Traceability Outcome & Uncertainty

Relative to ISO15189

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The Science of Metrology

Metrology:

'The science of measurement and its application'

Measurand:

'Quantity *intended* to be measured'

Measurement:

'Process of experimentally obtaining one or more **quantity values** that can reasonably be attributed to a **quantity'**

Measurement procedure:

'Detailed description of a **measurement** according to one or more **measurement principles** and to a given **measurement method,** based on a **measurement model** and including any calculation to obtain a **measurement result'**

VIM 2008 (Vocabulary in Measurement)

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Traceability

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Traceability

English Dictionary Definition

- **TRACE**:

Origin

Middle English (first recorded as a noun in the sense **'path that someone or something takes**'): from Old French *trace* (noun), *tracier* (verb), based on Latin *tractus*

- **TRACEABLE:**

(to somebody/something) if something is **traceable**, you can find out where it came from, where it has gone, when it began or what its cause was

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Measurement Traceability

'Traceability' means that the measurement results can be related to a stated reference by an unbroken chain of accredited comparisons
(NPL)

Property of a measurement result whereby the result can be related to a reference through a documented unbroken chain of calibrations, each contributing to the measurement uncertainty
(source: VIM 3, JCGM, 2008)

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BIPM - Centre of Global Metrology

Bureau International des Poids et Mesures

Metre

Kilogram

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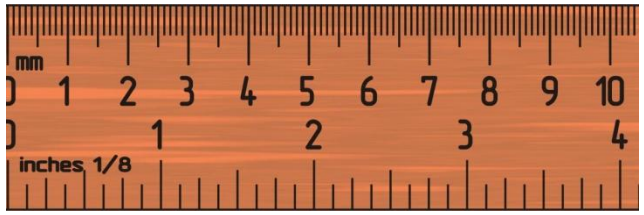
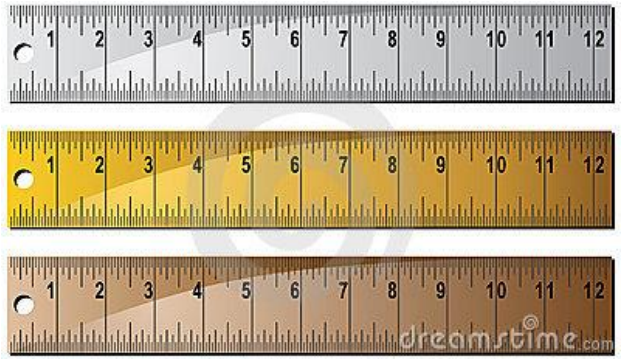
Traceability concept – metre measurement

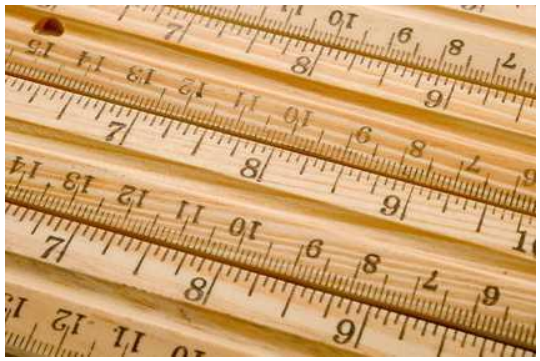
Prototype Metre bar, made of an alloy of platinum and iridium, that was the standard from 1889 to 1960 (stored in BIPM).



Standardised meter rule in NPL lab, London



Calibrated ruler, accredited organisation



Commercially available calibrated ruler

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Traceability in Clinical Measurement

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JCTLM Working Group -TEP

Traceability, Education and Promotion (WG-TEP)

Membership:

JCTLM Executive

Wider JCTLM Membership (ILAC, Eurachem, IFCC, BIPM)

Members co-opted on basis of skills and experience

Aims:

JCTLM Meeting

Promote Traceability (scientific meetings, educational material, JCTLM newsletter)

Production and maintenance of a traceability website

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Serum Rhubarb Traceability

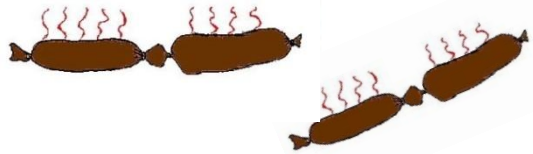
Reference Standard

Traceable, certified purity

Measurement system (s)

Reference value

Traceable, lower analytical uncertainty



Lab result

Greater analytical uncertainty

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Why Traceability?

- Diagnostic test results should be comparable independent of the hospital, country or time in which they are made
- This ensures that patients receive the correct diagnosis and treatment independent of the country or hospital they are in.
- It is the responsibility of the IVD manufacturer to ensure that the calibrators they provide are traceable to available and appropriate CRMs or RMPs.
- In house methods: ensure traceability during method validation
- Required by ISO15189 and ISO17025

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Reference Measurement Systems - Traceability concept and standardisation of methods

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The Goals Of A Reference System

- To establish global compatibility of clinical measurements.
- To evaluate the performance of routine laboratories within national QC systems.
- To evaluate the accuracy of routine analytical systems for routine use.

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Definition - Reference Method

"A thoroughly investigated method, clearly and exactly describing the necessary conditions and procedures, for the measurement of one or more property values that has been shown to have accuracy and precision commensurate with its intended use and that can therefore be used to assess the accuracy of other methods for the same measurement, particularly in permitting the characterisation of a reference material"

e.g. ID-MS

International Organization for Standardization. ISO Guide 30. 2nd Ed. Geneva: ISO, 1992.

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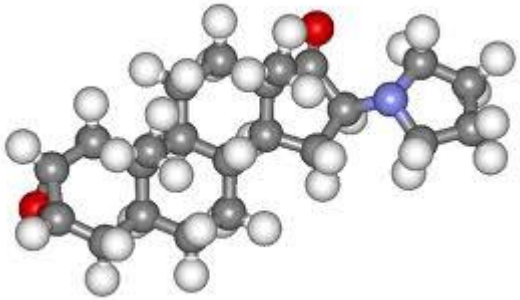
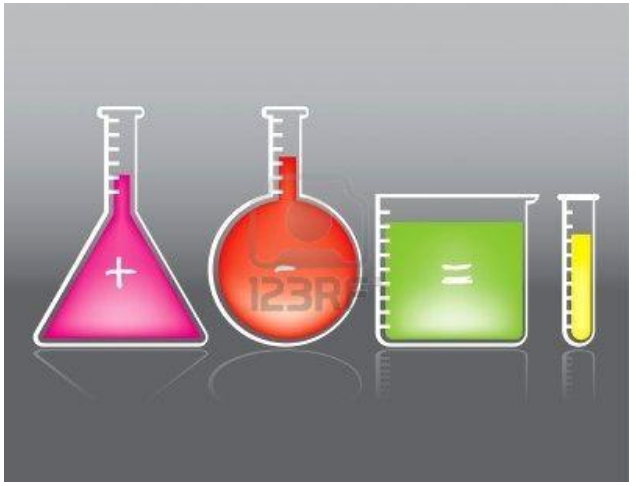
What Constitutes a Reference Method

Generally:

1. Defined measurand
2. Reference methods will have an end point detection that looks at the molecular species





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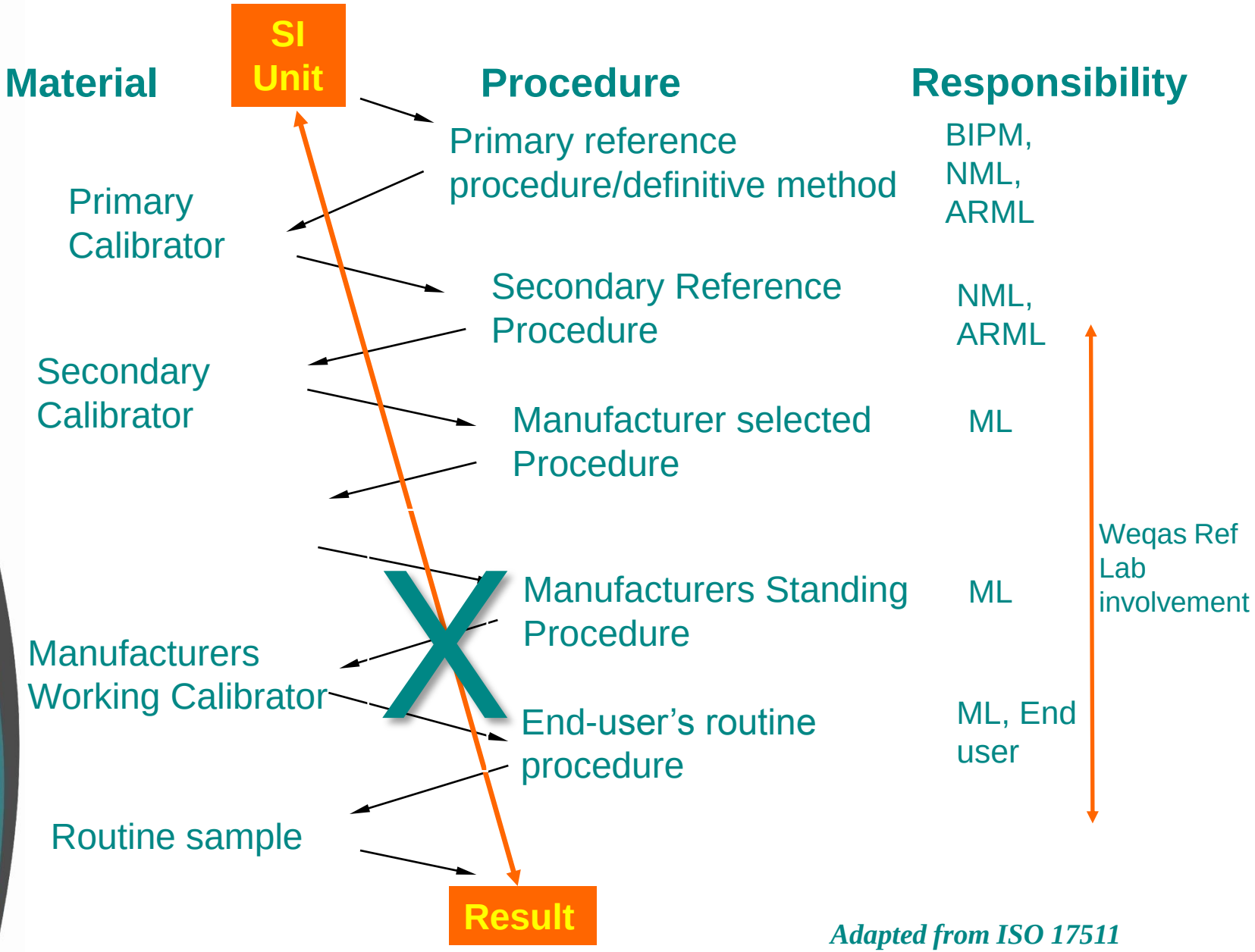

Adapted from ISO 17511

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ISO15189 – Traceability

- 5.3.2.4 Equipment calibration
- The laboratory shall have a documented procedure for the calibration of equipment that affects examination results and that:
- b) records the metrological traceability of the calibration standard

- 5.5.3 Documentation of examination procedures
- i) calibration procedures (metrological traceability);
- 5.6.3 Calibration of measuring systems
- NOTE Documentation of calibration traceability to a higher order reference material or reference procedure may be provided by an examination system manufacturer. Such documentation is acceptable as long as the manufacturer's examination system and calibration procedures are used without modification.

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CE Marked Methods

- Traceability of ‘out of the box’ methods

- This is the responsibility of the manufacturer <u>BUT</u> the lab must have documentation available for UKAS to view.

CE

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Manufacturer Traceability

Traceability of Method

Standardization

The ADVIA Chemistry concentrated CRE_2c method is traceable to the IDMS Reference Method via correlation of patient samples and reference material SRM967 from the National Institute of Standards and Technology (NIST), using the non-concentrated version of the assay which provides identical levels of all reaction components. See the correlation data in the *System Correlation* section for the relationship. The assigned value of the Siemens Chemistry Calibrator is traceable to this standardization.

10493976_EN Rev. D, 2013-01

10 - English

Calibrator Target Value and Uncertainty

Bayer HealthCare
Diagnostics Division

DECLARATION OF UNCERTAINTY

Method:
ADVIA® Chemistry Creatinine 2 Method (CREA 2) on ADVIA 1650/2400/1200

UNCERTAINTY

	TARGET VALUE (1)	TOTAL UNCERTAINTY (2)	PER CENT UNCERTAINTY
ADVIA 1650 CREA 2			
Calibrator	8.2 mg/dL	0.57 mg/dL	6.9
ADVIA 2400 CREA 2			
Calibrator	8.2 mg/dL	0.71 mg/dL	8.7
ADVIA 1200 CREA 2			
Calibrator	8.2 mg/dL	1.06 mg/dL	12.9

(1) The Calibrator value has been assigned in a Nested protocol from the Master Lot Calibrator.

(2) Uncertainty is calculated as the half-width of the 95% confidence interval of the calibrator assigned value. Therefore, the true value for a calibrator lot should fall in the interval (assigned value ± uncertainty) with 95% probability.

Issued: January 25, 2006

Advia Creatinine Method

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In House Methods

UKAS will want calibrators to be traceable where material is available.

Where traceability is not possible/relevant, other means of providing confidence in the results is required

How do we do this?

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Reference Materials

- **Primary Reference Standard (calibrator)**
  - Certified purity
- **Primary Reference Material**
  - Verification of Primary Reference Method
- **Secondary Reference Material**
  - Verification of Secondary Reference Method
- **EQA / QCRM**

Check certificate for appropriate usage (commutability).

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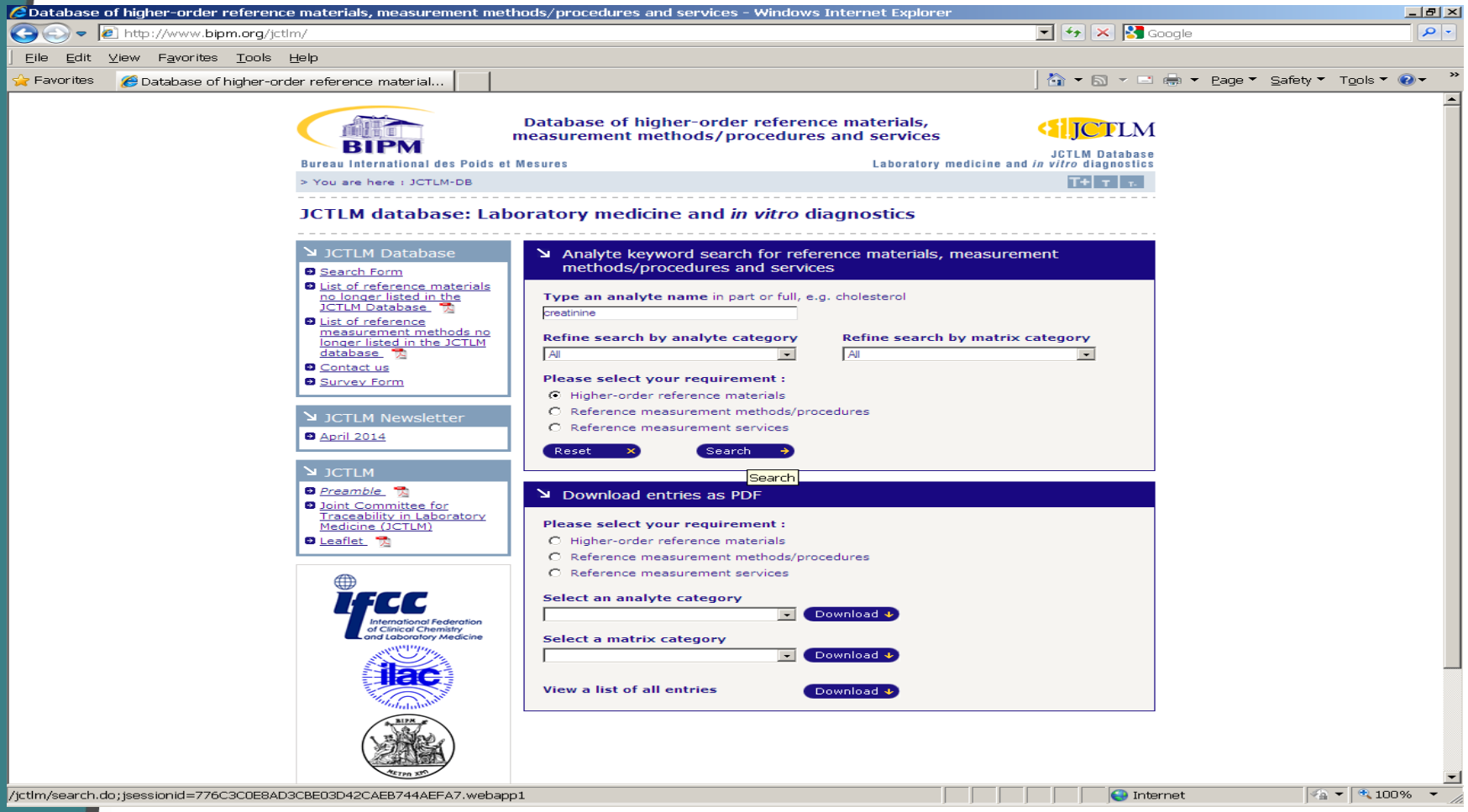
Sources of Certified Reference Material and Methods



JCTLM website hosted by BIPM (http://www.bipm.org/jctlm/)

1. Reference Materials 2. Reference Measurement Methods 3. Reference Measurement Services

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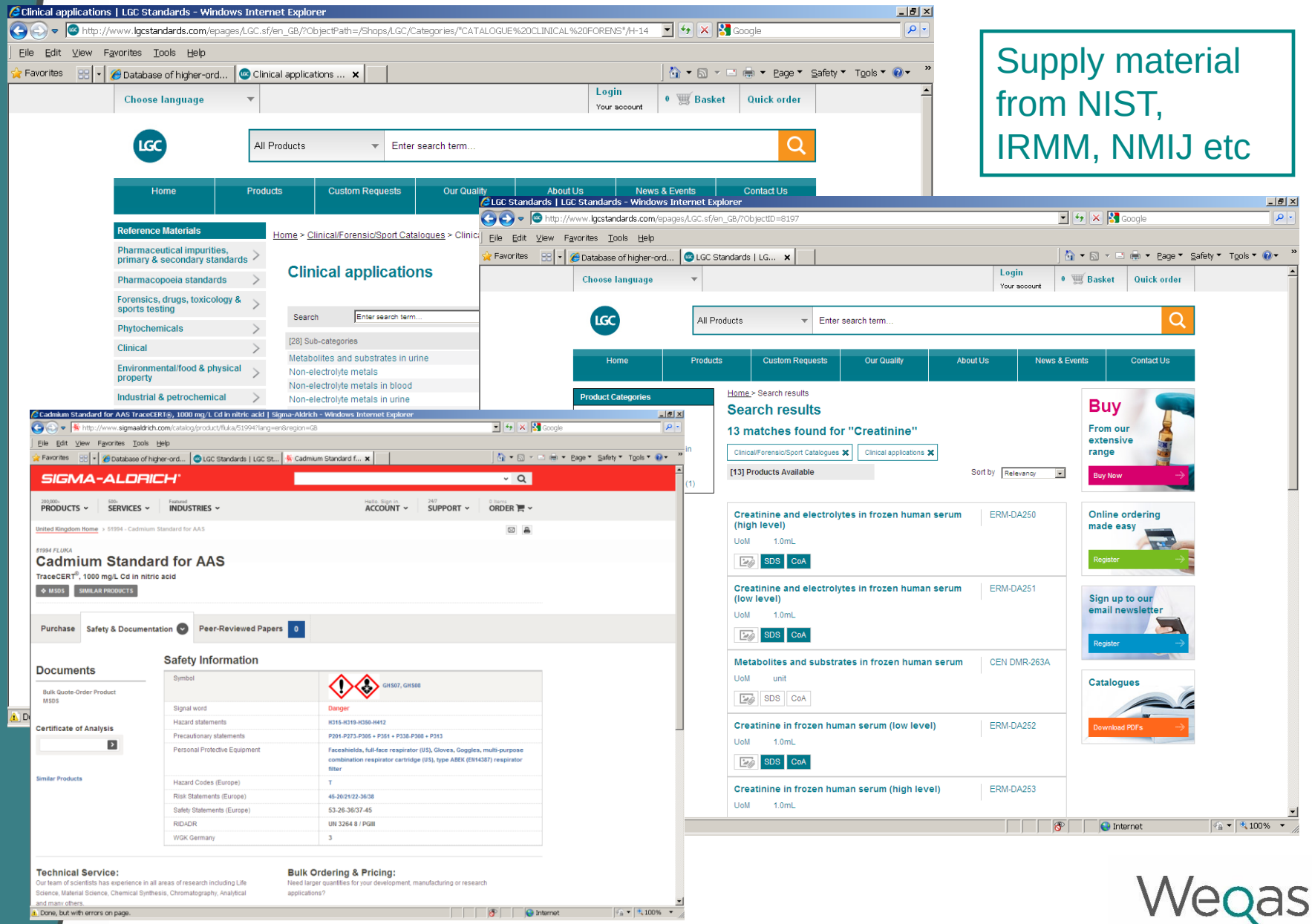
Commercial Suppliers



Supply material from NIST, IRMM, NMIJ etc

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Certificate of Analysis

National Institute of Standards & Technology

Certificate of Analysis

Standard Reference Material 914a

Creatinine

This Standard Reference Material (SRM) is certified as a chemical of known purity. It is inte
use in the calibration and standardization of procedures used for determination of creatinine conc
analysis and for routine evaluations of daily working standards used in these procedures. The p
is:

99.7 ± 0.3%

The estimated uncertainty of the purity is based upon scientific judgment and statistical analysi
analytical tests applied to the material in the certification process.

Contributions to the certification and characterization of this SRM were made by A. Cohen
Margolis, and E. White V of the Organic Analytical Research Division and M. Knoerdel
Marinenko, and S.F. Stone of the Inorganic Analytical Research Division.

This Certificate of Analysis has undergone editorial revision to reflect program and organization
and at the Department of Commerce. No attempt was made to reevaluate the certificate values or
presented on this certificate.

Purity

Concentration

TraceCERT®
Traceable Certified Reference Materials

Fluka Analytical

Certificate

Produced in double accredited laboratory fulfilling ISO/IEC 17025 and ISO Guide 34

This certificate is designed in accordance with ISO Guide 31 [1].

Object of certification:	**Calcium standard for AAS**
Fluka Product No.:	69349 (Lot BCBF8858V)
Composition:	Calcium carbonate (pure material) in 2% HNO_3 (prepared from HNO_3 *Trace***SELECT®** and water *Trace***SELECT®** Ultra, 18.2 MΩ cm and 0.22 µm filtered)
Density at 20°C:	ρ = 1012 kg m^{-3} $u_c(\rho)$ = 0.5 kg m^{-3}
Intended use:	Calibration of AAS, ICP-spectrometry, spectrophotometry or any other analytical technique
Storing and handling:	This reference material shall be stored between 5 °C and 30 °C. The bottle's temperature must be 20°C and shaked well before every use. If storage of a partially used bottle is necessary, the cap should be tightly sealed and the bottle should be stored at reduced temperature (e.g. refrigerator) to minimize transpiration rate.
Expiry date:	**JUN / 2014**
Bottle opening date:	

Certified value traceable to SI unit kg and uncertainty according to ISO Guide 35 [2] and Eurachem/CITAC Guide [3]		
Constituent	Certified value at 20°C [4]	Expanded uncertainty [$U = k u_c$; $k = 2$]
Calcium	**1000 mg L^{-1}** **988 mg kg^{-1}**	**4 mg L^{-1}** **4 mg kg^{-1}**

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Equipment Traceability

3.17 metrological traceability

NOTE 4 For measurements with more than one input quantity in the measurement model, each of the quantity values should itself be metrologically traceable and the calibration hierarchy involved can form a branched structure or a network.
The effort involved in establishing metrological traceability for each input quantity should be commensurate with its relative contribution to the measurement result.

- Where equipment is critical to the measurement and directly or indirectly affects results, the traceability must be confirmed:

  Pipettes, Balances, Thermometers, pH meters etc.

- Verification required at defined intervals

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Uncertainty

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Uncertainty Definition

Uncertain:

- Not completely confident or sure of something
- Not able to be accurately known or predicted

Uncertainty:

Also called: uncertainness. The state or condition of being uncertain

GUM definition:
The word “uncertainty” means doubt, and thus in its broadest sense “uncertainty of measurement” means doubt about the validity of the result of a measurement.

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Measurement Uncertainty

ISO Definition

- Non-negative parameter characterising the dispersion of the quantity values being attributed to a measurand, based on the information used

GUM Definition

- Parameter, associated with the result of a measurement, that characterises the dispersion of the values that could reasonably be attributed to the measurand

i.e. how confident you are with the provided result

Result +/- x (%?)

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Why Measure Uncertainty?

- It's there, we should understand it
- Assures comparability among tests (National, International)
- Required for accreditation
- Provides an objective quality measure
- Help with method improvement
- Guide for root cause analysis and corrective action

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Measure thrice, cut once

'Measure thrice, cut once'. You can reduce the risk of making a mistake by checking the measurement a second or third time.

- One measurement - mistake could go completely unnoticed.
- Two measurements that don't not agree: may not know which is 'wrong'.
- Three measurements - two agree with each other while the third is very different, then you could be suspicious about the third.

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Basic Factors Affecting Uncertainty

Imprecision good
Accuracy (bias) good
Uncertainty low

Imprecision good
Accuracy (bias) poor
Uncertainty low for imprecision, high for accuracy

Imprecision poor
Accuracy (bias) poor
Uncertainty high

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ISO15189 - Uncertainty

- 5.5.1.1 Validation of examination procedures

- NOTE 1 Performance characteristics of an examination procedure may include: measurement trueness, …….. *measurement uncertainty*, …….. diagnostic specificity and sensitivity.

- 5.5.1.3 Uncertainty of examination results

- The laboratory shall have procedures for estimating the uncertainty of measured quantity values, where it has practical utility. When estimating uncertainty, all uncertainty components of importance in a given situation shall be considered.

Upon request the laboratory shall make available its estimates of the uncertainty of its measured quantity values.

- 5.5.3 Documentation of examination procedures

- m) principle of procedure for calculating results, including uncertainty of examination results;

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What UKAS Expect

- Performance requirements for each measurement procedure to be defined
- Regularly reviewed
- Uncertainty estimates to be readily available
- Requirements cover examinations reporting measured quantity values and those that include a measurement step
- Lab needs to understand what impacts on the test result

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Identifying and Combining Uncertainty

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Type A Uncertainty

Type A evaluation of measurement uncertainty

Evaluation of a component of measurement uncertainty by a statistical analysis of measured quantity values obtained under defined measurement conditions.

Obtained during method validation:

Repeatability, Reproducibility etc

$U = SD/\sqrt{n}$ (Standard error of the mean)

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Type B Uncertainty

Type B evaluation of measurement uncertainty

Evaluation of a component of measurement uncertainty determined by means other than a Type A evaluation of measurement uncertainty.

These are uncertainty values generally associated with equipment and supplied by the manufacturer e.g. uncertainty associated with a balance, pH meter, thermometer

Generally assume a rectangular distribution:

$$U = a / \sqrt{3}$$

Where a = manufacturer stated uncertainty

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Combining Uncertainty

- Identify the components of uncertainty
- Calculate all uncertainty as Standard Deviation
- All uncertainty must be in the same units as the measurand
- Combine Uncertainty as the square root sum of squares

$$\text{Uncertainty} = \sqrt{(U_1^2 + U_2^2 + \ldots)}$$

Relative Standard Deviation (R_{SD}):

This is a measure of the spread of the data in comparison to the mean.

$$R_{SD} = SD / x = CV$$

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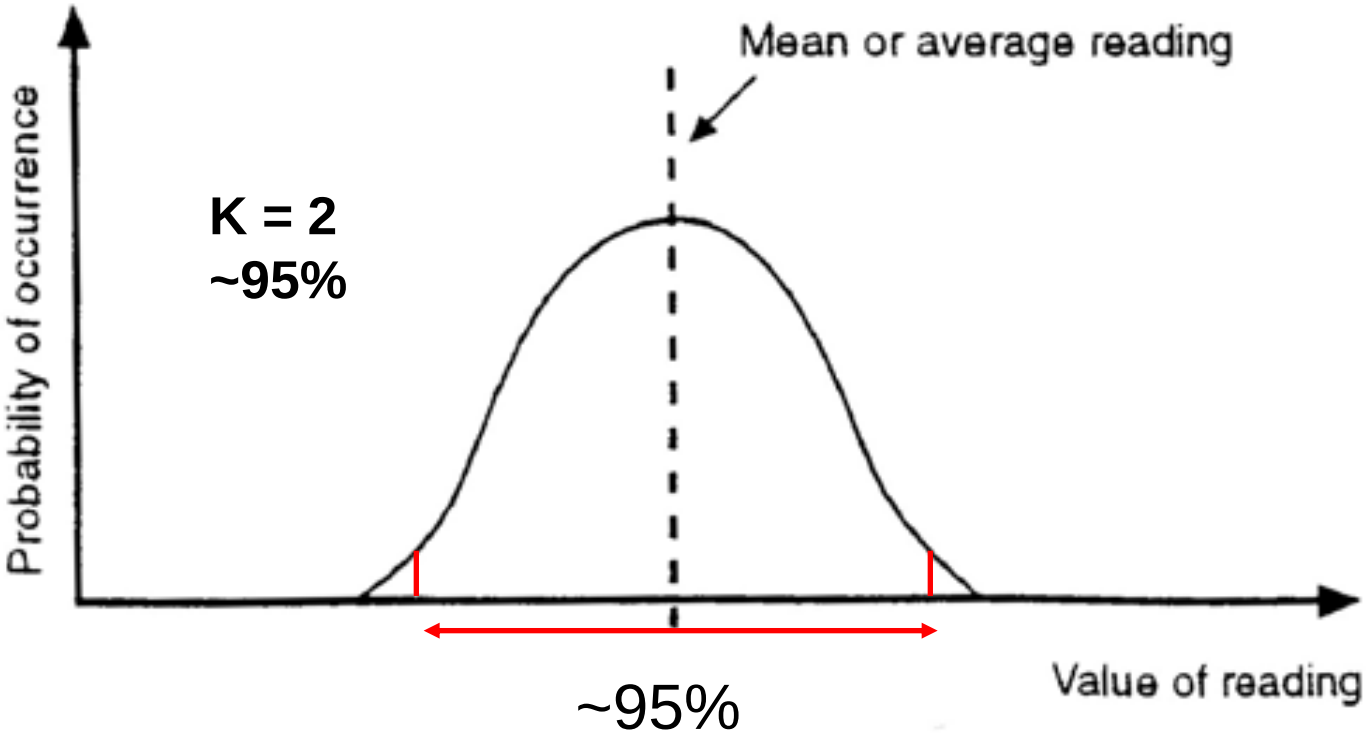
Coverage Factor



Confidence Interval: a range which includes a specified (usually 95%) of the possible values

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ISO Principles - Summary

- All uncertainty calculated as Standard Deviation (best to use R_{SD})
- Combined uncertainty, u_c, obtained from the combination of square root of variances (s^2)
- Express as 'expanded uncertainty', U_c, for additional confidence

$$U_c = k \, x \, u_c$$

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Uncertainty of target – Uncertainty Budget

Combined uncertainty =

$$2 \times \text{result} \times \{\sqrt{(U_{sample})^2} + \sqrt{(U_{std})^2} + \sqrt{(U_{Cont})^2}\}$$

Where

U_{sample}	= uncertainty associated with sample precision
U_{std}	= uncertainty associated with standard preparation
U_{Cont}	= uncertainty associated with the Controls

Coverage factor of 2 - 95% confidence

Uncertainty as Relative Standard Deviation (R_{SD})

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Identifying the Components of Uncertainty

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Identifying Uncertainty Components

- List the stages of the method (flow diagram) e.g. Sample prep, analytical stage etc

- Cause and Effect Diagrams

  - Ishikawa or Fishbone Diagram

  Causes are usually grouped into major categories to identify these sources of variation.

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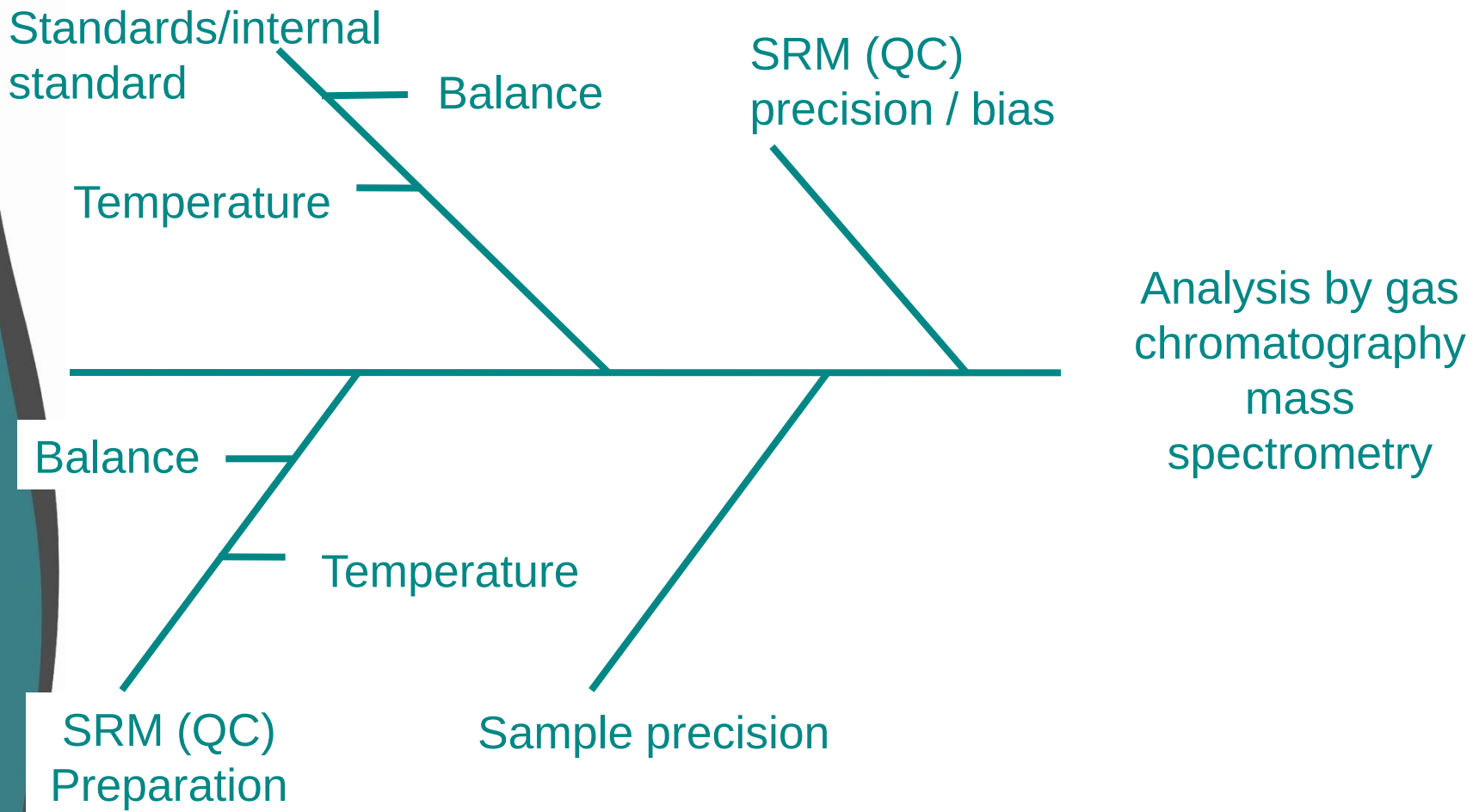
Uncertainty of target (ID-GCMS Reference method)



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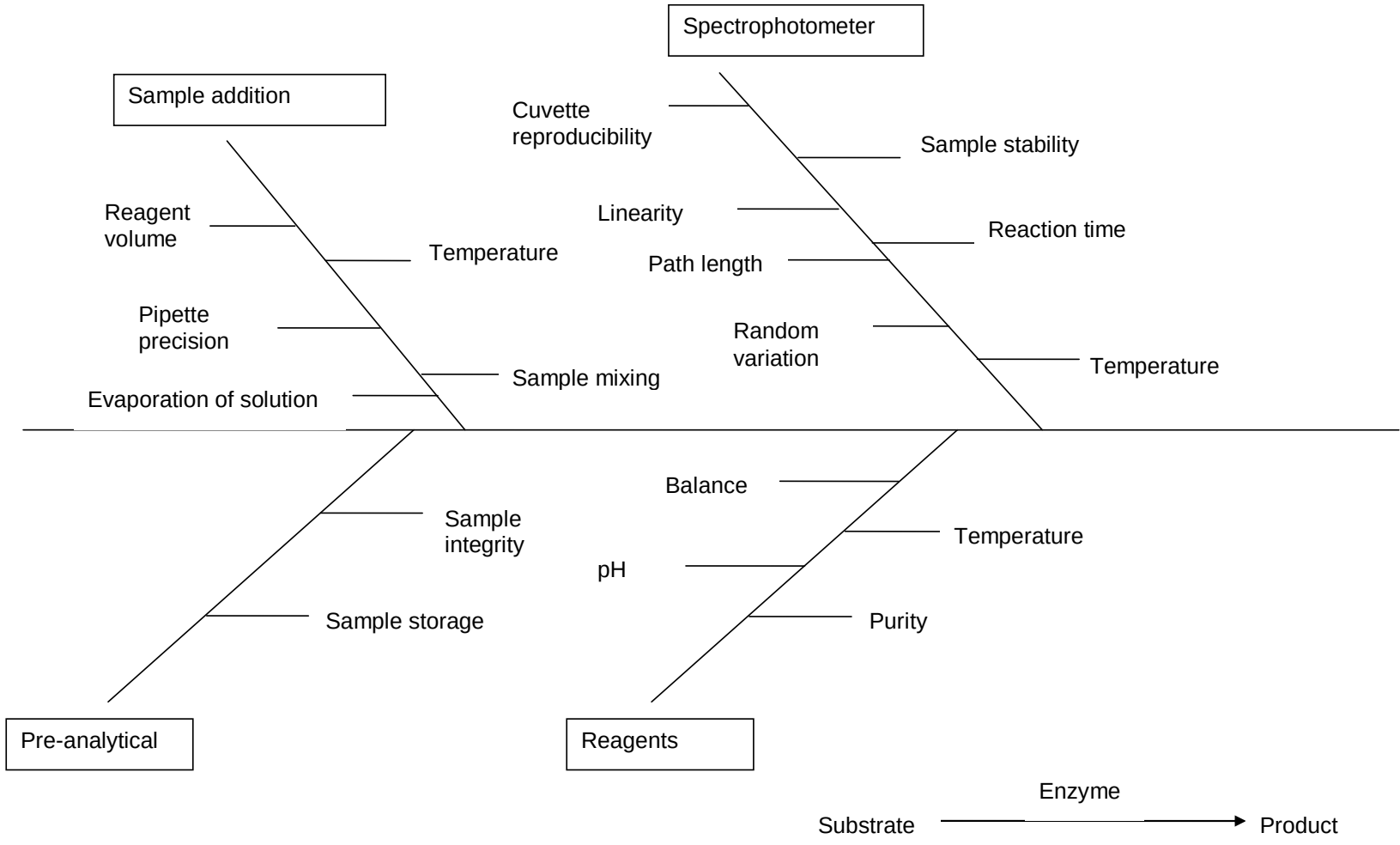
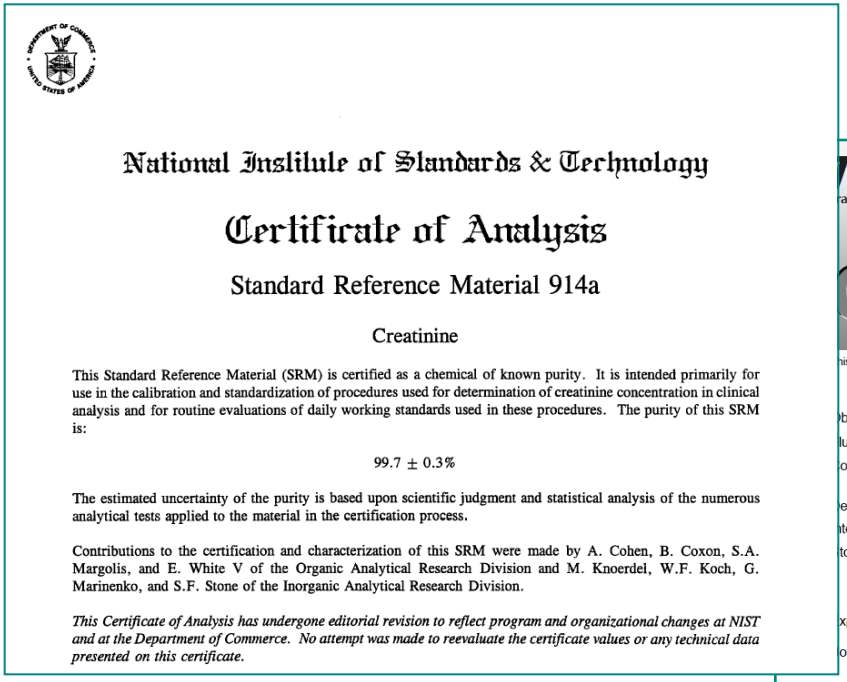
IFCC 37°C Enzyme Method

Enzyme kinetic uncertainty

L-(+)-Lactate + NAD_+ –LDH→ Pyruvate + NADH + H_+



Preparation of Standards



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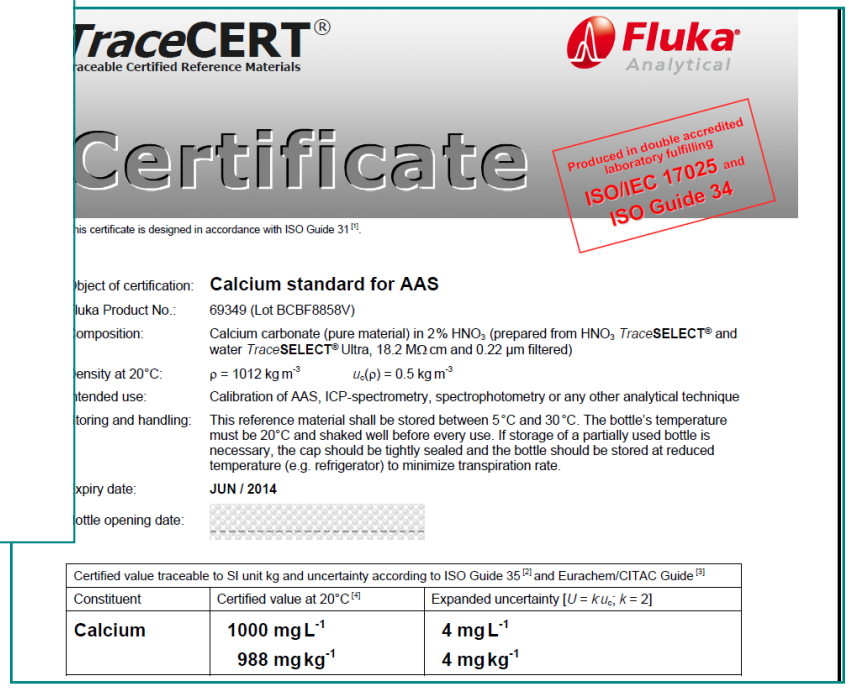

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Uncertainty from:

- Purity of standard – from certificate
- Balance – manufacturer or experimental
- Volumetric apparatus – manufacturer or experimental
- Matrix

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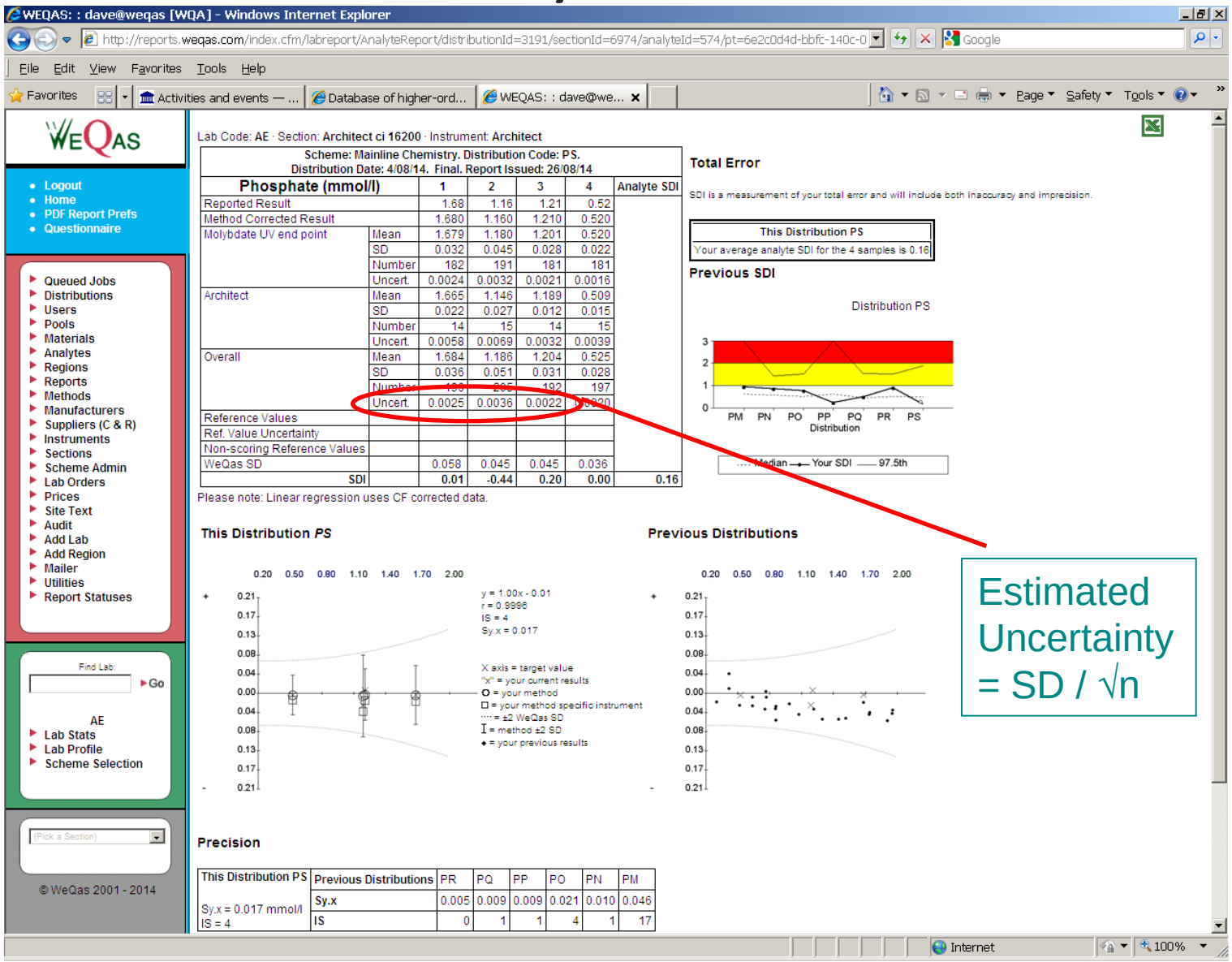
Pre-analytical events

- With a defined protocol, do these matter?
  - Method specific?
  - Measurand specific
- Sources of error could include:
  - Blood tube type
    Clotting time
    Storage temperature / time
    …….etc
  - For each measurand vary the items above and collate data e.g observe the obtained data from 2 types of blood tubes
  - Combine all uncertainties

Uncertainty From EQA Data



Estimated Uncertainty = SD / √n

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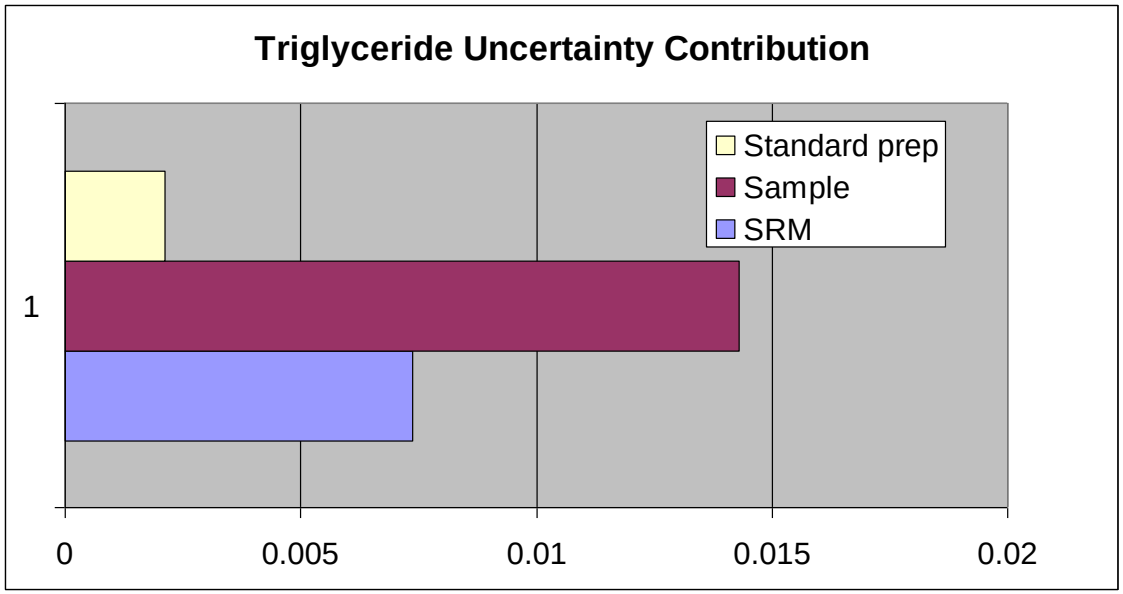
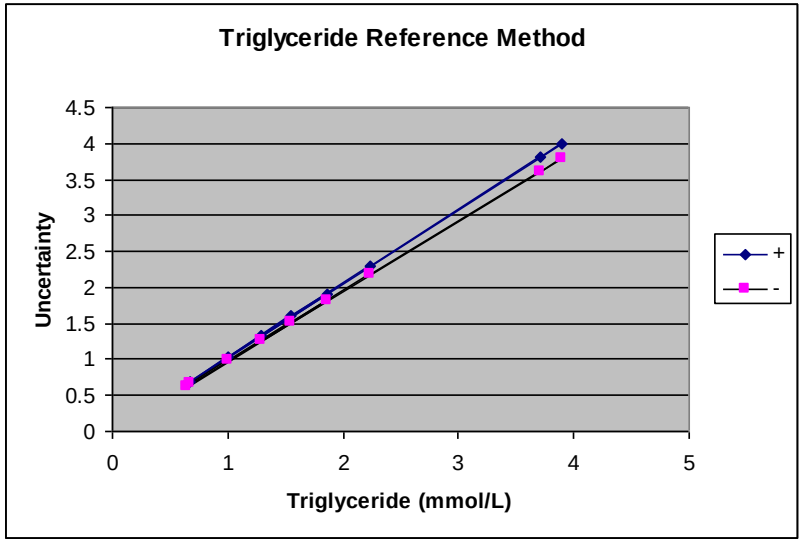
Graphical Representation



Combined uncertainty =
2 x result x {√ (Usample)² + √ (Ustd)² + √ (USRM)²}



Expanded Uncertainty

Coverage factor (K) = 2 (95%)

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Uncertainty in Practice

- For most methods, the majority of the uncertainty arises from the precision of the method
- CE marked methods generally ‘out of the box’. Manufacturer defines uncertainty (?)
- This can be expressed in terms of %cv (%R_{SD})

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RCPA Advice

Preparation for ISO 15189

The College recommends the following:

1. Make a list of all of the tests where the result is reported as a number.

2. From this, make a sub-list of every test which is already in the in-house CV% data.

3. Multiply the CV% by 2 and record this figure as the uncertainty of measurement against each of these tests. This should cover the majority of tests that a particular laboratory reports as a number.

4. Determine the CV% for the remaining tests, either by:

- reviewing internal QC data (30 sets) and determining the CV%
- obtaining CV% for method employed from an External QA Programme
- obtaining CV% for method employed from the manufacturer (reagent kit insert)

5. Check if it is either impractical or irrelevant to determine the uncertainty of measurement for the remaining tests, and document your reasons if these are not obvious.

6. Finally, document the policy for determining the uncertainty of measurement, the calculations used, and the sources of data used for these calculations.

RCPath: ISO 15189:2012 – An approach to the assessment of uncertainty of measurement for cellular pathology laboratories
May 2015

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Total Analytical Error

- BUT:
- This assumes the Bias is zero

Better to use total error calculation (?):

Total **A**nalytical **E**rror = Bias + 1.65 x imprecision SD

OR

Include the bias as a separate figure alongside the uncertainty value

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Example Calculation – from QC data

Multiple QC data points at different levels.

Need to combine uncertainty from each level

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Relative Standard Uncertainty – Sample Precision

- $R_{SD} = \sqrt{\left\{ \frac{[(n_1-1) \times (S_1/\chi_1)^2 + (n_2-1) \times (S_2/\chi_2)^2 \ldots.\text{etc.}]}{(n_1-1) + (n_2-1) \ldots\ldots} \right\}}$
- This is the overall coefficient of variation

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Lab QC Data

Date March 2015														
Assay	**Method**	**Feb-15**						**Mar-15**						
		N	**Mean**	**CV**	**SD**	**MU**	**CU**	**N**	**Mean**	**CV**	**SD**	**MU**	**CU**	**Comments**
		5	44.7	0.55	0.25	0.2236		8	39.1	2.1	0.81	0.573		
ACTH	Roche E411	5	855	0.67	5.7	5.0982	5.103	8	905	1.4	12.9	9.122	9.14	
		3	21.2	7.8	1.65	1.9053		2	23.2	15.2	3.54	5.006		
AMH	Beckman Elisa	3	55.2	4.9	2.7	3.1177	3.654	2	57.7	5.3	3.04	4.299	6.599	
		7	0.86	2.2	0.02	0.0151		7	0.84	1.51	0.01	0.008		
		7	9.33	1.8	0.16	0.1209	0.122	7	8.71	1.66	0.14	0.106	0.106	
Growth Hormone	Roche E411													
		4	4.1	2.4	0.1	0.1								
P3NP	Orion	8	5.6	4.3	0.24	0.1697	0.197	9	5.6	4.6	0.26	0.173	0.173	
		5	11.4	2.9	0.33	0.2952		4	11.1	2.7	0.3	0.3		
Insulin	Mercodia	5	52.2	4.3	2.22	1.9856	2.007	4	49	2.9	1.41	1.41	1.442	
		5	575	13.1	75.3	67.35		4	561	5.8	32.6	32.6		
C-Peptide	Mercodia	5	1500	5.4	81.1	72.538	98.98	4	1524	4.1	62.2	62.2	70.23	
		6	2.3	8.4	0.2	0.1633		4	2.6	12	0.31	0.31		
		6	11.4	5	0.57	0.4654		4	11	3.1	0.34	0.34	0.46	
		6	21.5	4.2	0.9	0.7348		4	20.8	6.5	1.34	1.34		
17OHP serum/saliva	In House RIA	6	49.1	3.9	1.9	1.5513	1.786	4	47.3	12.3	5.82	5.82	5.972	
		10	60	7.8	4.7	2.9725		6	56	5.5	3.1	2.531		
		10	130	8.1	10.4	6.5775		6	120	4.7	5.7	4.654		
17OHP blood spot	In Hous RIA	10	302	10.7	32.4	20.492	21.73	6	288	6.8	19.7	16.08	16.93	
		4	0.24	5.13	0.012	0.012		8	0.23	7.5	0.02	0.012		
		6	11	3.5	0.38	0.3103		8	11.1	3.4	0.38	0.269		
		6	92.1	3.1	2.83	2.3107		8	88.7	1.4	1.27	0.898		
Thyroglobulin	Beckman Access	6	204.5	2.9	5.95	4.8582	5.389	8	198	1.4	2.71	1.916	2.133	
		8	1.42	7.54	0.11	0.0778		8	1.46	7.2	0.1	0.071		
		8	4.8	3.3	0.16	0.1131		7	4.8	3.5	0.17	0.129		
TSH Receptor Ab	Roche E411	8	15.5	1.7	0.31	0.2192	0.259	7	15.8	1.6	0.25	0.189	0.239	
		8	32.8	3.6	1.16	0.8202		8	30	3	0.92	0.651		
	Tandem mass spec	8	515	1.9	9.62	6.8024	6.852	8	500	2.6	13.2	9.32	9.342	
UFC	Retention time	8	1.21			0		4	1.22					

Weqas

Calculated Example from QC Data

- $R_{SD} = \sqrt{[(n_1-1) \times (S_1/\chi_1)^2 + (n_2-1) \times (S_2/\chi_2)^2}$

$$\frac{}{(n_1-1) + (n_2-1)}$$

- **For ACTH** QC data (March 2015):

QC 1 Mean = 39.1, SD = 0.81, n=8

QC 2 Mean = 905, SD = 12.9, n = 8

$$R_{SD} = \sqrt{[(7 \times (0.81/39.1)^2 + 7 \times (12.9/905)^2)/7+7]}$$

$$= \sqrt{[(7 \times (0.021)^2 + 7 \times (0.014)^2)/14]}$$

$$= \sqrt{[(0.003 + 0.0014)/14]} = 0.0031$$

Therefore the method error for ACTH is 0.31% (R_{SD})

Expanded error is 0.62% (k=2)

Weqas

Questions

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Useful References

- **Metrology:**
  International vocabulary of basic and general terms in metrology (VIM) JCGM 200:2008 (E/F)
  Terminology in Analytical Measurement: Introduction to VIM 3, Eurachem 1st edition 2011

- **Traceability**
  JCTLM database: http://www.bipm.org/en/committees/jc/jctlm/ (Reference materials):

- Meeting the traceability requirements of ISO 17025: An analyst's guide (3rd edition) – LGC
  http://www.lgcgroup.com/LGCGroup/media/PDFs/Our%20science/NMI%20landing%20page/Publications%20and%20resources/Guides/Traceability_Guide.pdf

- **Uncertainty:**
  Evaluation of measurement data — Guide to the expression of uncertainty in measurement, JCGM 100:2008 (GUM)
  M3003 The Expression of Uncertainty and Confidence in Measurement
  (UKAS)
  Lab 12 The Expression of Uncertainty in Testing (UKAS)

- Evaluating Measurement Uncertainty in Clinical Chemistry - LGC (https://www.lgcstandards.com/WebRoot/Store/Shops/LGC/MediaGallery/case_studies/Clinical_worked_examples_report_Final.pdf)

- A Model for an Uncertainty Budget for Preanalytical Variables in Clinical Chemistry Analyses Clinical Chemistry 53:7 1343–1348 (2007)

- Hitchhiker's Guide to Measurement Uncertainty (MU) in Clinical Laboratories (Westgard website): https://www.westgard.com/hitchhike-mu.htm#telimits)

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