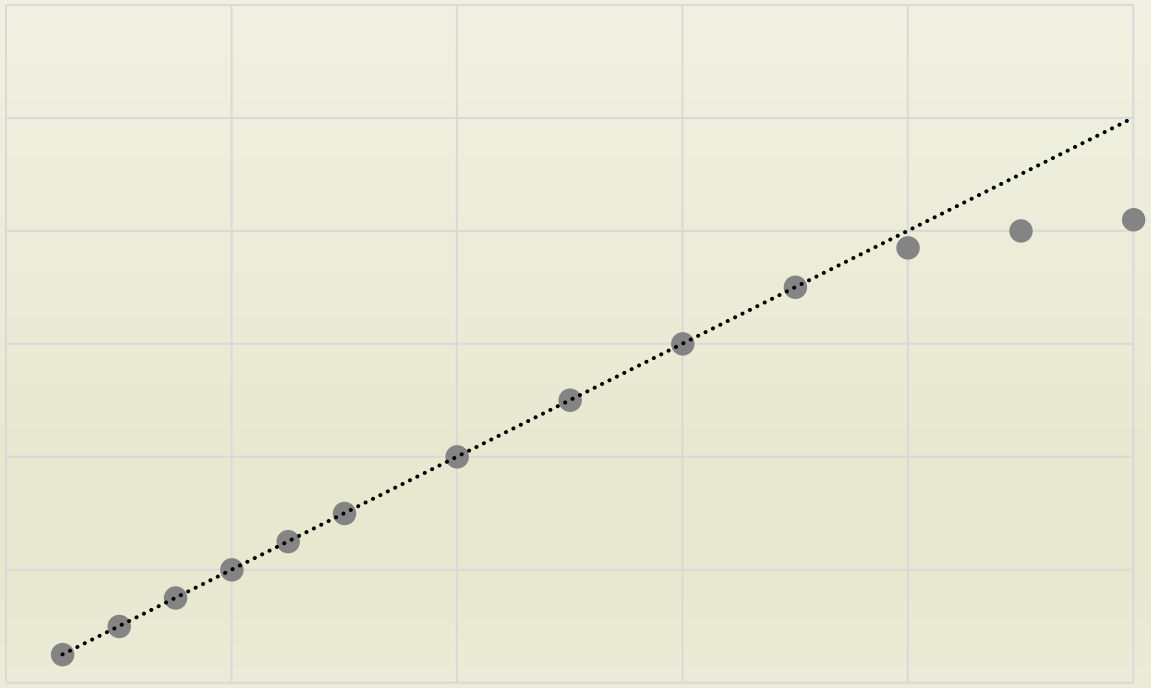
Potentiometry : ensure no Pd is impacting on the titration

❷ Working range



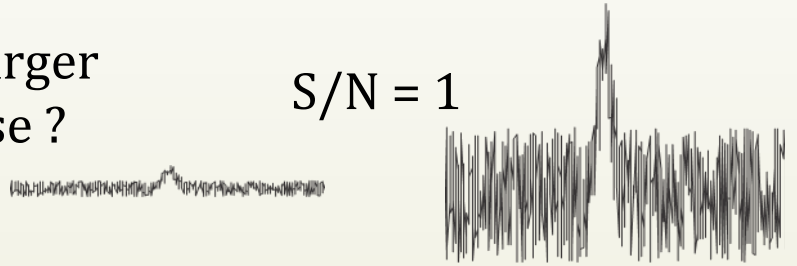
Working range

- Detection & Quantification Limits
- Linearity
- Sensitivity



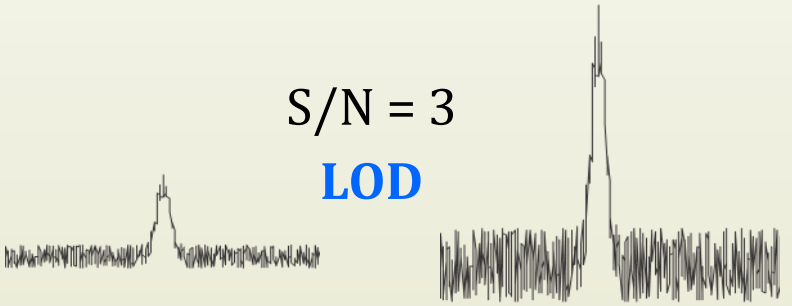
❷ Limits of Detection & Quantification

Is the signal larger than the noise ?



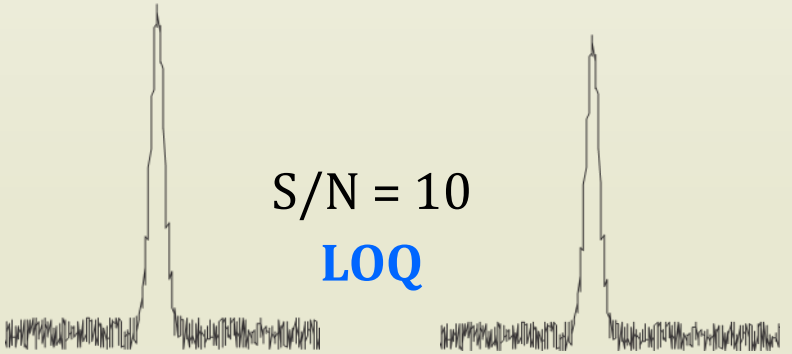
Limit of Detection LOD

- Lowest amount of a substance that can be distinguished from a blank (signal > its uncertainty)
- Quantity of the analyte that provides a signal / noise ratio (S/N) = 3



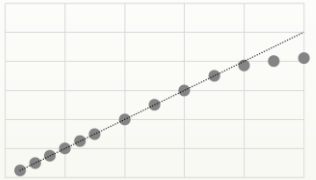
Limit of Quantification LOQ

- Lowest amount that can be quantified reliably
- Quantity of the analyte that provides a S/N = 10



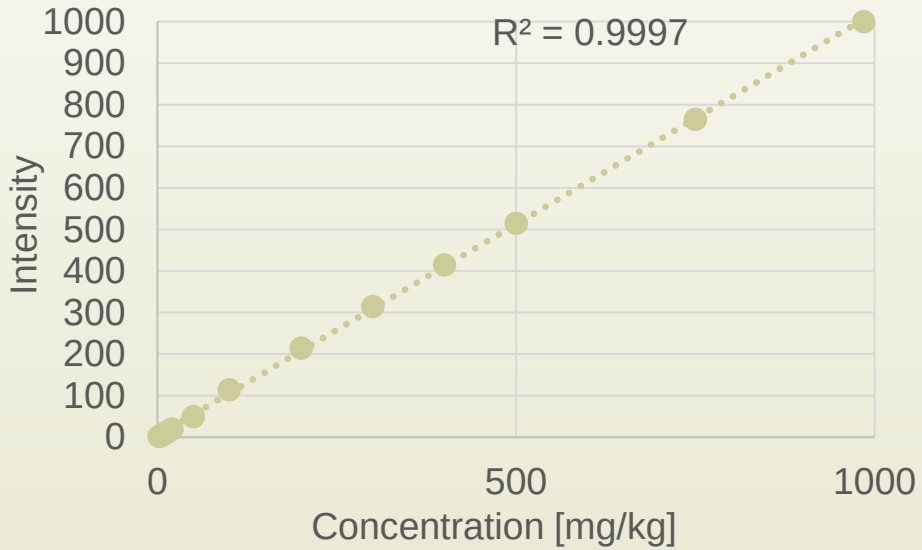
How to determine ? Easiest method : blank measurements

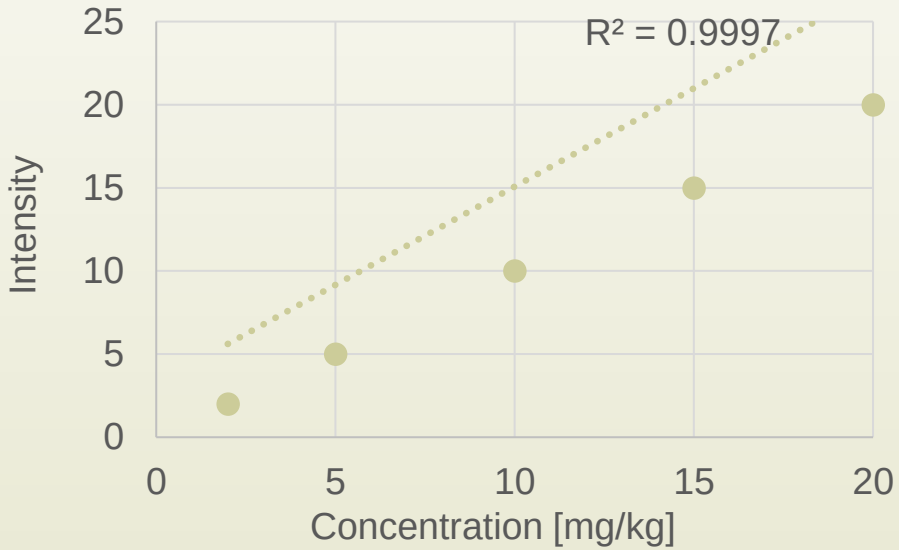
❷ Linearity



- Most quantitative analytical methods are based on a linear calibration
- But some equipment can use quadratic models (like SPARK-OES)
- Linearity and Working range have to be considered simultaneously
- Don’t rely on R / R^2 as an indicator of the quality of your model !

❷ Linearity

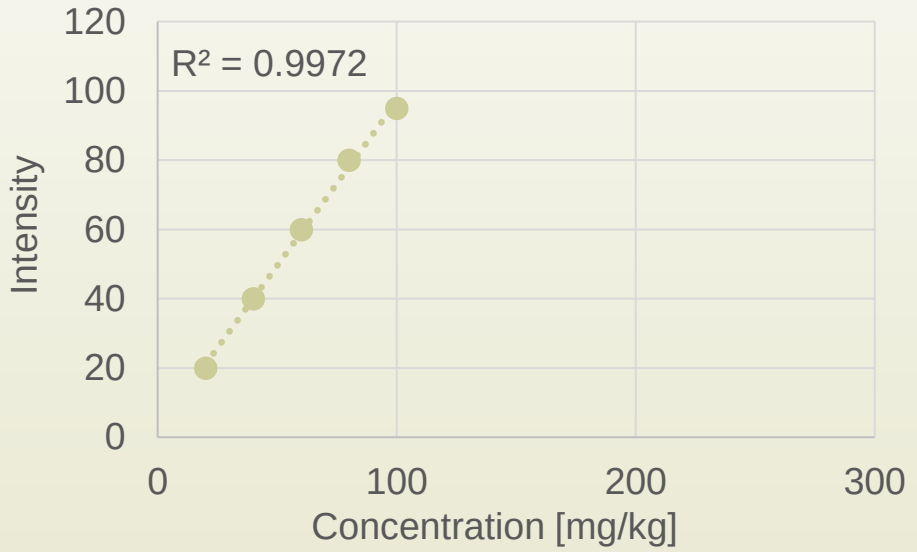


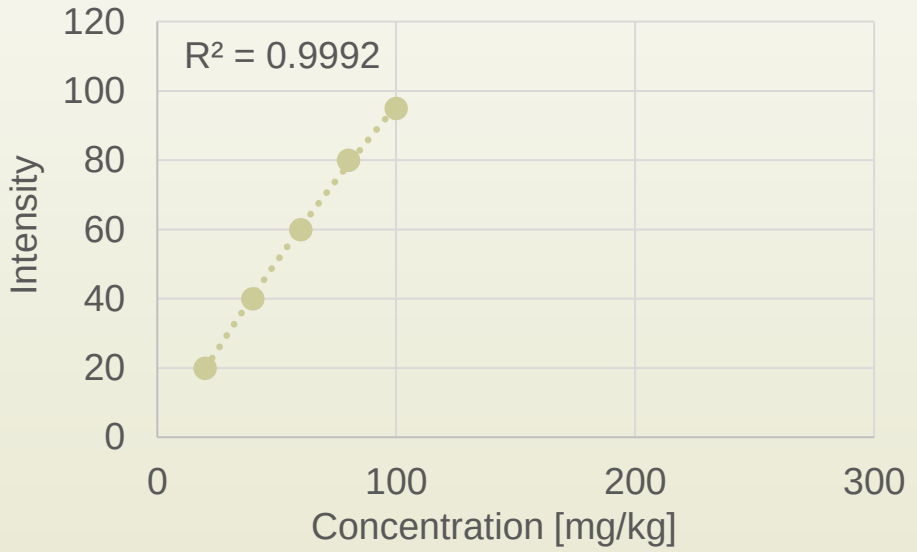


R^2 indicates an excellent fit…

… but it does not show potential issues at low concentration

❷ Linearity

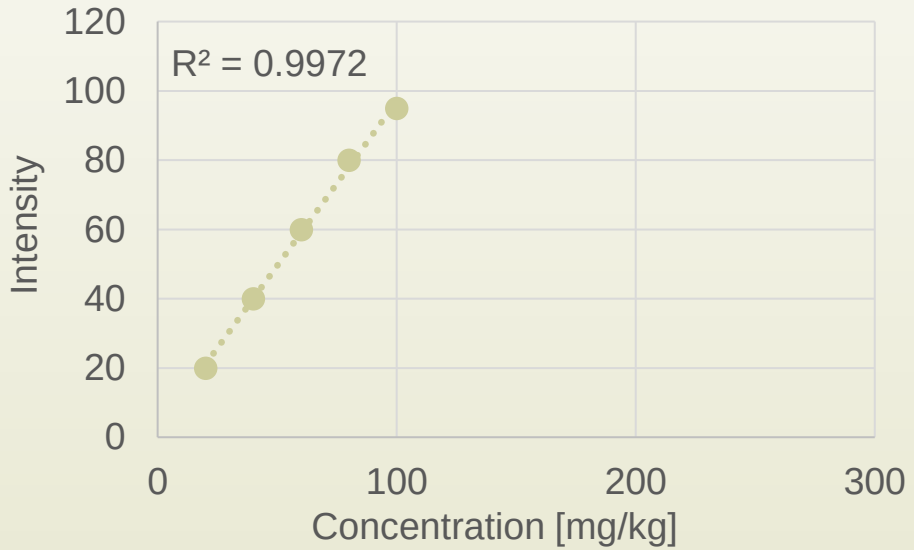


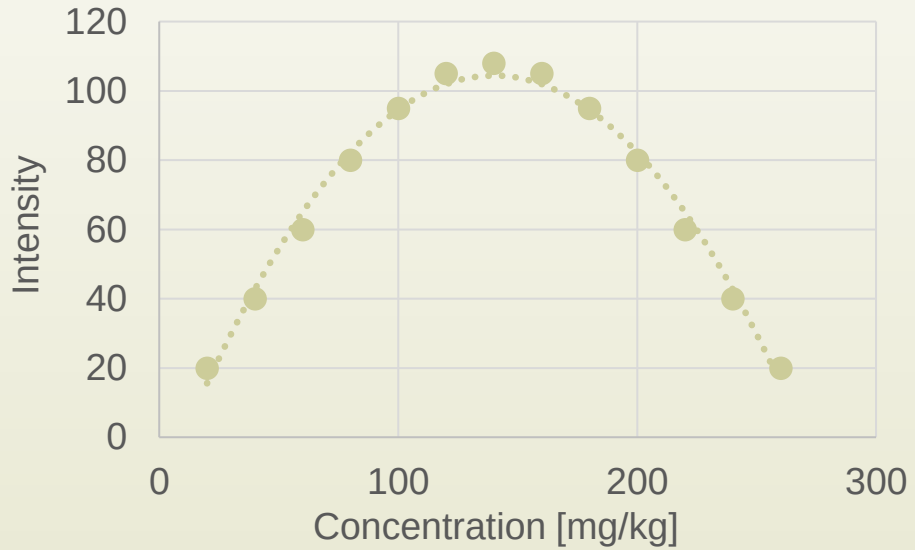


R^2 indicates an excellent fit for the linear model

Some instruments might even select a quadratic model (x^2…), which will improve further R^2

❷ Linearity





R^2 indicates an excellent fit for the linear model

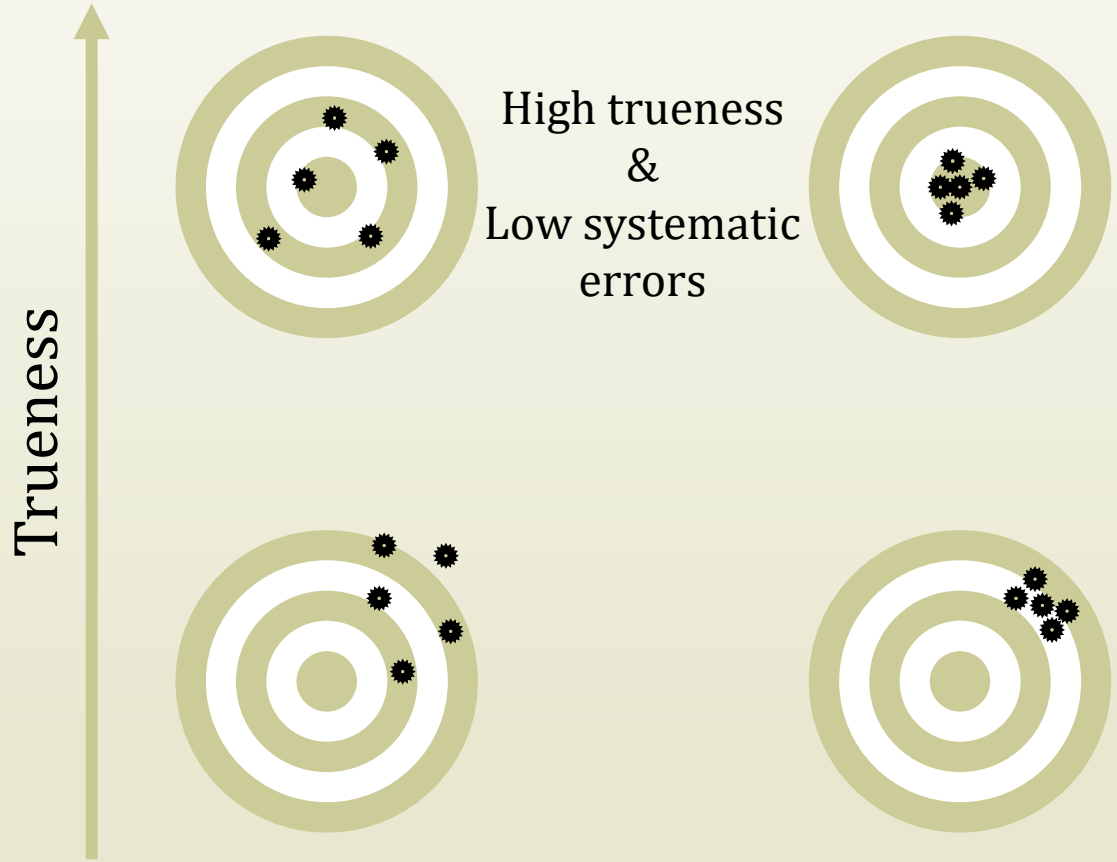
Quadratic models can be dangerous! Especially when you go away from the validated working range…

Definitions

There are many terms used to describe how an analytical method is performing :

Trueness
Accuracy
Systematic error
Random error
Repeatability
Ruggedness
Repeatability…

Definitions

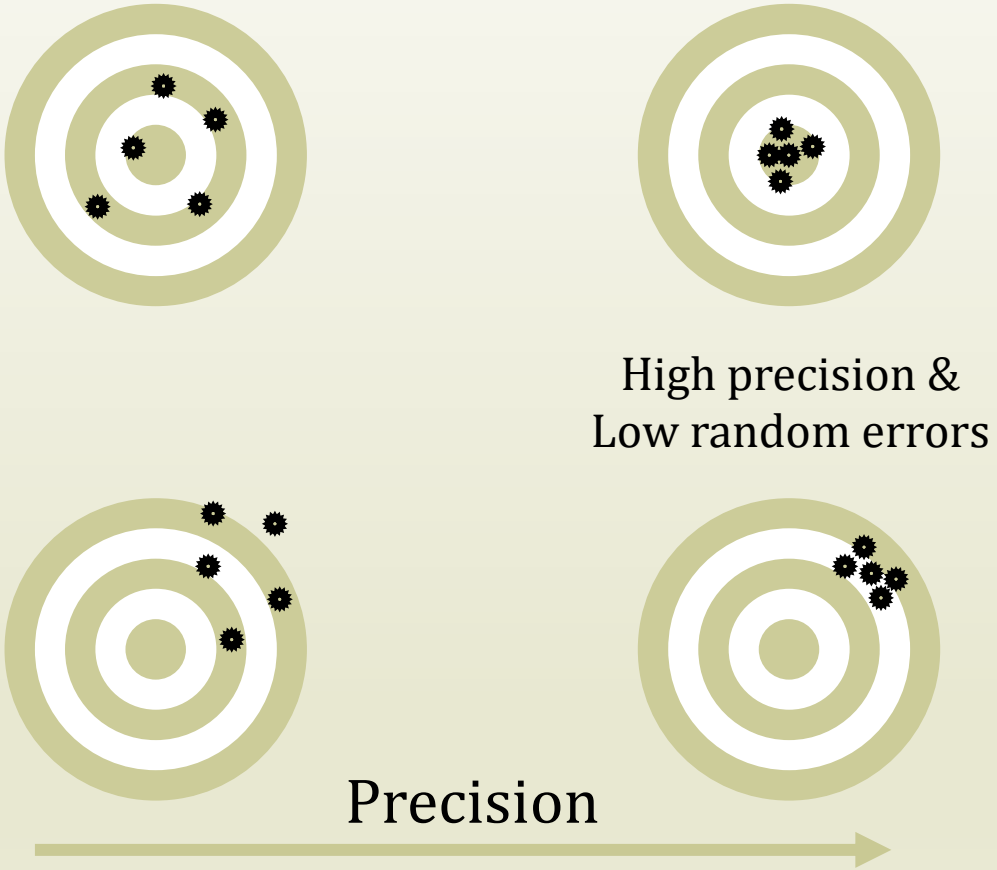


Trueness
≠ Systematic error

agreement of a collection of measurements with the true value

See ISO 5725-1 – Accuracy (trueness and precision) of measurement methods and results — Part 1: General principles and definitions

Definitions

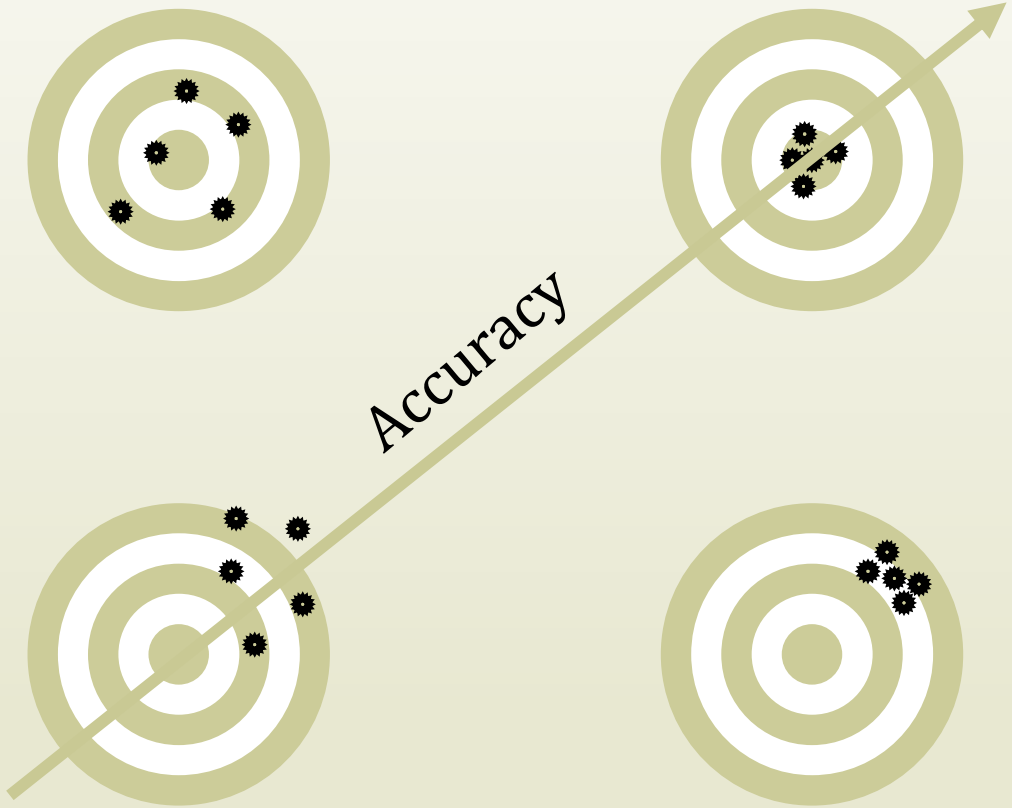


Precision
≠ Random error

agreement of a collection of measurements with each other

Precision → Step ❸

Definitions



High accuracy &
Low uncertainty

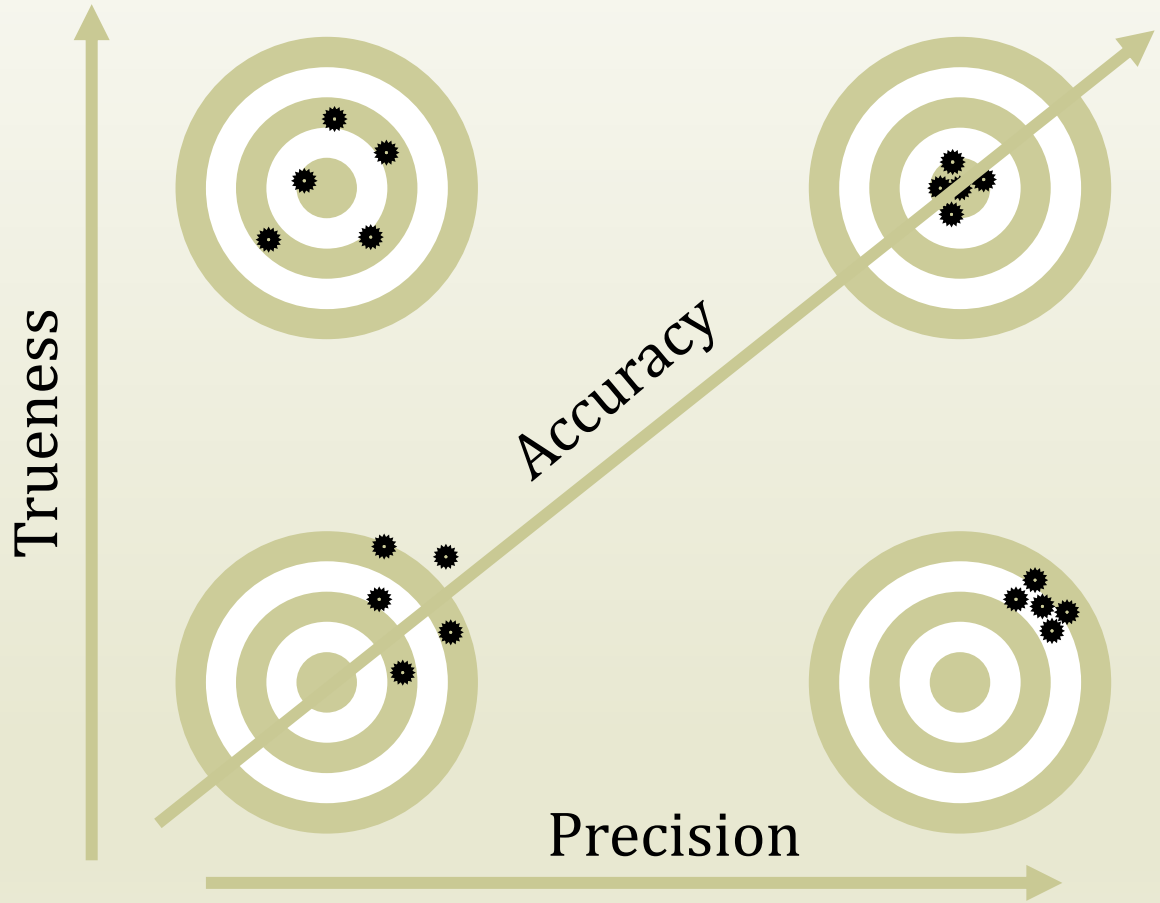
Accuracy
≠ *Uncertainty*

encompasses both trueness and precision

Accuracy → Step ❹

Uncertainty → Step ❺

Definitions



High accuracy
=
High trueness
+
High precision

❸ Precision

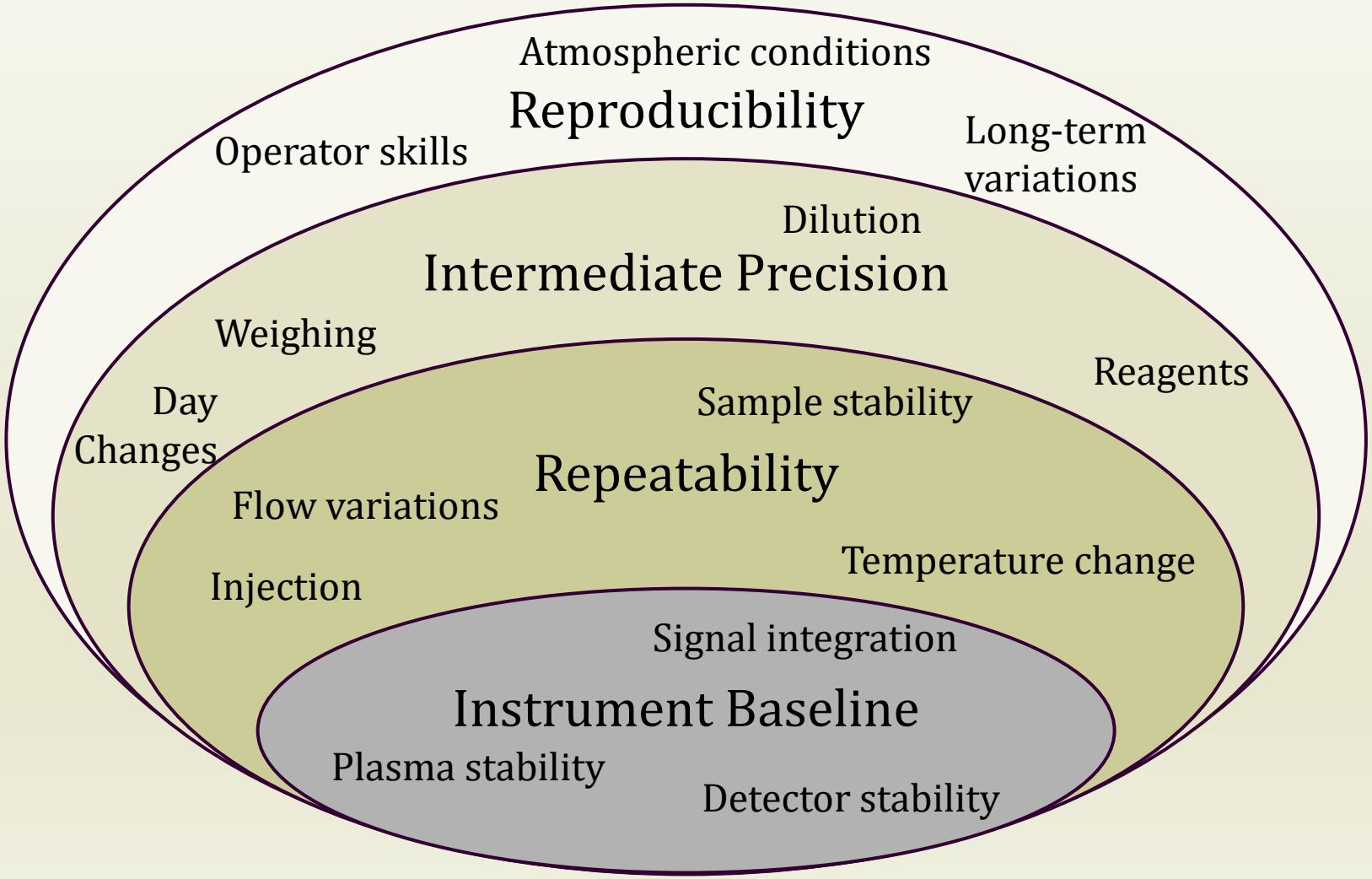
Precision can be quantified through Repeatability & Reproducibility

They differ in the external factors considered

Repeatability	**Ruggedness**	**Reproducibility**
	intermediate precision	*higher variability*
Single laboratory variability	Short term lab variability	Long term variability
Within a single day Single analyst Single instrument	Within a single day Single or different analysts Single or different instruments	Different days Different analysts If possible different instruments

❸ Repeatability & Reproducibility

Another representation :
for ICP-OES

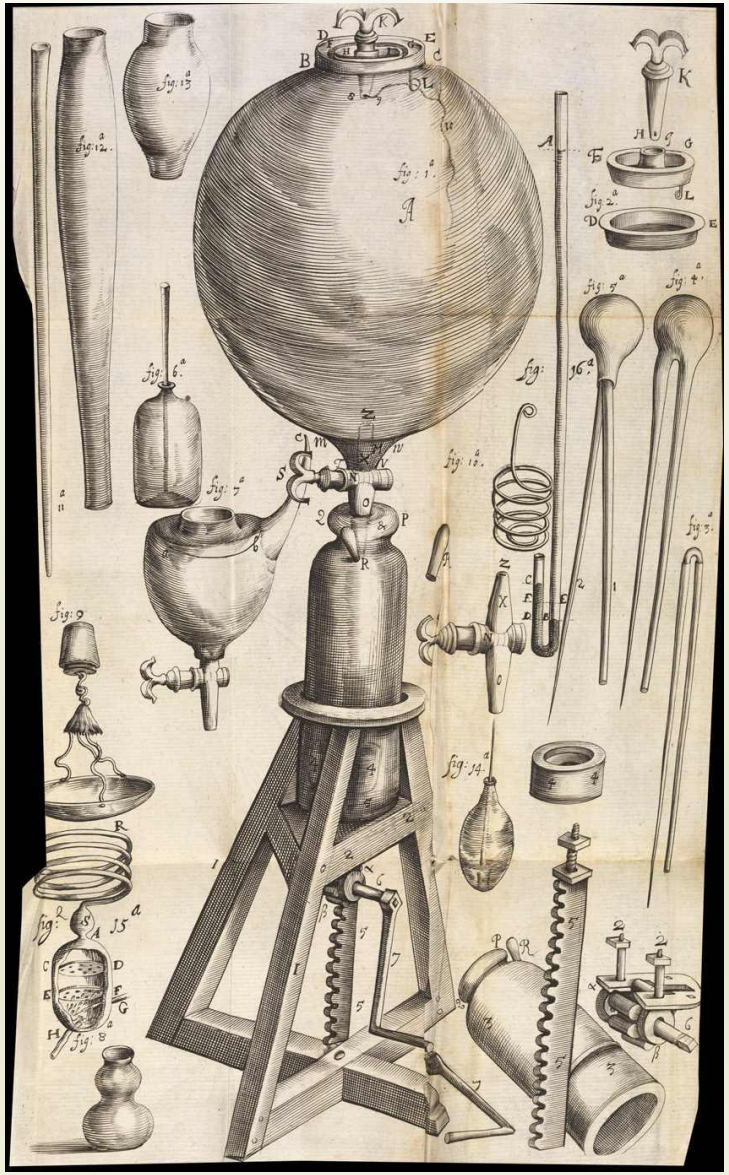


❸ Reproducibility is Key in Sciences

Robert Boyle's first air pump (17th century)

- One of the first scientific debate settled through reproducibility
- Vacuum was a very controversial concept – philosophers (René Descartes, Thomas Hobbes) denied its existence
- Boyle repeated the same experiment over and over again, often in public, to prove the phenomenon

Karl Popper (philosopher of science, 1934) : “non-reproducible single occurrences are of no significance to science”



❸ Repeatability & Reproducibility Determination

	Repeatability	Reproducibility
	10 measures same day same operator same instrument	10 measures 10 different days different operators difference instruments (if possible)

Define clearly which parameters are being changed

❸ Repeatability & Reproducibility Determination

Example : Au (999.3‰, ICP-OES, trace analysis)

	Repeatability		Reproducibility	
	Average	St Dev	Average	St Dev
Ag 328.0	20.88	0.10	21.91	0.84
Ag 338.2	20.50	0.10	21.38	0.73
Al 167.0	22.91	0.08	22.86	0.25
As 189.0	47.37	0.28	47.75	0.37
Bi 222.8	12.61	1.08	12.96	1.46
Ca 396.8	3.76	0.02	3.87	0.23
Cd 228.0	19.80	0.11	20.38	0.27
Co 228.6	21.34	0.11	21.69	0.28
Cr 359.3	22.30	0.12	23.20	0.72
Cu 327.3	19.19	0.11	20.09	0.59
Fe 259.9	20.15	0.12	20.48	0.58

… same for 125 lines (all lines, all elements)

- Reproducibility > Repeatability
- Different behavior per element

- Results can be displayed in multiple formats : St Dev, St Dev%, confidence intervals,

or repeatability : $\frac{t_{(0.975;n-1)} \times s}{\sqrt{n}}$

❸ ANOVA Approach

Alternative approach based on Analysis of Variance (ANOVA), often used in Japan

Measure repeatability & reproducibility in one experiment

Date 1	Date 2	Date 3	Date 4	Date 5	Date 6
Op. 1	Op. 1	Op. 2	Op. 2	Op. 1	Op. 2
Instru. 1	Instru. 2	Instru. 1	Instru. 2	Instru. 1	Instru. 2
Rep. 1,2	Rep. 3,4	Rep. 5,6	Rep. 7,8	Rep. 9,10	Rep. 11,12

- Requires some statistic treatment
- Useful for complex analyses (like gravimetry)
- Other parameters (identified during the validation) can be added

❹ Accuracy

Accuracy : Reference Material, Interlaboratory & Recovery rate

This is a clear target !

but reality is more complicated…

What is the real target value ?

The challenge is to find ways to have such reference value

❹ Accuracy

There are 4 ways to get such “true value”, which will allow you to compare it with your lab results.

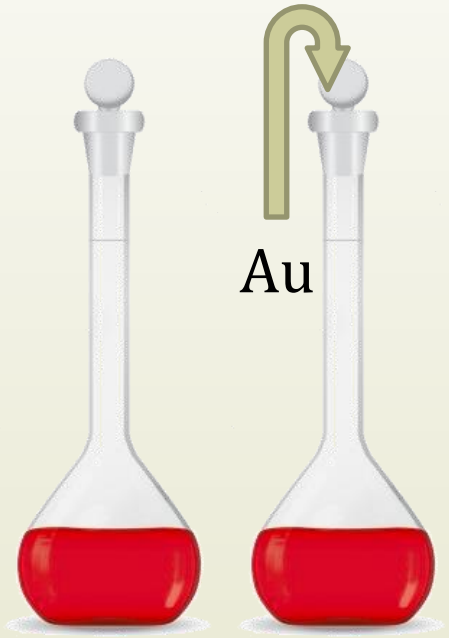
Reference Material

Interlaboratory Testing

Alternative Method

Spiked Recovery Test

❹ Spiked Recovery Test



Platinum matrix for trace analysis

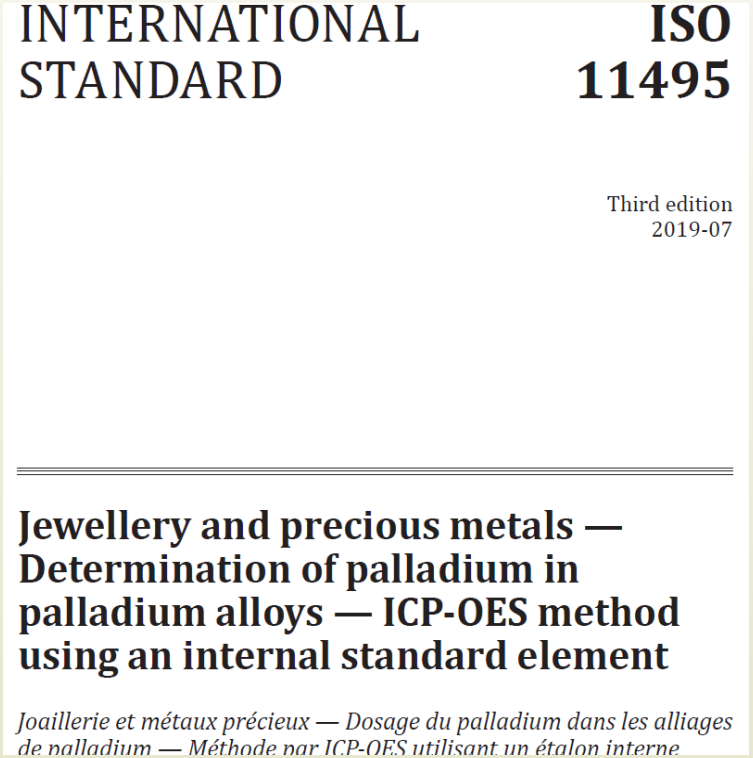
- Add known amount of element to quantify (*e.g.* add 100 mg/kg of Au)

- Analyse starting and spiked solutions in same conditions (matrix…)
- Determine recovery rate (*e.g.* if spiked solution is measured with +98 mg/kg compared to starting one, recovery rate is 98%)

Recovery must test the complete analytical procedure (full sample preparation)
Spiking process adds significant uncertainty
Method cannot be applied to apply to low concentrations & solid state analysis

❹ Alternative Method

Using 2 independent methods in the same lab is an easy way to validate a method

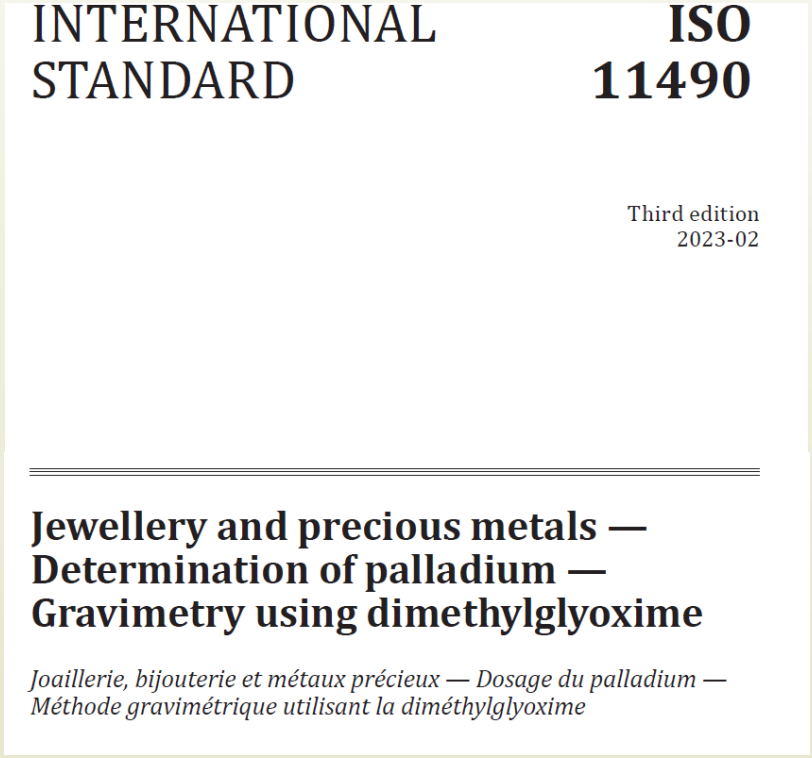


INTERNATIONAL STANDARD **ISO 11495**

Third edition
2019-07

Jewellery and precious metals — Determination of palladium in palladium alloys — ICP-OES method using an internal standard element

Joaillerie et métaux précieux — Dosage du palladium dans les alliages de palladium — Méthode par ICP-OES utilisant un étalon interne



INTERNATIONAL STANDARD **ISO 11490**

Third edition
2023-02

Jewellery and precious metals — Determination of palladium — Gravimetry using dimethylglyoxime

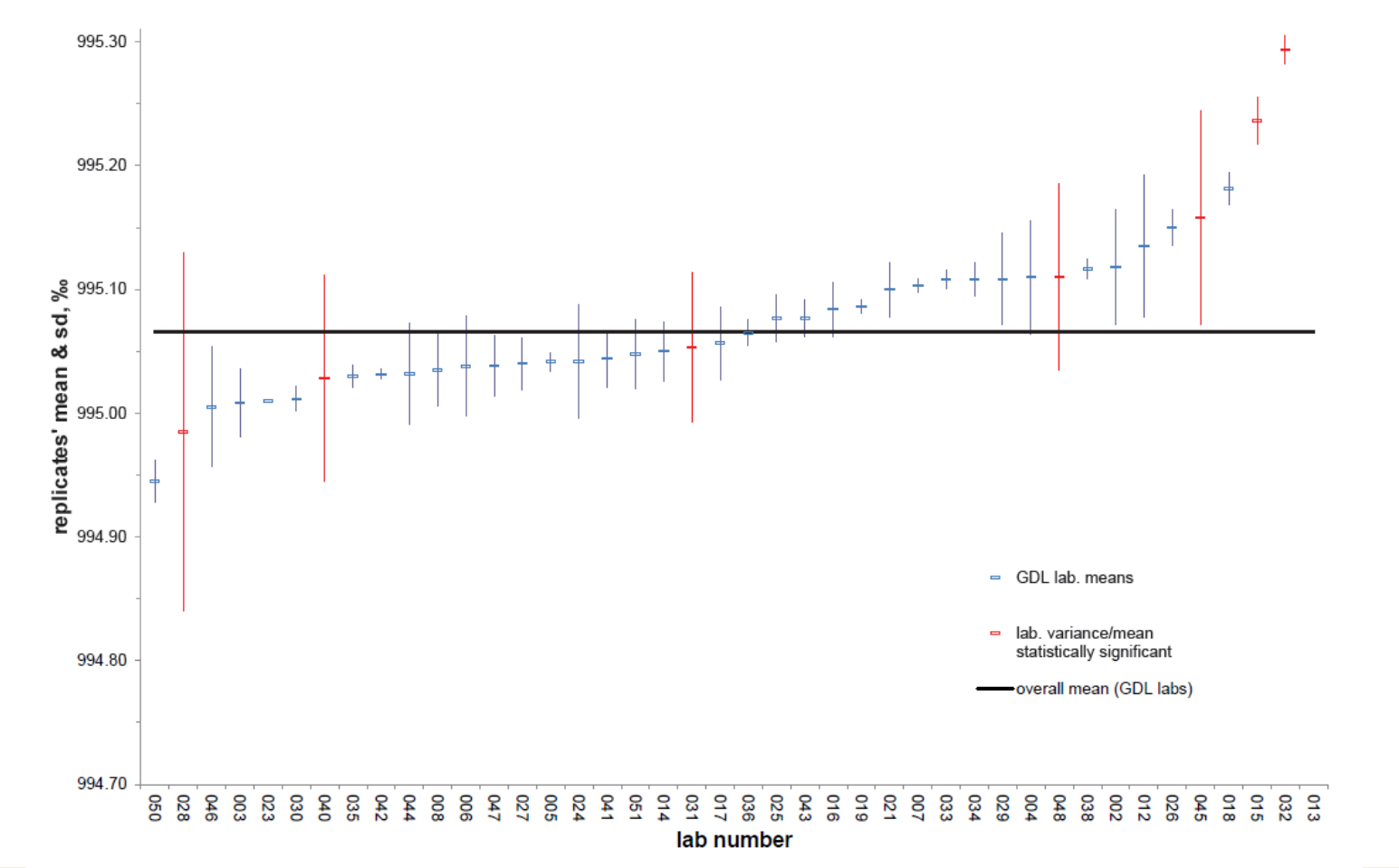
Joaillerie, bijouterie et métaux précieux — Dosage du palladium — Méthode gravimétrique utilisant la diméthylglyoxime

Only possible for specific analyses

What to do is you get different results ?

❹ Interlaboratory Testing

Interlaboratory testing (also called Round Robin or Proficiency Testing)



- Allows a laboratory to anonymously compare its performance with the "competition"
- Average of the labs is considered as the reference value
- Only possible for specific analyses

❹ Interlaboratory Testing

Some of the Interlaboratory Testing providers for the precious metals laboratories

LBMA fapas

ASTM INTERNATIONAL

IPMI

Au > 995‰, Ag > 999‰ (trace analysis)	200 < Au < 950‰ (cupellation)	Multiple topics
Annual, lots of participants, interesting samples	4 samples per year, lots of participants, very easy composition (Au-Ag-Cu-(Zn))	Twice a year, limited participants, real life samples
www.lbma.org.uk/good-delivery/proficiency-testing-scheme	www.astm.org/ptp/bulkorder	contact : Algis Naujokas atn@sabinmetal.com

❹ Interlaboratory Testing

Some of the Interlaboratory Testing providers for the precious metals laboratories

Type	Analysis	Supplier
Platinum/Ruthenium Ash	Pt, Ru	SMC
High Carbon Reforming Cat	Pt, Re	Gemini
EO Catalyst	Sol Ag, Tot Ag	BV
Platinum Plate	Pt, impurities	Metalor
Mixed Autocatalyst	Pd, Pt, Rh	Techemet
Pd, Pt Spent Petro Cat	Pd, Pt	
High Rhodium Auto Catalyst	Pd, Pt, Rh	Legend Smelting
Raw Spent Petro Catalyst	Pt	Cotecna
Palladium Sponge	Pd	Johnson Matthey
Palladium on Carbon	Pd	Metalor

IPMI

Multiple topics

Twice a year, limited participants, real life samples

contact : Algis Naujokas
atn@sabinmetal.com

❹ Interlaboratory Testing

Here are some resources to potentially interesting interlaboratory testings…

- www.nilpt.com – China NIL Research Center for Proficiency Testing
  non-precious but including hardness, grain size, gas analysis

- www.eptis.org – German BAM database
  >6300 testings listed, essentially non-precious, gold ore available

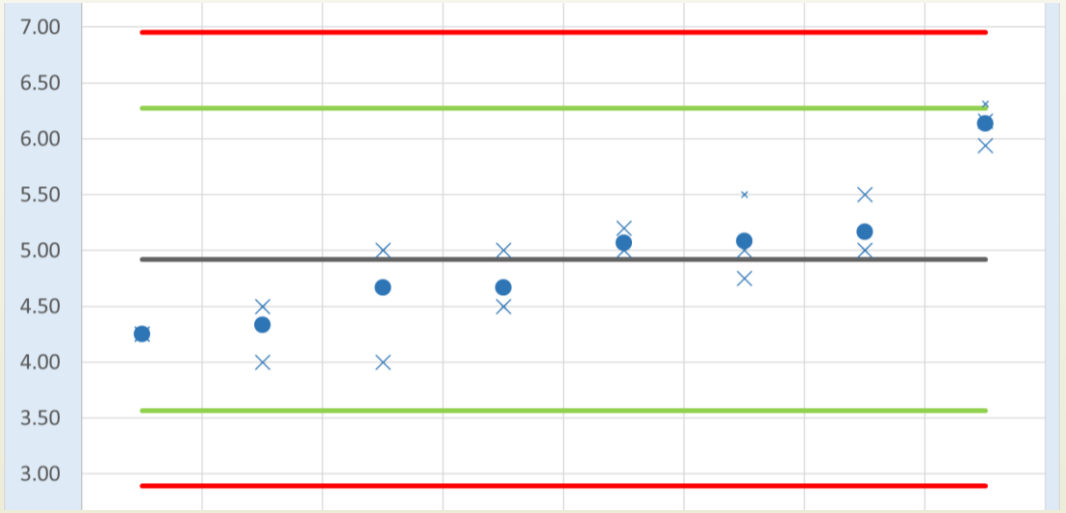
But in many cases, there is only one option :

Create your own interlaboratory testing !

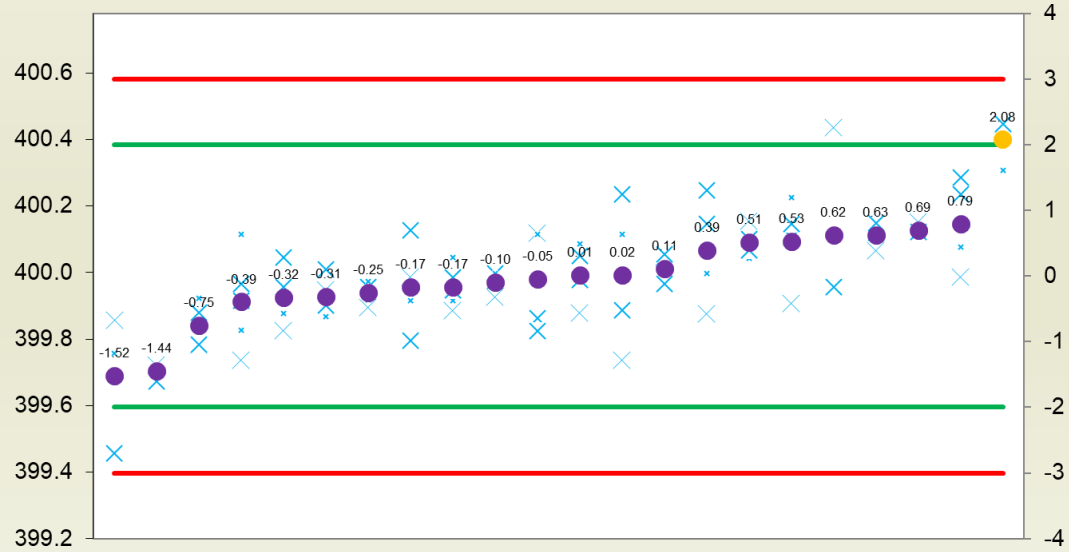
❹ Interlaboratory Testing

Good examples of small-scale interlaboratory testing

- ASTM grain size (2020)
  No existing interlaboratory testing
  for 18-karat gold alloys
  Metalor organised a testing for 8 Swiss
  companies (refiners, watch makers, labs)



- Gold cupellation of doré (2021)
  joined exercise Metalor – Tanaka
  8 laboratories, 22 operators



❹ Interlaboratory Testing

Poor examples of small-scale interlaboratory testing :

- Determination of Pb in precious metal alloy by ICP-OES
  2 laboratories joined : results obtained are 30 mg/kg & 210 mg/kg

- Determination of organic deleterious material in leather by HPLC
  5 laboratories joined : results obtained between 120-132 mg/kg
  but HPLC method accredited from 0 to 50 mg/kg

❹ Reference Material

The best to validate a method accuracy !

But be careful which material you are using:

- ISO 17034 material ?
- Metrological traceability of property values to SI ?
- Terms “Reference Material” (RM) and “Certified Reference Material” (CRM) only defined in an ISO 17034 environment – often used for marketing

Metalor Technologies SA
Laboratory
Route des Perveuils 8
CH-2074 Marin-Epagnier
Switzerland

SWISS ACCREDITATION
sas.admin.ch SRMS 0005

Period of accreditation:
27.03.2018 until 26.03.2023
(1st accreditation: 27.03.2018)

the accreditation as

Producer of reference materials and certified reference materials in the field of precious metals

Metalor is accredited ISO 17034 since 2018 and offers a large portfolio of CRMs
metalor.com/laboratory-instrumentation/iso-17034-reference-materials

Contact : Daniela Manara
Daniela.Manara@Metalor.com

❹ Reference Material

The best to validate a method accuracy ! With one major limitation !

METALOR®
REFINING

Certified Reference Material Certificate

Certificate No: MER19023

Analysis 1: Fire assay (accredited under ISO/IEC 17025, registration STS 0478)

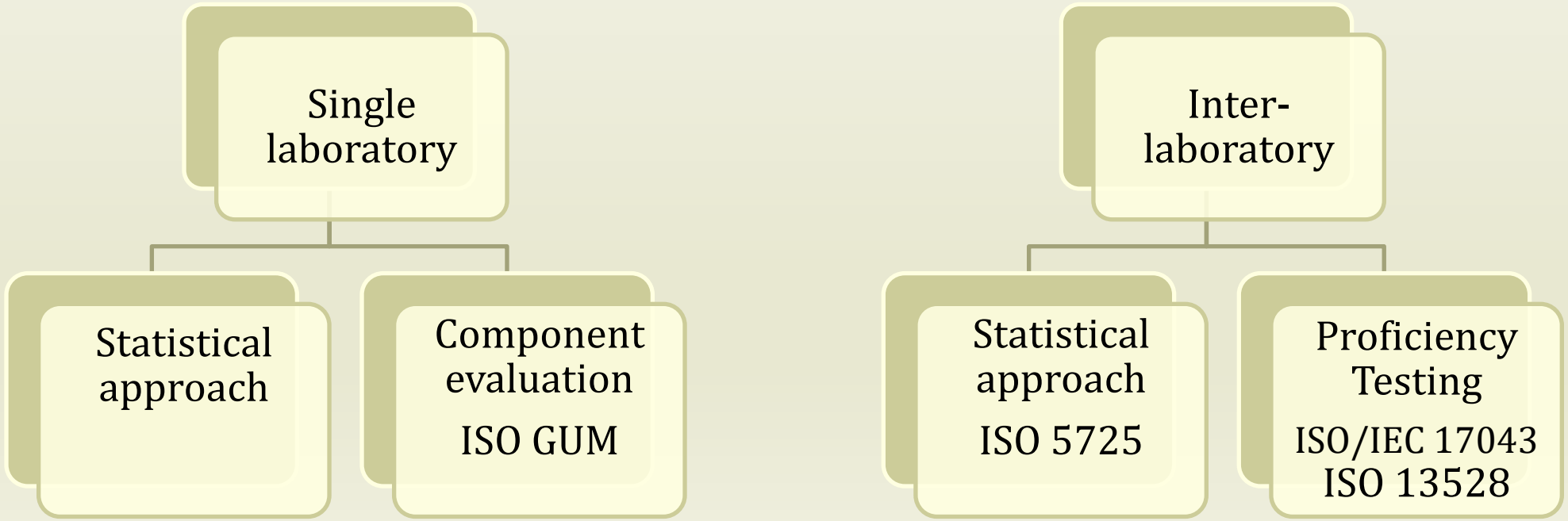
Element	Unit	Result	Uncert.
Au	‰	749.94	0.23

A Reference Material will validate the accuracy for a specific composition only

Another concentration / presence of other elements might lead to different results

❺ Uncertainty

- Uncertainty shall be reported at customer's request, and shall be evaluated for ISO 17025 accreditation
- However, we cannot reference the "uncertainty of a method" – it must be associated with a specific result (or range)
- There are 4 methods to determine the uncertainty :



❺ Uncertainty by Statistical Approach

Example : Au 750‰ alloy by cupellation

3 operators, 3 scales, 3 furnaces, multiple days : 90 cupellations (corrected)

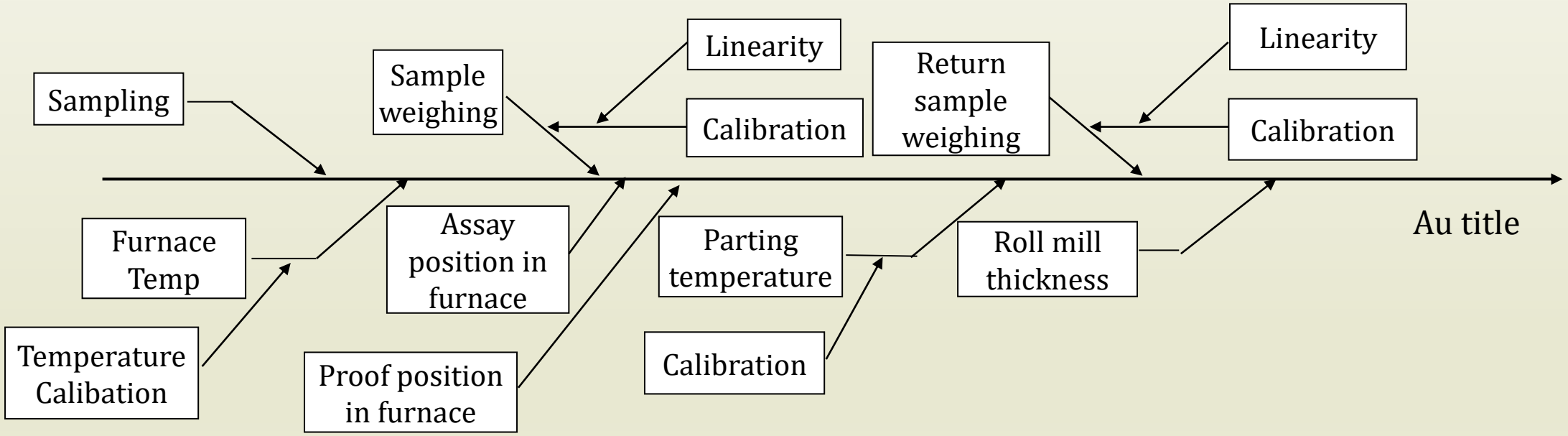
mean	751.42‰
standard deviation	0.112‰
expanded uncertainty (k=2)	0.224‰

Result : 751.42 ± 0.22‰ (k=2)

❺ Uncertainty by Component Evaluation

Example : Au 750‰ alloy by cupellation

Time consuming & Complex – Ishikawa diagram to find all contributions to uncertainty



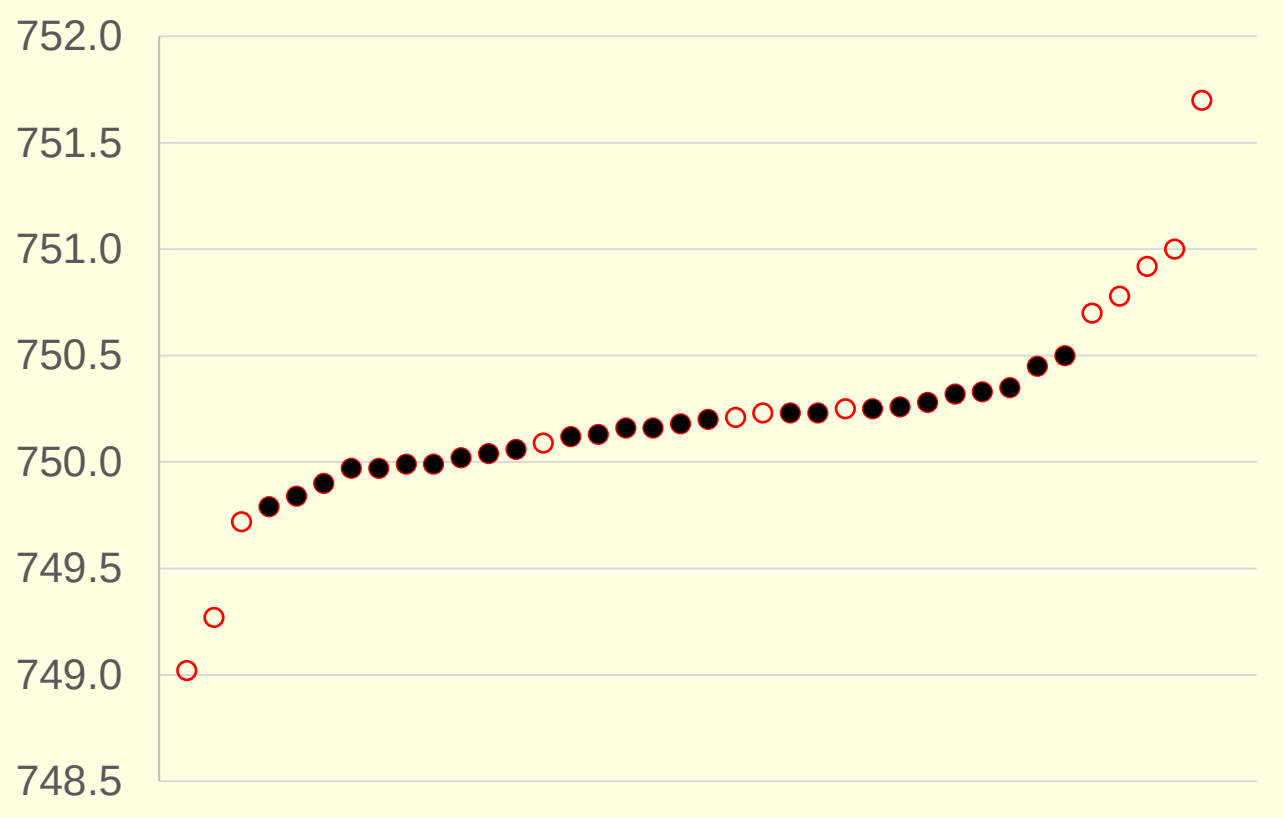
❺ Uncertainty by Component Evaluation

Example : Au 750‰ alloy by cupellation

uncertainty source	unit	y = f(x)	Range	dC/dX [‰]	dC [‰]	2 dC [‰]	Contribution [%]
scale	mg		0.005		0.0283	0.0566	7
sample weight	mg	linear	5	0.0033	0.0165	0.0330	2
Pb weight	g	linear	0.5	-0.058	-0.0290	-0.0580	7
Ag weight for inquartation		linear	0.25	0.0673	0.0168	0.0337	2
oven temperature & position	°C	linear	20		0.0000	0.1586	0
variance cupellation					0.0793	-0.0104	54
cupellation duration	min	linear		-0.00104	-0.0052	-0.0104	0
parting					0.0550	0.1100	26
hammering					0.0000	0.0000	0
roll mill thickness	mm				0.0000	0.0000	0
annealing duration	min				0.0080	0.0160	1
sum of squares					0.0116	0.0465	
standard deviation calculated & expanded uncertainty					**0.108**	**0.216**	

❺ Uncertainty by Proficiency Testing

Example : Au 750‰ alloy by cupellation – ASTM 2021 (GOLD2105)



mean	750.14‰
standard deviation	0.180‰
expanded uncertainty (k=2)	0.360‰

expanded uncertainty (k=2)	
by statistical approach	0.224‰
by component evaluation	0.216‰
by proficiency testing	0.360‰

Important – all participants shall use the same method !

❻ Stability

Stability is a source of variability that can negatively impact on the results

Stability study is often neglected with potentially risky consequences

- Sample stability : analyte level can be changed due to chemical / physical transformations, sometimes just over a couple of hours !

Evaluate impact of chemical & physical transformations on the sample integrity

- temperature
- light
- oxidation / reduction
- evaporation

Mitigation

- control of the environment
- Define clearly preparation method
- limit analysis time

❻ Stability

- Reagent & calibration stability : reagents and calibration solutions (purchased and home-made) used over a long period can concentrate & undergo transformations

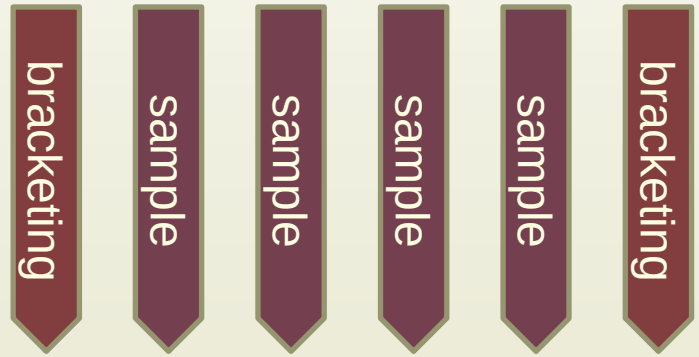
All calibration solutions have to be validated over their life time, and their shelf life clearly defined

❻ Stability

- Instrumentation stability (drift) : instruments tend to drift over time; this process can be fast (ICP-OES) or slow (SPARK-OES), but needs to be quantified

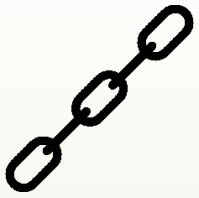
ICP-OES : analyzing using a bracketing sample at regular interval allows to quantify the drift (and prevent it)

SPARK-OES : using a control sample allows the same



Validation determines how long an instrument can perform as required. After this period, recalibration shall be performed

❼ Robustness



Determines the capacity of a method to provide reliable results when affected by small variations

It evaluates how the method performs on “real life” analyses

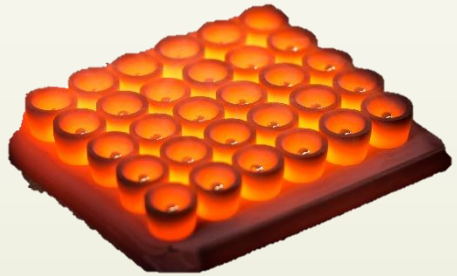
Critical thinking is required: use your imagination to evaluate the robustness !

Once factors which have an important impact on the result have been identified, they need to be put under control for routine analysis

❼ Robustness

SPARK-OES

- No cleaning of the tungsten electrode
- Room temperature
- Sample temperature
- Presence of inclusion



Cupellation

- Proof fineness
- Sample weight
- Rolling mill thickness
- Furnace temperature
- Position in the furnace
- Annealing time

ICP-OES (trace analysis)

- Sample weight
- Matrix composition (acid + metal)
- Analysis duration
- Carryover

Potentiometry

- Sample weight
- Sample mineralization time
- HNO_3 concentration
- Analysis temperature

Resources

- Eurachem
  - The Fitness for Purpose of Analytical Methods
- SAS (Swiss Accreditation Service)
  - Guide for validation of chemical and physical analytical methods (in French, also available in German)
- PALA (Accreditation Program for Analytical Laboratories, Québec, Canada)
  - Protocol for the validation of a chemical analytical method (in French)
- ISO
  - Guides to the expression of uncertainty in measurement (GUM series)
- International Council for Harmonization (ICH)
  - Validation of Analytical Procedures: Q2(R1)
- FDA
  - Analytical Procedures and Methods Validation for Drugs and Biologics
- Eurachem
  - Selection, Use and Interpretation of Proficiency Testing (PT) Schemes by Laboratories (2021)

Thanks for your attention

A preformatted method validation report will be available at this link:

http://validation.jodry.com

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LBMA Assaying & Refining Conference

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