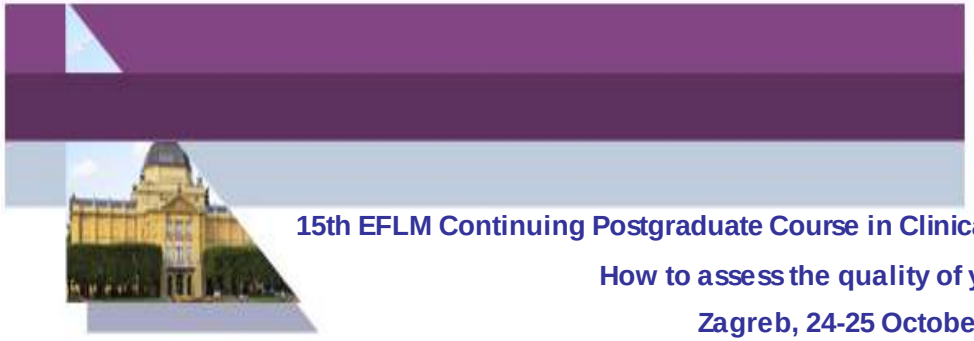

15th EFLM Continuing Postgraduate Course in Clinical Chemistry and Laboratory Medicine

How to assess the quality of your method?

Zagreb, 24-25 October 2015

HOW TO ASSESS THE MEASUREMENT UNCERTAINTY

Ilenia Infusino

Centre for Metrological Traceability in Laboratory Medicine (CIRME), University of Milan, Milan, Italy

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Università degli Studi di Milano

Centre for Metrological Traceability in Laboratory Medicine (CIRME)

Director: Prof. Mauro Panteghini

site: http://users.unimi.it/cirme

STANDARDIZATION – WHY BOTHER?

★ Result today will be the same as tomorrow

★ Result in Milan will be the same as the result in Zagreb

★ We can set common reference limits and clinical cutpoints for intervention

★ We all measure to the same set of rules

…….so we can diagnose, monitor and treat patients appropriately.

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EQUIVALENCE IN LABORATORY MEDICINE

Interchangeability of results over time and space would significantly contribute to improvements in healthcare by allowing results of clinical studies undertaken in different locations or times to be universally applied

Standardize clinical decision limits (i.e., cutpoints for intervention)

Effective application of evidence-based medicine

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- **Use of clinical guidelines is becoming more and more prominent in the clinical practice**
- **Analytes in these guidelines have specific cutoffs that are independent of the assay used**
- **To globally utilize these cutoffs, the assay results for the analyte in question must be equivalent:**

TO BE EQUIVALENT THEY MUST BE "TRACEABLE"

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OBJECTIVE OF TRACEABILITY IMPLEMENTATION

To enable the results obtained by the calibrated routine procedure to be expressed in terms of the values obtained at the highest available level of the calibration hierarchy

Advantages:

- **All routine methods will be standardized to the same reference with no additional effort by laboratories**
- **The process can be sustained over time by the IVD manufacturers**


INTERNATIONAL STANDARD ISO 17511

In vitro diagnostic medical devices — Measurement of quantities in biological samples — Metrological traceability of values assigned to calibrators and control materials

ISO

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[ISO/EN 17511 - Measurement of quantities in samples of biological origin - Metrological traceability of values assigned to calibrators and control materials]

LEGAL BACKGROUND FOR THE USE OF METROLOGICALLY CORRECT MEASUREMENT SYSTEMS IN LABORATORY MEDICINE

Requirement of the EU 98/79/EC-IVD Directive:

The traceability of values assigned to calibrators and/or control materials must be assured through available reference measurement procedures and/or available reference materials of a higher order

[Annex I - Essential Requirements (Part A. General Requirements)]

Official Journal of European Communities (1998)

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METROLOGICAL TRACEABILITY

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 (VIM:2012, 2.41)

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[International Vocabulary of Metrology Basic and general concepts and associated terms (VIM). 3rd ed. 2012]

MEASUREMENT UNCERTAINTY

Non negative parameter characterizing the dispersion of the quantity values being attributed to a measurand, based on the information used (VIM: 2012, 2.26).

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[International Vocabulary of Metrology Basic and general concepts and associated terms (VIM). 3rd ed. 2012]

WHY UNCERTAINTY IS NEEDED

The estimation of measurement uncertainty is mandatory for:

1. **reference measurement laboratories to obtain/maintain the accreditation according to ISO 17025:2003 and ISO 15195:2005;**

2. **clinical laboratories to obtain the accreditation according to ISO 15189:2012.**

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WHAT IS UNCERTAINTY

Uncertainty is the quantification of the doubt about the measurement result:

$$\text{Result} = x \pm u$$

quantity value — measurement uncertainty

"….In general use, the word uncertainty relates to the general concept of doubt…Uncertainty of measurement *does not imply doubt about the validity of a measurement*; on the contrary, knowledge of the uncertainty implies *increased confidence in the validity of a measurement result*…"

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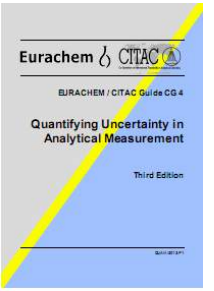
[Ellison S L R, Williams A (eds) (2012). *Eurachem Guide: Quantifying Uncertainty in Analytical Measurement, Eurachem, third edition]*



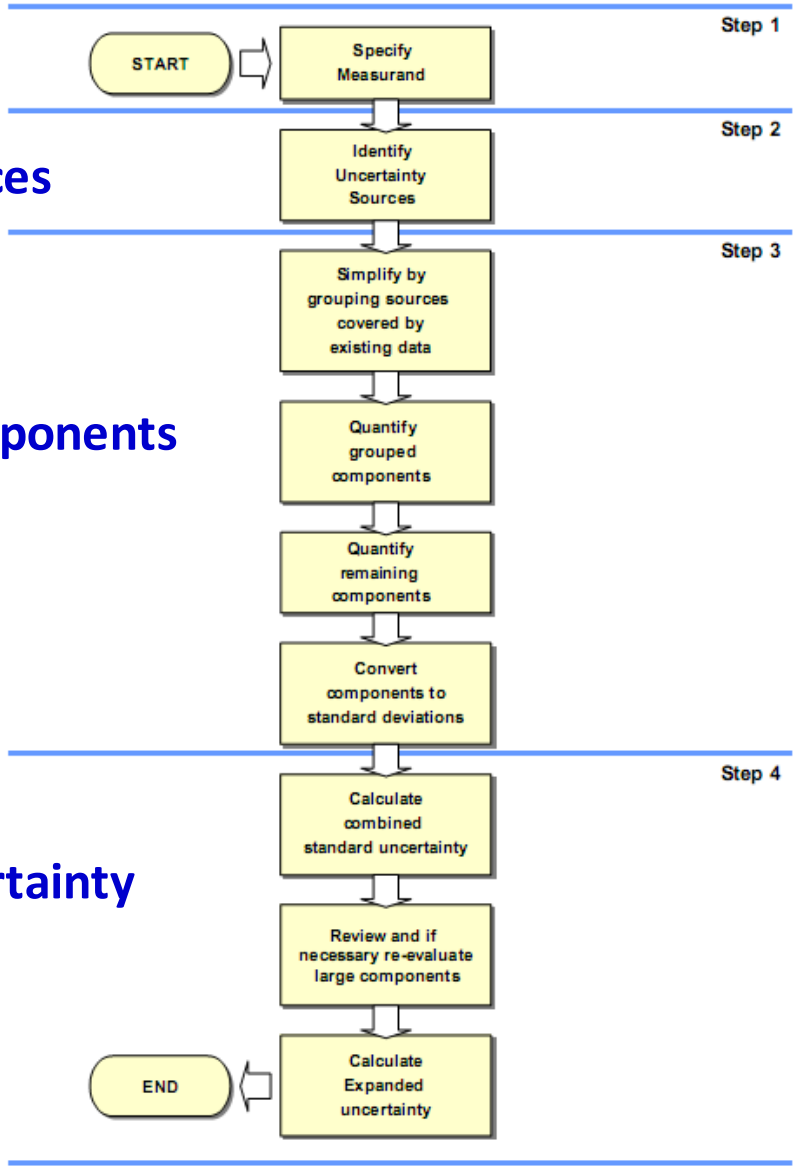
ESTIMATION OF UNCERTAINTY

Step 1: Specify the measurand

Step 2: Identify uncertainty sources

Step 3: Quantify uncertainty components

Step 4: Calculate combined uncertainty



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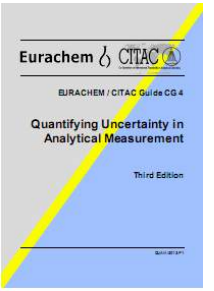

STEP 1: SPECIFY THE MEASURAND

The first step is to identify the measurand, which is a clear and unambiguous statement of what is intended to be measured. Also required is a quantitative expression (quantitative equation) relating the value of the measurand to the parameters on which it depends.
All the information should be in the Standard Operating Procedure (SOP) o the manufacturers' instrument and method descriptions.

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STEP 2: IDENTIFY UNCERTAINTY SOURCES

A comprehensive list of *relevant sources of uncertainty* should be assembled. It is often useful to structure this process, both to ensure comprehensive coverage and to avoid over-counting.

1. **Identifying the effects on a result:**

   In practice, the necessary structured analysis is effected using a *cause and effect diagram*.

2. **Simplifying and resolving duplication:**

   The initial list is refined to simplify presentation and ensure that effects are not unnecessarily duplicated.

The aim is to be completely clear about what should be considered.

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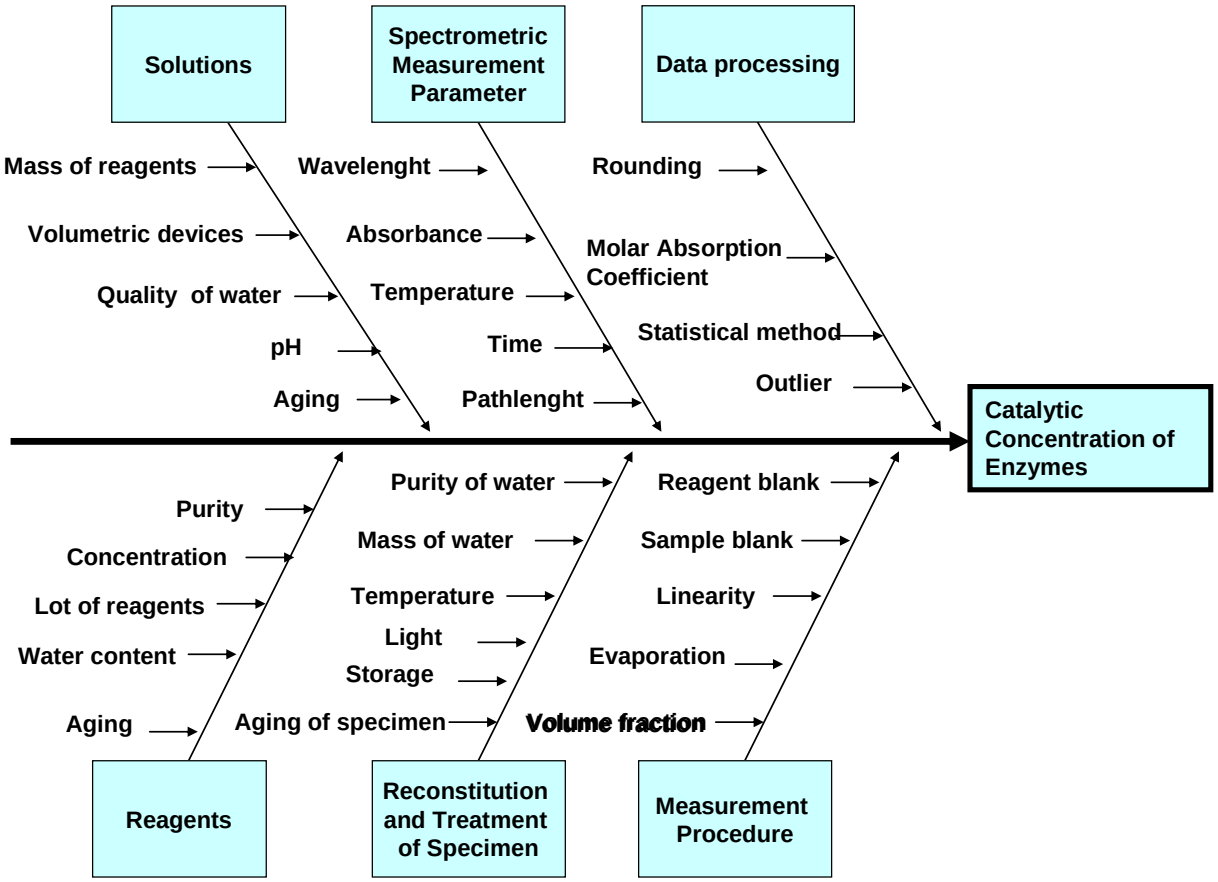
EXAMPLE: CAUSE AND EFFECT DIAGRAM OF THE MOST RELEVANT UNCERTAINTY SOURCES OF THE PRIMARY REFERENCE PROCEDURE FOR ENZYMES MEASUREMENT



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STEP 3: QUANTIFY UNCERTAINTY COMPONENTS

It is essential when establishing a realistic uncertainty budget to identify the variables that give rise to the uncertainty and their sizes.

THE UNCERTAINTIES HAVE TO BE EXPRESSED AS *STANDARD DEVIATIONS*

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STEP 3: TWO APPROACHES TO QUANTIFY MEASUREMENT UNCERTAINTY

The bottom-up approach according to Guide to the Expression of Uncertainty of Measurement (GUM) principles is based on a comprehensive categorization of the measurement in which each potential source of uncertainty is identified, quantified and combined to generate a combined uncertainty of the result using statistical propagation rules. This model has been fully endorsed by metrology institutions and suppliers of reference materials and is used in accredited reference laboratories that perform reference measurement procedures.

The top-down approach uses available laboratory test performance information, such as method validation, intra-laboratory and inter-laboratory data, to calculate estimates of the overall uncertainty associated with the result produced by a given measuring system. This model may be used by clinical laboratories to estimate measurement uncertainty.

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STEP 4: CALCULATE THE COMBINED STANDARD UNCERTAINTY

The information obtained in step 3 will consist of a number of quantified contributions to overall uncertainty, whether associated with individual sources or with the combined effects of several sources.

The contributions expressed as standard deviations are combined according to the appropriate rules to give a *combined standard uncertainty* (u_c). The appropriate coverage factor should be applied to give an *expanded uncertainty (U)*:

$$U = k \times u_c$$

The choice of the factor k is based on the desired level of confidence.
For an approximate level of confidence of 95 %, k is 2.

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BOTTOM-UP APPROACH

Standard uncertainty (u) is calculated for the measurement uncertainty (MU) components that can have influence on the final result in two ways.

Type A evaluation: MU components are typically estimated as the standard deviation (SD) of repeated measurements;

Type B evaluation: MU components are estimated from specific information based on literature, calibration certificate, professional experience, manufacturer's specifications, etc. This requires information or assumptions on how values for the specific quantity are distributed (i.e., normal, rectangular or triangular).

TYPE A EVALUATION

In this model the estimation of the standard uncertainty (u) is based on:

a) ***SD*** **derived from repeated measurements (n);**
SD and u will therefore have the same size :

$$u(\bar{x}) = \frac{SD}{\sqrt{n}}$$

b) sometimes the variation is given as a coefficient of variation (*CV*):

$$u(\bar{x}) = \frac{CV}{\sqrt{n}}$$

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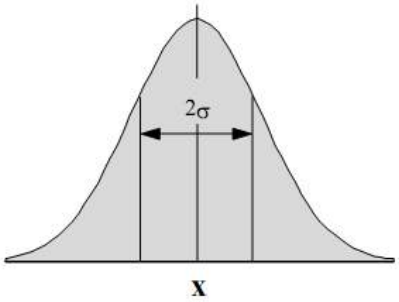
TYPE B EVALUATION: NORMAL DISTRIBUTION

When an uncertainty estimate is derived from previous results and data, it may already be expressed as a *standard deviation*.

However, where *a confidence interval is given* with a level of confidence p% (in the form ±a at p%), then divide the value a by the appropriate percentage point of the normal distribution for the level of confidence given to calculate the standard deviation.

Normal distribution

Form	Use when:	Uncertainty
	▪ An estimate is made from repeated observations of a randomly varying process.	$u(x) = s$
	• An uncertainty is given in the form of a standard deviation s, a relative standard deviation $s/\bar{x}$, or a percentage coefficient of variance %CV without specifying the distribution.	$u(x) = s$ $u(x) = x \cdot (s/\bar{x})$ $u(x) = \frac{\%CV}{100} \cdot x$
	• An uncertainty is given in the form of a 95 % (or other) confidence interval $x \pm c$ without specifying the distribution.	$u(x) = c/2$ (for c at 95 %) $u(x) = c/3$ (for c at 99.7 %)

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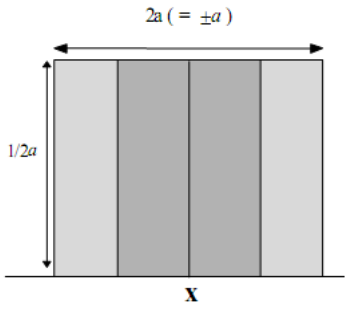
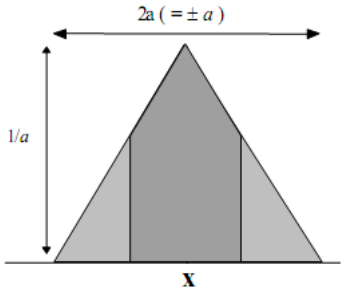
TYPE B EVALUATION: RECTANGULAR AND TRIANGULAR DISTRIBUTION

If limits of ±a are given *without a confidence level* and there is reason to expect that extreme values are *likely*, it is appropriate to assume a rectangular distribution, with a standard deviation of a/√3.

Rectangular distribution		
Form	Use when:	Uncertainty
	• A certificate or other specification gives limits without specifying a level of confidence (e.g. 25 mL ± 0.05 mL) • An estimate is made in the form of a maximum range (±a) with no knowledge of the shape of the distribution.	$u(x)=\frac{a}{\sqrt{3}}$

If limits of ±a are given *without a confidence level*, but there is reason to expect that extreme values are *unlikely*, it is appropriate to assume a triangular distribution, with a standard deviation of a/√6.

Triangular distribution		
Form	Use when:	Uncertainty
	• The available information concerning x is less limited than for a rectangular distribution. Values close to x are more likely than near the bounds. • An estimate is made in the form of a maximum range (±a) described by a symmetric distribution.	$u(x)=\frac{a}{\sqrt{6}}$

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EXAMPLE: UNCERTAINTY BUDGET FOR ENZYMES WITH SOURCES OF UNCERTAINTY

Parameter	Type of uncertainty	Distribution of uncertainty	Estimation
Wavelenght	B	Rectangular	Manufacturer's specification
Absorbance	B	Rectangular	Manufacturer's specification
pH	B	Rectangular	IFCC-document
Temperature	B	Rectangular	IFCC-document
Reagent concentration	B	Rectangular	IFCC-document
Lot of reagent	B	Rectangular	Experiment
Volume fraction of sample	B	Rectangular	IFCC-document
Time	B	Rectangular	Experiment
Evaporation	B	Rectangular	Experiment
Aging of specimen	B	Rectangular	Experiment
Linearity	B	Normal	Experiment
Mean of the means	A	Normal	Result of reference method value investigation

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STEP 4: CALCULATE COMBINED STANDARD UNCERTAINTY FOR UNCORRELATED (INDEPENDENT) QUANTITIES

1. **For *uncorrelated (independent) quantities*, the general relationship between the combined standard uncertainty $u_c(y)$ of a value y and the uncertainty of the independent parameters $x_1, x_2, \ldots x_n$ on which it depends is:**

$$u_c(y(x_1,x_2,\ldots)) = \sqrt{\sum_{i=1,n} c_i^2 u(x_i)^2} = \sqrt{\sum_{i=1,n} u(y,x_i)^2}$$

- **$y(x_1,x_2,..)$ is a function of several parameters $x_1,x_2\ldots$;**
- **c_i is a *sensitivity coefficient* evaluated as $c_i=\partial y/\partial x_i$ (the partial differential of y with respect to x_i) and is *set equal to 1.0* when an uncertainty contribution is expressed as an effect on the final result otherwise it must be *estimated*;**
- **$u(y,x_i)$ denotes the uncertainty in y arising from the uncertainty in x_i.**

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STEP 4: CALCULATE COMBINED STANDARD UNCERTAINTY FOR CORRELATED (NON-INDEPENDENT) QUANTITIES

2. For *correlated (non-independent) quantities*, the general relationship between the combined standard uncertainty $u_c(y)$ of a value y and the uncertainty of the independent parameters $x_1, x_2, \ldots x_n$ on which it depends is:

$$u(y(x_{i,j\ldots})) = \sqrt{\sum_{i=1,n} c_i^2 u(x_i)^2 + \sum_{\substack{i,k=1,n \\ i \neq k}} c_i c_k \cdot u(x_i, x_k)}$$

- $u(x_i, x_k)$ is the covariance between x_i and x_k;
- c_i and c_k are the sensitivity coefficients.

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"….If there is correlation between any components, this has to be taken into account by determining the covariance. However, it is often possible to evaluate the combined effect of several components. This may reduce the overall effort involved and, where components whose contribution is evaluated together are correlated, there may be *no additional need to take account of the correlation*…."

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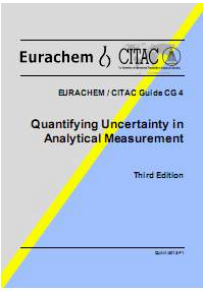
[Ellison S L R, Williams A (eds) (2012). *Eurachem Guide: Quantifying Uncertainty in Analytical Measurement, Eurachem, third edition]*



SIMPLER FORMS FOR EXPRESSION OF COMBINED STANDARD UNCERTAINTIES

Rule 1

For models involving only a *sum or difference* of quantities, e.g. $y=(p+q+r+...)$, $u_c(y)$ is given by:

$$u_c(y(p,q..)) = \sqrt{u(p)^2 + u(q)^2 + ...}$$

Rule 2

For models involving only a *product or quotient*, e.g. $y=(p \times q \times r \times ...)$ or $y= p / (q \times r \times ...)$, $u_c(y)$ is given by:

$$u_c(y) = y\sqrt{\left(\frac{u(p)}{p}\right)^2 + \left(\frac{u(q)}{q}\right)^2 + ...}$$

EXAMPLE: CALCULATION OF COMBINED STANDARD UNCERTAINTY FOR ENZYME MEASUREMENT

Parameter	Declared uncertainty		Reference	Distribution of uncertainty	Type of uncertainty	Standard uncertainty	Coefficient of sensitivity	Pro		Relative standard uncertainty
wavelenght	0,1	nm	manufacturer's specification	rectangular	B	0,06	0,14	1	nm	0,01
absorbance	0,3	%	manufacturer's specification	rectangular	B	0,17	1	1	%	0,17
pH	0,05	pH	IFCC-document	rectangular	B	0,03	0,14	0,05	pH	0,08
temperature	0,1	°C	IFCC-document	rectangular	B	0,06	4,14	1	°C	0,24
reagent concentration	1,5	%	IFCC-document	rectangular	B	0,87	0,26	1	%	0,23
lot of reagent	1,5	%	IFCC-document	rectangular	B	0,87	1	1	%	0,87
volume fraction of sample	0,4	%	data basis	rectangular	B	0,22	1	1	%	0,22
time	0,03	%	experiment	rectangular	B	0,02	1	1	%	0,02
evaporation	0,1	%	experiment	rectangular	B	0,06	1	1	%	0,06
aging of specimen	0,5	%	IFCC-document	rectangular	B	0,29	1	1	%	0,29
linearity	0,6	%	experiment	normal	B	0,30	1	1	%	0,30
mean of the means	0,8	U/L	result of the RMV investigation	normal	A	0,40	1	1	U/L	0,40
							u combined			1,1
							U expanded (k=2)			2,3

u_c is calculated according to our model as the square root of the *sum* of the squares of the relative standard uncertainty of each components

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GUM AND MEDICAL LABORATORY MEASUREMENTS

The GUM (bottom-up) model is not easily applied in clinical laboratories because:

- **clinical analytes are often physico-chemically ill-defined;**
- **measurement procedures may lack adequate analytical specificity, reference materials and/or reference measurement procedures suitable for evaluation of bias;**
- **measuring system may be 'closed' and not amenable to statistical evaluation of individual uncertainty inputs to measured values.**

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Clin Chem Lab Med 2010;48(1):7–10 © 2010 by Walter de Gruyter • Berlin • New York. DOI 10.1515/CCLM.2010.020

Editorial

Application of traceability concepts to analytical quality control may reconcile total error with uncertainty of measurement

Mauro Panteghini

"… if the uncertainty concept should meet more widespread practical acceptance, the complexity of the evaluation process for uncertainty must be markedly reduced so that clinical laboratories can estimate this important characteristic preferably using the *information that already exists*…"

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'TOP-DOWN' APPROACH

‘TOP-DOWN’ APPROACH

The *GUM also endorses the top down (empirical) approach* based on measurement of control samples.

“…whenever feasible, the use of empirical models of the measurement founded on *long-term quantitative data*, and the use of *check standards* and *control charts* that can indicate if a measurement is under statistical control, should be part of the effort to obtain reliable evaluations of uncertainty…”

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[Evaluation of measurement data. Guide to the expression of uncertainty in measurement. 1st ed. 2008. JCGM 100:2008]

Many 'top-down' approaches have been proposed for the estimation of uncertainty in clinical laboratories.

The *Eurolab report from 2007* summarized the various 'top-down' approaches that laboratories can choose based on data from:

(1) validation and quality control,

(2) collaborative trials, or

(3) proficiency testing.

All these approaches are *fully compliant with the GUM principles* and the basic requirement for a valid uncertainty evaluation can be summarized by:

- **a clear definition of the measurand,**
- **a comprehensive specification of the measurement procedure and the test items,**
- **a comprehensive analysis of *random and systematic effects* on the measurement results.**

Limitation: the proposed approaches estimate the uncertainty of measurement from bias and imprecision analysis, but don't take into account the uncertainty accumulated in upper levels of the metrological traceability chain including the *uncertainty associated to the end-user calibrators*

SOURCES OF UNCERTAINTY WITH THE 'TOP-DOWN' APPROACH

Using the 'top-down' approach, the sources of measurement uncertainty are associated with:

- **the values assigned to end-user calibrator (u_{cal}),**
- **bias (u_{bias}),**
- **imprecision (u_{imp}).**

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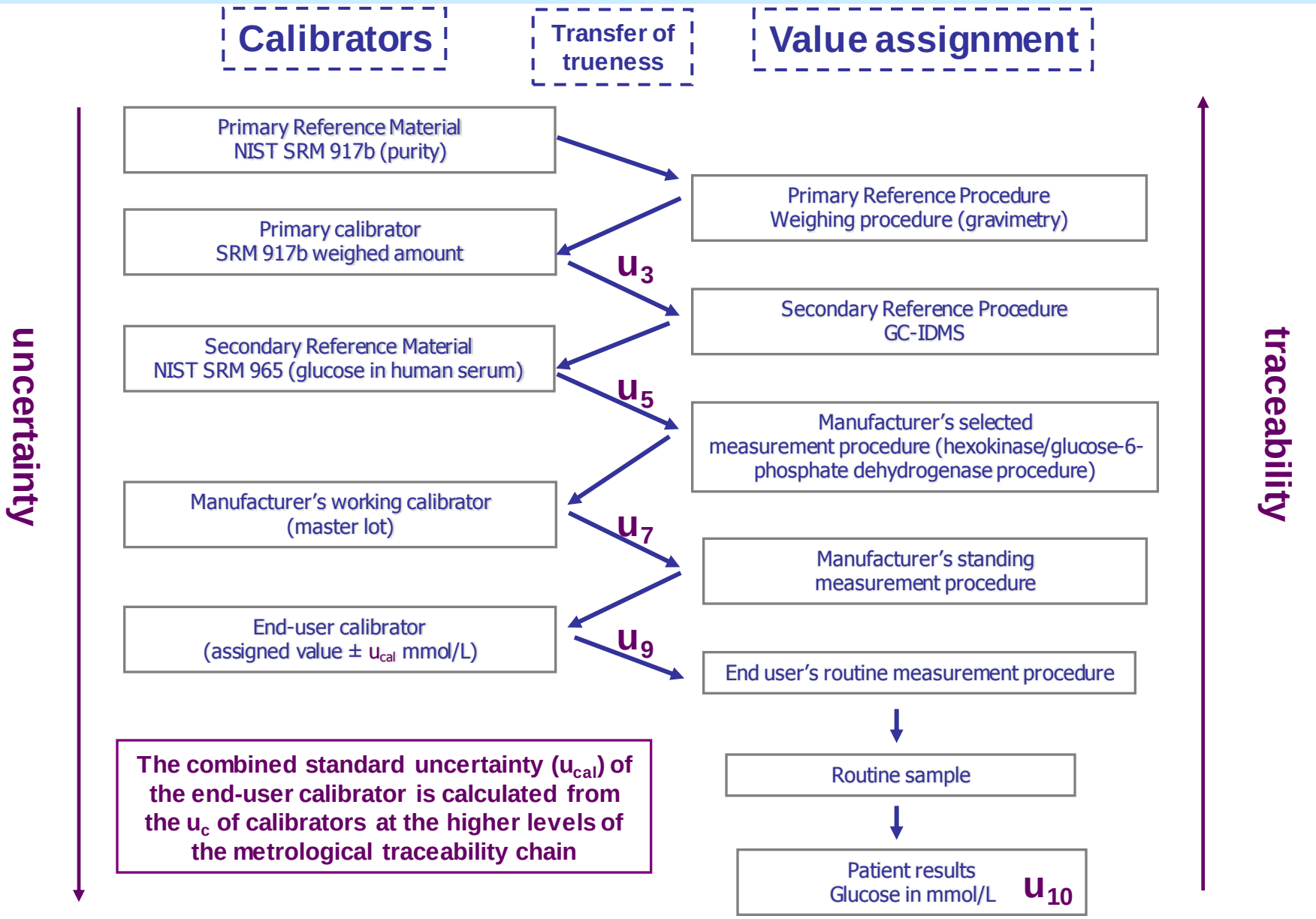
UNCERTAINTY OF END-USER CALIBRATOR VALUES (u_{cal})



Opinion Paper

Federica Braga*, Ilenia Infusino and Mauro Panteghini

Performance criteria for combined uncertainty budget in the implementation of metrological traceability

Table 2: The information that in vitro diagnostics manufacturers should provide to laboratory users about the implementation of metrological traceability of their commercial systems. Adapted from [7].

a) An indication of higher order references (materials and/or procedures) used to assign traceable values to calibrators;
b) Which internal calibration hierarchy has been applied by the manufacturer, and
c) A detailed description of each step;
d) The (expanded) combined uncertainty value of commercial calibrators, and
e) Which, if any, acceptable limits for uncertainty of calibrators were applied in the validation of the analytical system.

Ensuring that the uncertainty of all steps in the calibration traceability chain have been included

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UNCERTAINTY DUE TO SYSTEMATIC ERROR (u_{bias})

Bias is an estimate of a systematic error relative to a selected and suitable reference:

a. **reference material,**
b. **commutable trueness control or EQA material,**
c. **panel of patient samples with values assigned by a reference measurement procedure.**

It is recommended to use high order reference materials to *fully* estimate uncertainty of the bias (u_{bias})!

If a bias is clinically significant for a measurement procedure, it should be eliminated, for example, by recalibration. However, *u_{bias} value used for calibration correction should be estimated*.

As a rule-of-thumb, if u_{bias} is <0.25 u_{imp}, it can be ignored; otherwise, its magnitude is sufficiently large that it should be considered for combination with u_{imp} to provide u_c.

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ESTIMATION OF u_{bias}

$$u_{bias} = \sqrt{(u^2_{ref} + SD^2_{mean})}$$

- u_{ref} is the uncertainty of the reference value (e.g. from certificate of reference material);
- $SD_{mean} = SD/\sqrt{n}$;

It is necessary to calculate the SD of the mean value (SD_{mean}) obtained from a single study, because slightly different mean values would be obtained if the repeatability study were repeated a number of times.

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UNCERTAINTY DUE TO RANDOM ERROR (u_{imp})

Imprecision is generally the largest contributor to the uncertainty of measured quantity values. Typical sources of imprecision can be categorised as:

1. **instrumentation (e.g. temperature control, ageing of equipment…),**
2. **consumables (e.g. reagent and calibrator stability, new reagent and calibrator lots),**
3. **operators,**
4. **variations in measuring conditions (e.g. recalibration, instrument maintenance…).**

Internal quality control (IQC) materials **should be used to estimate u_{imp}: a precision study under intermediate reproducibility conditions over time for a given measurand should be performed in order to collect imprecision data over sufficient time to include the relevant sources of imprecision.**

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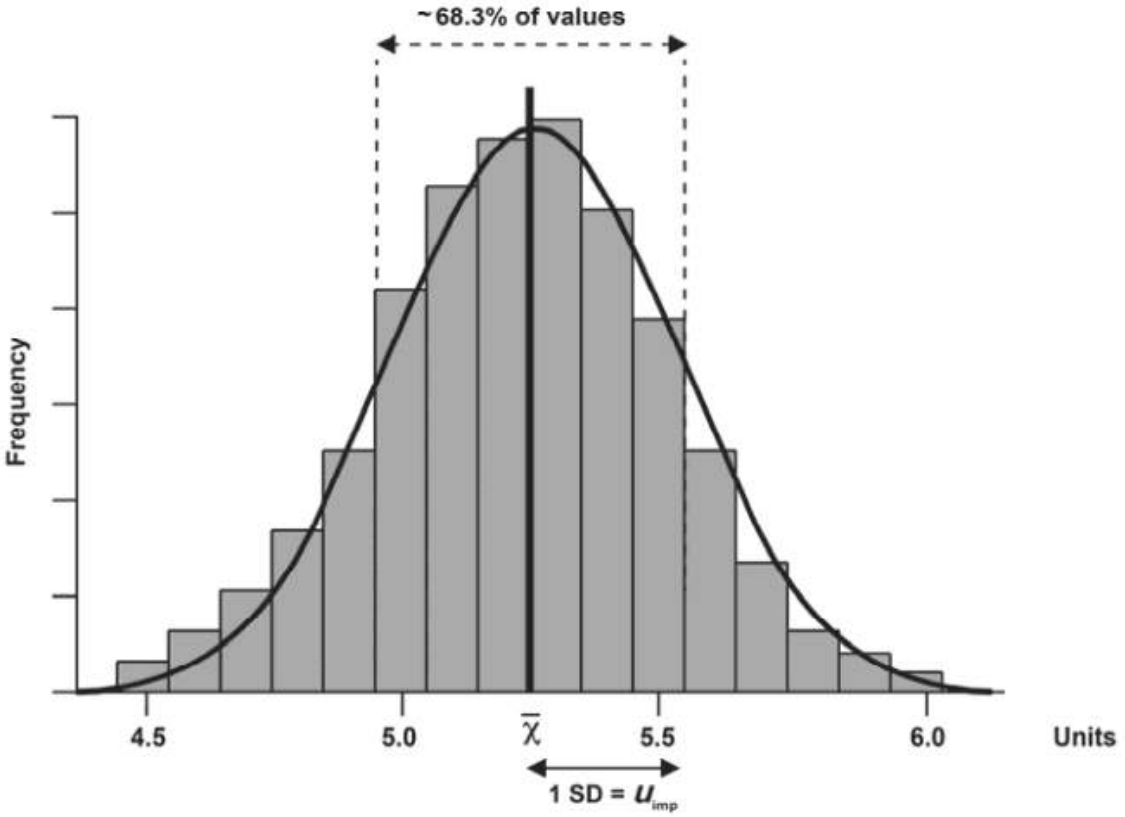
ESTIMATION OF u_{imp}



The dispersion of values obtained by a precision study represents generally a Gaussian distribution and can be quantified by calculation of the mean (x) and SD of the contributing IQC values: an SD is termed a standard measurement uncertainty (u) that under reproducibility conditions is designated u_{imp} (*imprecision standard mesurement uncertainty*).

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STEP 4: CALCULATE COMBINED STANDARD UNCERTAINTY WITH 'TOP-DOWN' APPROACH

The combined standard uncertainty (u_c) is:

$$u_c = \sqrt{(u^2_{cal} + u^2_{bias} + u^2_{imp})}$$

The appropriate coverage factor should be applied to give an *expanded uncertainty (U)*:

$$U = k \; x \; u_c$$

The choice of the factor k is based on the desired level of confidence.
For an approximate level of confidence of 95 %, k is 2.

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EXAMPLE: CALCULATION OF COMBINED STANDARD UNCERTAINTY FOR CREATININE MEASUREMENT OF THE ABBOTT ENZYMATIC CREATININE ASSAY

u_c is calculated with the "top-down" approach according to Nordtest report TR 537 05/2003, using data obtained by measurements of *NIST SRM 967a* in triplicate for four consecutive days on two identical Abbott Architect *c*16000 platforms:

$$u_c = \sqrt{u(R_w)^2 + (u(bias))^2}$$

- **$u(R_w)$, mean of SDs obtained from the replicate of each analytical run for two SRM levels divided by the respective mean of means (M):**

$$u_{Rw} = \frac{\Sigma\ \text{SD}}{\text{M}} \text{ x } 100$$

- **u(bias), three components contributed to the standard uncertainty of bias**

$$u(bias) = \sqrt{(bias)^2 + \left(\frac{s_{bias}}{\sqrt{n}}\right)^2 + u(Cref)^2}$$

bias variability

NIST SRM 967a

1. **Bias = difference between the obtained mean of the means for two SRM levels and the target value,**
2. **bias variability = SD of individual bias at two SRM levels divided by the square root of number of measurements;**
3. **u(Cref) = the relative standard uncertainty of the certified value of reference material.**

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Letter to the editor

The calibrator value assignment protocol of the Abbott enzymatic creatinine assay is inadequate for ensuring suitable quality of serum measurements

Note: For serum creatinine measurements on patient samples, the acceptable limits for expanded uncertainty derived from its CV_I are 6.0% (desirable) and 9.0% (minimum quality level), respectively.

Table 1
Uncertainties for each contributing factor in determination of serum creatinine with Abbott enzymatic assay on Architect *c*16000 platform after calibration with two different lot of system calibrator. Data obtained by measurements of NIST SRM 967a reference material (certified value ± expanded uncertainty: L1, 0.847 mg/dL ± 0.018 mg/dL and L2, 3.877 mg/dL ± 0.082 mg/dL).

	SRM 967a level 1	SRM 967a level 2
Multigent Clin Chem Calibrator lot no. 40043Y600		
Imprecision (u_{Rw})	0.47%	0.40%
Bias (u_{bias})	3.57%	7.05%
Relative combined standard uncertainty [$u_c = (u_{bias}^2 + u_{Rw}^2)^{0.5}$]	3.60%	7.06%
Expanded uncertainty ($U = k \times u_c$)	7.20%	14.12%
Multigent Clin Chem Calibrator lot no. 40496Y600		
Imprecision (u_{Rw})	0.53%	0.42%
Bias (u_{bias})	4.02%	1.71%
Relative combined standard uncertainty [$u_c = (u_{bias}^2 + u_{Rw}^2)^{0.5}$]	4.05%	1.76%
Expanded uncertainty ($U = k \times u_c$)	8.10%	3.52%

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THANK YOU FOR YOUR ATTENTION

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Take a home massage

HOW TO ASSESS THE MEASUREMENT UNCERTAINTY

- The ISO GUM model, which uses the "bottom-up" approach for estimating the measurement uncertainty, should be used when the principle of the measurement procedure is well understood and sources of measurement uncertainty are known (e.g., with reference measurement procedures).
- The 'top-down' approach uses available information on the laboratory test performance (e.g., from method validation, intra- and inter-laboratory use, quality control) to calculate measurement uncertainty associated with the result produced by a given measuring system. This model may be used by clinical laboratories to estimate uncertainty of their clinical measurements.