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EVALUATION OF MEASUREMENT UNCERTAINTY
ANNEX 2.4

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Annex 2 to Guideline "Evaluation of Measurement Uncertainty"
PA/PH/OMCL (18) 145 (in its current version)

Estimation of measurement uncertainty using Top-down approach

Annex 2.4: Use of data from collaborative studies for the estimation of measurement uncertainty

Collaborative studies conducted as a part of establishment of reference standards (RS) or biological reference preparations (BRP), or validation of a published method, offer the opportunity to estimate the uncertainty of measurement in routine testing. For the validation of a published method, the data typically include estimates of reproducibility standard deviation, S_R, for several levels of response, a linear estimate of the dependence of S_R on level of response, and may include an estimate of bias based on Certified reference material (CRM) studies, which depend also on the how the study was carried out [1]. For the establishment of RS or BRP, the uncertainty estimation comprises the use of the standard deviation of results within and between participating laboratories, which can be combined to calculate the uncertainty around the consensus value of the RS or BRP and/or estimate the reproducibility of a test method (precision and bias related components) and its applicability. It could be also used as a valuable source of data (reproducibility standard deviation) recommended for estimation of uncertainty of measurement in routine testing using the same method [1]. Contribution of the sample matrix should be taken in to account in the uncertainty budget (e.g. recovery studies), if different from the matrix used in the collaborative study.

Example: Use of data from collaborative studies for the estimation of measurement uncertainty for quantitative determination of content of a test sample

1. Description of the analytical procedure

The laboratory has participated in the collaborative study for determination of the content (mg/mL) of a new batch of a reference standard. The test method used in the collaborative study is applied to a routine sample testing. This routine sample has the same sample matrix which was targeted during the collaborative study, and it is subjected to three independent preparations / measurements (n = number of replicates). The results are given in Table 1.

Table 1. Test results for a routine sample

N	Content (mg/mL)	Mean	S_r	RSD (%)
1	2.48	2.49 mg/mL	0.02 mg/mL	0.61
2	2.51			
3	2.49			

2. Estimation of measurement uncertainty

2.1 Specification of measurand

The measurand is the content of a test sample expressed as mg/mL.

2.2 Quantification of the uncertainty of measurement using collaborative study data

The consensus value obtained from the collaborative study is the overall mean (2.43 mg/mL) of the assay results of 10 laboratories. The expanded uncertainty is ± 0.11 mg/mL (k = 2 for a 95% level of confidence), and covers the preparation of the stock solution (i.e. purity, weighting and dissolution of the reference material), the uniformity of content of vials and the reproducibility of the test method (Table 2).

The uncertainties associated with the preparation of the stock solution are estimated from either a rectangular distribution (uniform content) or triangular distribution (calibration-based data). S_{Vial} and S_{Lab}, the within- and between-laboratory standard deviations, are estimated using a one-way random analysis of variance, where S_{Vial} reflects both the variability among vials and the repeatability of the test method as each laboratory has reported one single value per each of 4 vials [2].

Table 2. Uncertainty components

Source of *u*	Step	Type of distribution	Units	RSD (%)	
Stock solution (prior to filling)	Purity	Rectangular	%	RSD_{Purity}	0.6
	Weighting	Triangular	mg	$RSD_{Weighting}$	0.05
	Solvent	Triangular	mg	$RSD_{Solvent}$	0.01
Vials and Test method	Within-Lab (experimental) [Uniformity of content of vials]		mg/mL	RSD_{Vial}	1.4
	Between-Lab (experimental)		mg/mL	RSD_{Lab}	5.1

2.2.1 Calculation of combined standard uncertainty and expanded uncertainty associated with the content of the reference standard

The reference standard has a content of 2.43 mg/mL, obtained as the mean of the 40 measurements (one measurement per vial) from the collaborative study.

The combined standard uncertainty is quantified using relative standard deviations, due to the fact that the sources of variation have different units, as shown in Table 2.

The combined relative standard uncertainty of the content of the reference standard is:

$$\frac{u_c(ref)}{(Mean\ content)} = \sqrt{RSD_{Purity}^2 + RSD_{Weight}^2 + RSD_{Solvent}^2 + RSD_{Vial}^2 + \frac{RSD_{Vial}^2}{n_{Vial}} + \frac{RSD_{Lab}^2}{n_{Lab}}}$$

where:

- n_{Lab} - number of participating laboratories;
- n_{Vial} - number of vials tested.

The first part of the formula, from RSD^2_{Purity} to RSD^2_{Vial}, is the uncertainty associated with the production of individual vials, while the last part of the formula is the uncertainty associated with the content determination (standard error of the mean).

$$\frac{u_c(ref)}{(Mean\ content)} = \sqrt{0.6^2 + 0.05^2 + 0.01^2 + 1.4^2 + \frac{1.4^2}{40} + \frac{5.1^2}{10}} = 2.23\%$$

The combined standard uncertainty of the content of the reference standard is:

$$u_c(ref) = \frac{2.23}{100} \times 2.43 = 0.0542\ mg/mL$$

The expanded uncertainty, U(ref), for k = 2 and 95% level of confidence is:

$$U(ref) = 2 \times 0.0542\ mg/mL = 0.11\ mg/mL$$

2.2.2 Establishment of reference standard

The reference standard is established as follow:

One vial contains: 2.43 ± 0.11 mg/mL (k = 2 for a 95% level of confidence).

2.2.3 Calculation of combined standard uncertainty and expanded uncertainty associated with the test method (Reproducibility)

Table 3 provides the estimates of RSD_{Vial} and RSD_{Lab} obtained in the collaborative study, together with their contribution to the uncertainty of measurement. Most of the uncertainty is coming from RSD_{Lab}, as the contribution is 93% [= $(5.1/5.3)^2$]. With one measurement per vial, S_{Vial} reflects both the repeatability of the test method and the variability among vials.

Table 3. One-Way Random Anova - RSD Estimates

Source of variation	RSD	Contribution
Within-laboratory (S_{Vial})	1.4%	7%
Between-laboratories (S_{Lab})	5.1%	93%
Reproducibility	$\sqrt{RSD^2_{Vial} + RSD^2_{Lab}}$ =5.3%	/

The relative combined standard uncertainty (reproducibility) associated with individual measurements of different laboratories is:

$$\frac{u_c(repr.)}{(Mean\ content)} = \sqrt{RSD^2_{Vial} + RSD^2_{Lab}}$$

$$\frac{u_c(repr.)}{(Mean\ content)} = \sqrt{1.4^2 + 5.1^2} = 5.3\%,$$

The combined standard uncertainty is:

$$u_c(repr.) = \frac{5.3}{100} \times 2.43 = 0.12879\ mg/mL$$

Uncertainties associated with the preparation of the stock solution are not considered, since these are negligible.

Therefore, the expanded uncertainty (U), is:

$$U = k \cdot u_c(repr.)$$

The obtained values for U, depending on the coverage factor used are given in Table 4.

Table 4. U of the test method

Coverage factor, k	**Level of Confidence**	**U**	
2	95%	10.6%	0.26 mg/mL
3	99%	15.9%	0.39 mg/mL

These ranges of measurement errors can be further compared to the specification limits to assess the fitness-for-purpose of the test method.

The expanded uncertainty (U) obtained from reproducibility standard deviation represents an estimate for the uncertainty of measurement in routine testing performed on the sample (for which the obtained mean value is 2.49 mg/mL).

Reporting of results

The result should be reported as:

2.49 ± 0.26 mg/mL, for k = 2 and level of confidence 95%.

3. References

1. Eurachem / CITAC Guide CG 4, Quantifying Uncertainty in Analytical Measurements, (3rd Edition) (2012)
2. ISO/TR 22971:2005(en) Accuracy (trueness and precision) of measurement methods and results - Practical guidance for the use of ISO 5725-2:1994 in designing, implementing and statistically analysing interlaboratory repeatability and reproducibility results.