Measurement uncertainty in medical laboratory: empirical models for computation

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Measurement uncertainty in medical laboratory: empirical models for computation

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"Interpretação dos resultados da avaliação externa da qualidade", INSA

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Contents

What is happening?

What is happening?

- The quality control skills in medical laboratory staff is probably at the weakest level of past two decades
- The medical laboratory quality control is limited in several areas, opposing what happens in chemistry and physics
- There is a need for harmonized practices in the European Union
- ISO 15189 has not been successfully implemented worldwide, and it presents several limitations regarding standardize practices, and quality control is one of these fields

What is happening?

- The “Uncertainty Approach” is not systematically used in medical laboratories
- Medical laboratories are probably the only field on chemistry (or physics) representing an unsuccessful case of its implementation close to 23 years after the publication of the Guide to the Expression of Uncertainty in Measurement (GUM)
- The implementation of the “Uncertainty Approach” remains a complex challenge
- A consistent and reliable discussion is needed to assure a successful implementation of the “Uncertainty Approach”

What is happening?

- Myths:

a) Total analytical error (TAE) = measurement uncertainty: only true if bias is zero or nonsignificant

If bias is significant, the TAE is systematically higher, and that's a fact!

This is due to the major difference between both models: the combination of bias - TAE sums to the precision multiplied by a coverage factor *k*, and measurement uncertainty follows the standard variation rules to combine uncertainty components (root of the sum of the squared deviations)

What is happening?

- Myths:

b) Measurement uncertainty cannot combine biological variation components

This is false! Biological variation components published on tables can be interpreted as Type B sources. When they are know, they should be included or the measurement uncertainty will be misestimated!

c) EQA/PT standard deviation is a contributor to a reliable and consistent measurement uncertainty

Absolutely false! EQA/PT is reliable uniquely to determine bias! Its standard deviation is a well-recognized cause of overestimation/unrealistic/inapplicable!

A brief introduction to the “Uncertainty Approach”

A brief introduction to the “Uncertainty Approach”

- Guide to the Expression of Uncertainty in Measurement (GUM) (“uncertainty bible”) is firstly published in 1993 and two years later is corrected and reprinted.
- GUM is an open access document since it is republished with minor correction by Bureau International des Poids et Mesures (BIPM) in 2008
- Measurement uncertainty (MU) is defined as “non-negative parameter characterizing the dispersion of the quantity values being attributed to a measurand, based on the information used” (entry 2.26 of VIM)

A brief introduction to the “Uncertainty Approach”

- “The uncertainty in the result of a measurement generally consists of several components which may be grouped into two categories according to the way in which their numerical value is estimated:

Type A - Those which are evaluated by statistical methods, e.g., within-laboratory reproducibility uncertainty and bias uncertainty.

Type B - Those which are evaluated by other means, e.g., biological variation

A brief introduction to the “Uncertainty Approach”

- MU characterizes “the quality of a result of a measurement” expressed in uncertainty (quantitative indication)
- MU is not intended to be applied to another quantity than numerical, for what it cannot be a standard to the determination of measurement uncertainty in all estimations
- Measurement uncertainty provides information on the level of confidence on the measurement result.
- It is the results of multiplying the standard combined uncertainty u_c by a coverage factor k

A brief introduction to the “Uncertainty Approach”

- For an approximate level of confidence of 95%, *k* is usually set to 2 and with a confidence higher than 99% *k* is typically set to 3 when degrees of freedom for the combined uncertainty are more than 20
- Commonly, the measurement uncertainty result is expressed as value ± expanded uncertainty
- For example, in an alanine aminotransferase test: 60 ± 0.3 IU/L (expanded uncertainty *k* = 2) corresponds to the interval 59.7-60.3 considering the clinical decision limit equal to 60 IU/L
- Allows assessment of “fitness for purpose” of result

A brief introduction to the “Uncertainty Approach”

- Eurachem/CITAC publishes in 2000 “Quantifying Uncertainty in Analytical Measurement” (QUAM) (revised for the third time in 2012) intended to be applied uniquely to measurement uncertainty in chemistry
- This document takes into account the practical experience of estimation of measurement uncertainty in chemistry laboratories
- This guideline answered to the need of MU models based on empirical data (“top-down” approach)
- Alternative to modular models, given that these models are often inapplicable in medical laboratory methods

A brief introduction to the “Uncertainty Approach”

- European Federation of National Associations of Measurement, Testing and Analytical Laboratories (Eurolab) Technical Report 1/2007 along with Nordest TR 537 proposes four empirical approaches:
  a) Modelling: partial derivative and propagation of distributions by Monte Carlo simulation methods
  b)Single laboratory validation (including QC)
  c) Interlaboratory comparisons
  d) External Quality Assessment (EQA) (Proficiency Testing (PT))
- Modelling is a “bottom-up” approach oriented to the manufacturing of medical laboratory reagents

“Uncertainty Approach”

- The Finnish Environment Institute (SYKE) releases a freeware, MUKit, featuring TR 537 mathematical models.
- The National Pathology Accreditation Advisory Council (NPAAC) published in 2007 a public document “Requirements for the estimation of measurement uncertainty” to support the Australian accreditation of medical laboratories
- Clinical and Laboratory Standards Institute (CLSI) C51-A “Expression of measurement uncertainty in laboratory medicine” is published during January 2012 (the code changed to EP29-A without text revision)

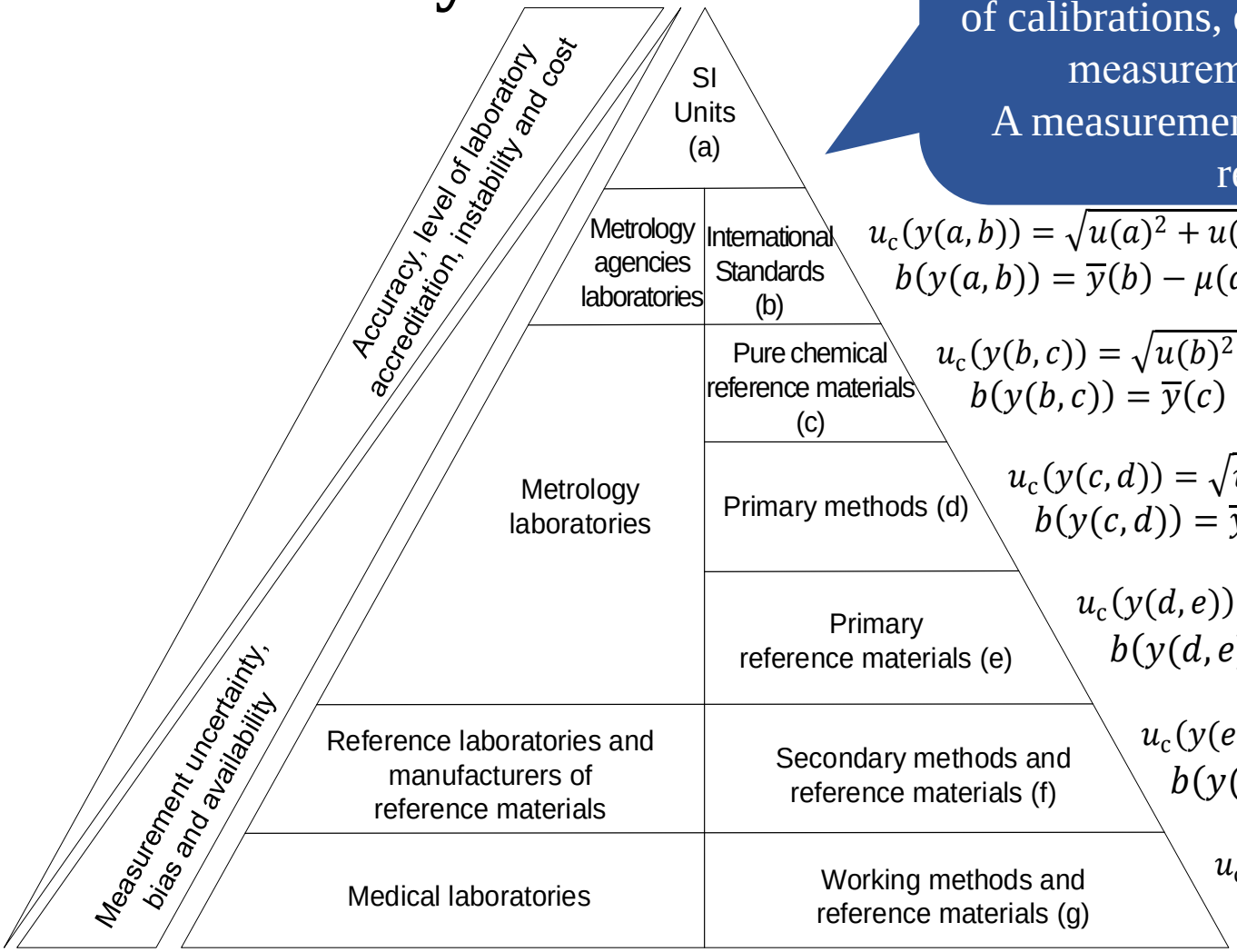
“Uncertainty Approach”

- ISO/PDTS 25680 “Medical laboratories-Calculation and expression of measurement uncertainty” was written initially as an International Standard and later as a Technical Specification is canceled on June 2011
- The contents of the last draft were analogous to the CLSI C51-P
- Currently, the determination of measurement uncertainty is required in ISO/IEC 17025 and ISO 15189
- ISO 15189 is mandatory in Australia, Latvia and France

What is the importance of measurement traceability?

What is the importance o traceability?

Why is it important? It assures the reliability of the measurements due to "the result can be related to a reference through a documented unbroken chain of calibrations, each contributing to the measurement uncertainty".
A measurement result is related to a reference.



$$u_c(y(a,b)) = \sqrt{u(a)^2 + u(b)^2}$$
$$b(y(a,b)) = \overline{y}(b) - \mu(a)$$

$$u_c(y(b,c)) = \sqrt{u(b)^2 + u(c)^2}$$
$$b(y(b,c)) = \overline{y}(c) - \mu(b)$$

$$u_c(y(c,d)) = \sqrt{u(c)^2 + u(d)^2}$$
$$b(y(c,d)) = \overline{y}(d) - \mu(c)$$

$$u_c(y(d,e)) = \sqrt{u(d)^2 + u(e)^2}$$
$$b(y(d,e)) = \overline{y}(e) - \mu(d)$$

$$u_c(y(e,f)) = \sqrt{u(e)^2 + u(f)^2}$$
$$b(y(e,f)) = \overline{y}(f) - \mu(e)$$

$$u_c(y(f,g)) = \sqrt{u(f)^2 + u(g)^2}$$
$$b(y(f,g)) = \overline{y}(g) - \mu(f)$$

What is the importance of measurement traceability?

- However… there are several limitation in the medical laboratory…
- It is not widely employed in most of medical laboratory tests due to the unavailability of reference materials and reference methods for most of the tests
- Also the “medical traceability” is hard to achieve due to the “physicochemical complexity” of human samples caused principally by the within-individual and inter-individual biological variation

How to combine uncertainty components?

How to combine uncertainty components?

- *Rule 1* for combination of uncertainty: Sum or difference
  "For models involving only a sum or difference of quantities, e.g., $y = (p + q + r + \ldots)$, the combined standard uncertainty $u_c(y)$ is given by":

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

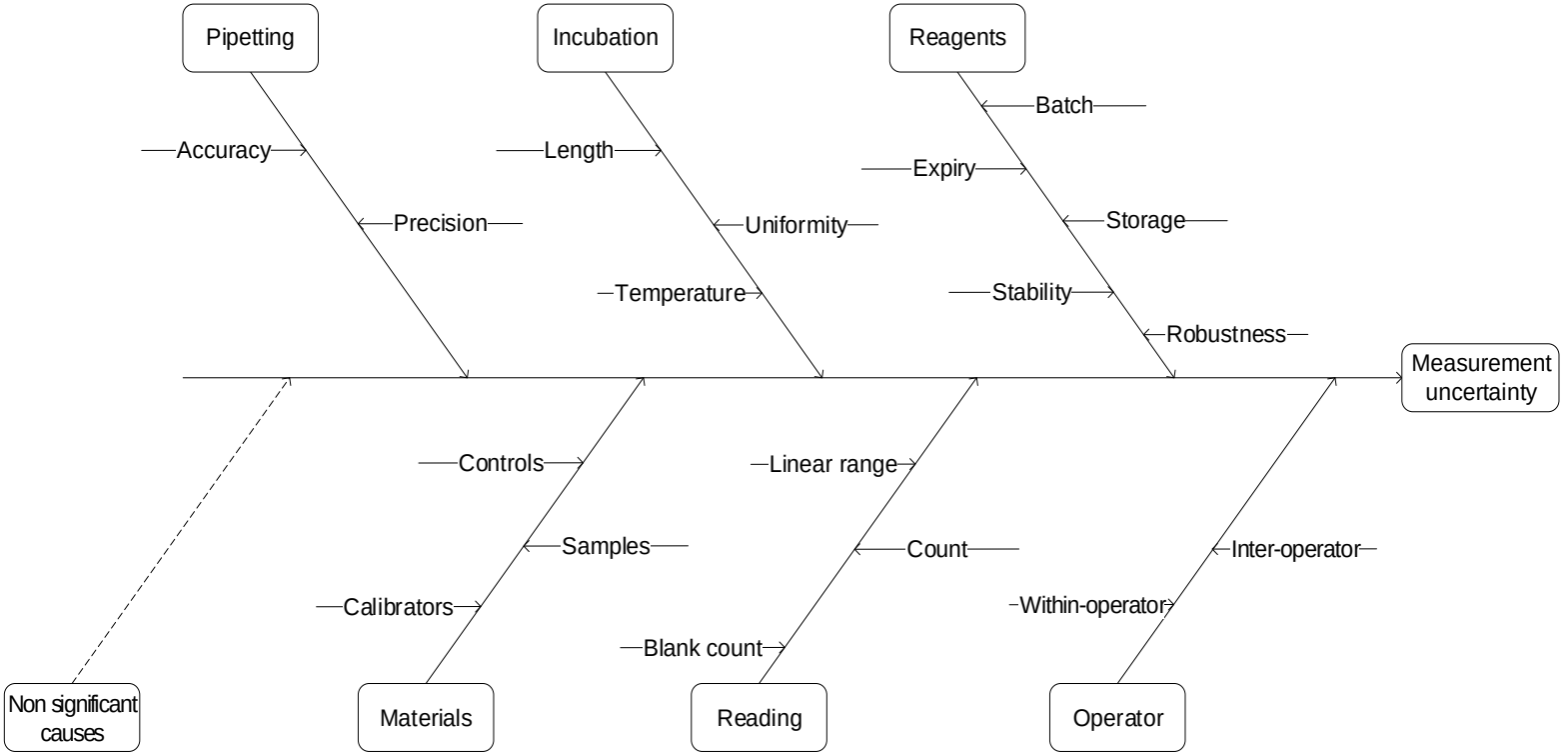
- *Rule 2* for combination of uncertainty: Product or quotient
  "For models involving only a product or quotient, e.g., $y = (p \cdot q \cdot r \cdot \ldots)$ or $y = p/(q \cdot r \cdot \cdots)$ the combined standard uncertainty $u_c(y)$ is given by":

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

Why are modeling models not suitable for the medical laboratory?

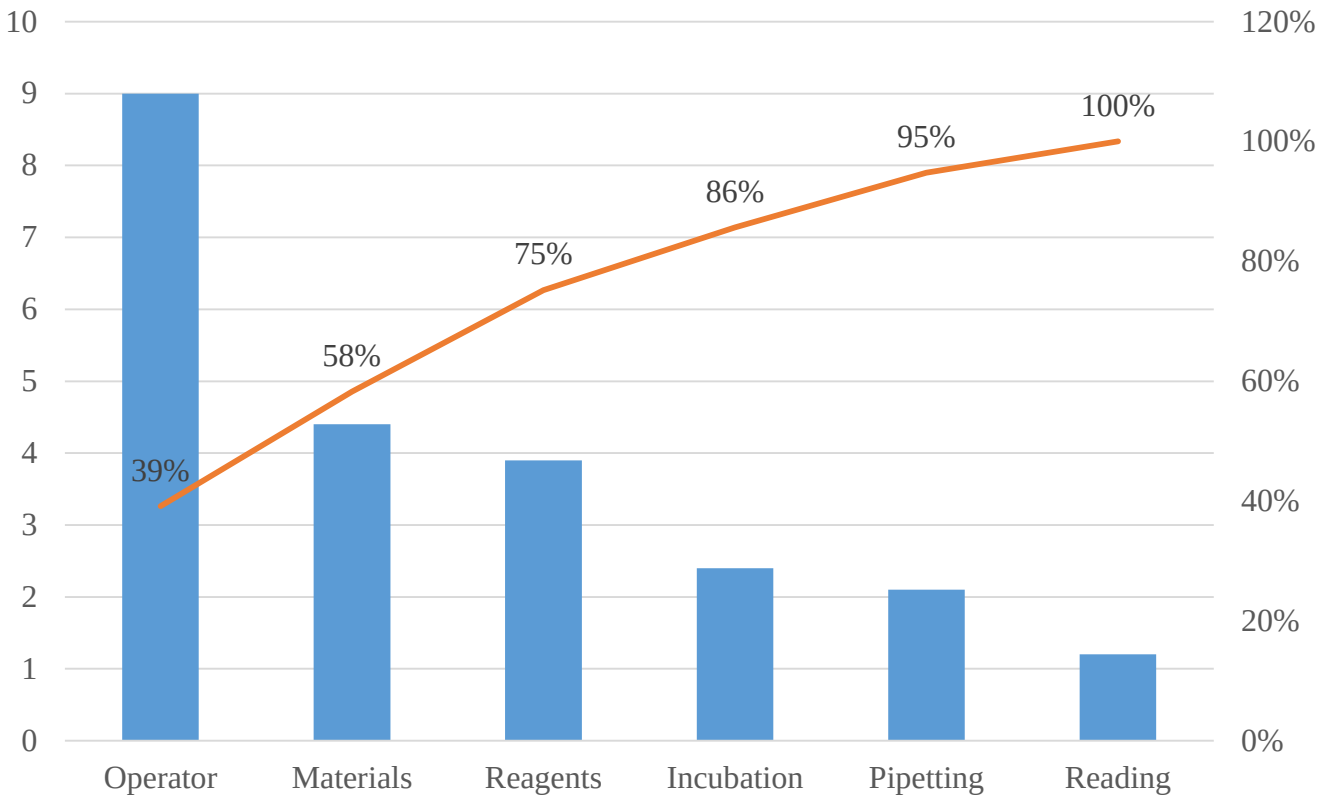
Why are modeling models not suitable for the medical laboratory?

- A cause-and-effect diagram to the determination of measurement uncertainty in a hypothetical medical laboratory test



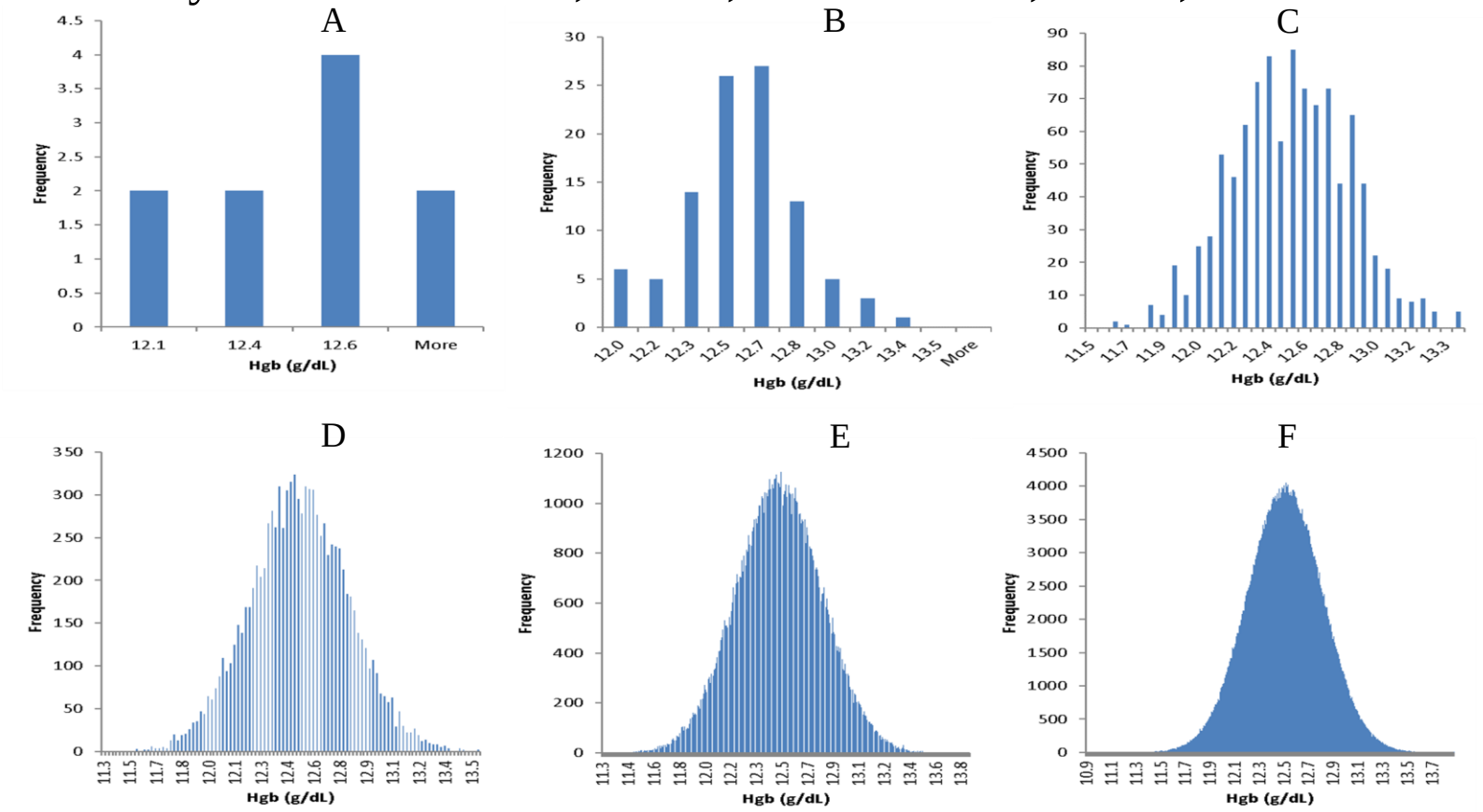
Why are modeling models not suitable for the medical laboratory?

- A Pareto diagram to the determination of measurement uncertainty in a hypothetical medical laboratory test



Why are modeling models not suitable for the medical laboratory?

- Simulation technique: Histograms from six simulations with data normally distributed: A: 10; B: 10^2; C: 10^3; D: 10^4; E: 10^5; and F: 10^6



Why are modeling models not suitable for the medical laboratory?

- Modeling models require a model equation
- Depth chemistry, mathematical and statistical skills are required – not commonly available in medical laboratories
- Compared to the empirical models, they misestimate measurement uncertainty
- They are very complex to calculate and expensive
- They are adequate to the manufacturer of reagents, where the most critical sources of uncertainty should be controlled to assure more realistic results

Why are empirical models suitable for the medical laboratory?

Why are empirical models suitable for the medical laboratory?

- They do not require a model equation
- They do not require depth statistical skills
- They are focused on “total uncertainty” instead “uncertainty components”
- They are based on empirical data readily available and well-known by the medical laboratory staff
- They use data from method validation, including Interlaboratory comparisons, internal quality control (IQC), and External Quality Assessment (EQA)/(Proficiency Testing (PT))

Why are empirical models suitable for the medical laboratory?

- The computation of the within-laboratory reproducibility standard deviation (combining repeatability standard deviation) is similar to those used on TAE
- Bias uncertainty can also easily be computed
- Practicable in a common spreadsheet
- The empirical models are successfully used in chemistry for close to 20 years - let learn with successful cases of application!

Why are empirical models suitable for the medical laboratory?

- Single laboratory validation (including quality control)

a) The within-laboratory reproducibility uncertainty s_{Rw} is calculated by pooling the repeatability standard deviation s_{r} arising from replicate measurements of human samples, and the intermediate standard deviation, s_{I} from between runs:

$$s_{\mathrm{Rw}} = \sqrt{s_{\mathrm{r}}^2 + s_{\mathrm{I}}^2}$$

b) Bias b is the result of the mean deviation of measurement results of replicates from the corresponding reference value. s_b is the bias standard deviation, $u_{c_{\mathrm{ref}}}$ the reference value standard uncertainty, and m the number of replicate determinations:

$$u_b = \sqrt{b^2 + (s_b/\sqrt{m})^2 + u_{c_{\mathrm{ref}}}^2}$$

Why are empirical models suitable for the medical laboratory?

- Single laboratory validation (including quality control)

c) To obtain the combined standard uncertainty the uncertainty due to precision and that due to bias are combined:

$$u_{\mathrm{c}}(y) = \sqrt{s_{\mathrm{Rw}}^2 + u_b^2}$$

Why are empirical models suitable for the medical laboratory?

- Single laboratory validation (including quality control)

This approach considers the within-laboratory reproducibility standard deviation according to two different methods:

a) Method validation protocol intended for validating the precision of numerical quantity tests: It is recommended for most of the quantitative tests, the approach described in Clinical Laboratory Standards Institute (CLSI) EP15-A3 protocol to evaluate the precision (and bias). Short-term data is required. A series of five analytical runs with three replicates per run is suitable.

a) Using data from between-run variation. Long-term data is required, usually using CLSI EP5-A3 protocol or IQC data to compute the precision.

Why are empirical models suitable for the medical laboratory?

- Interlaboratory comparisons

a) In the inter-laboratory validation approach, the principal sources of variability can often be assessed by inter-laboratory studies performed and evaluated according to ISO 5725.

b) This approach to estimating uncertainty is fully described in ISO 21748

c) The approach requires the determination of the between-laboratories reproducibility standard deviation s_R from the results in an inter-laboratory trial according to ISO 5725. In a standardized method, these precision data are usually given in an Appendix.

Why are empirical models suitable for the medical laboratory?

- External Quality Assessment (EQA)/(Proficiency Testing (PT))

a) EQA programs are proposed to verify periodically the performance of a laboratory test based in data of a laboratories' group using proficiency tests
b) Medical laboratory could also use the comparison data to determine the measurement uncertainty
c) EuroLab Technical Report 1/2007 presents an approach to laboratories evaluate measurement uncertainty
d) The use of standard uncertainty measured from the results of group's participants is risky, since it is not realistic and cannot be used to evaluate the uncertainty of a particular test's results!

Why are empirical models suitable for the medical laboratory?

- External Quality Assessment (EQA)/(Proficiency Testing (PT))

e) The mathematical model could be the same than in the single laboratory validation

f) Use the EQA/PT data just to compute bias when a reference material is not available

g) Therefore, combine the standard uncertainty as follows:

$$u_c(y) = \sqrt{s_{Rw}^2 + u_b^2}$$

How to compute the expanded uncertainty?

How to compute the expanded uncertainty?

- Its purpose is the designation of an interval which may be expected to include a large fraction of the distribution of values which could reasonably be attributed to the measurand.
  $U = k \cdot u_c$
- Tipically k is assumed as 2 for a confidence interval of 95% when the effective degrees of freedom v_{eff} are higher than about six (on a Type A evaluation is equal to n - 1)
- An accurate k is dependent from n
- Simply use the Microsoft® Excel® function =TINV(probability,deg_freedom)

How to report measurement uncertainty?

How to report measurement uncertainty?

- Unless otherwise required, the result *x* should be stated together with the expanded uncertainty *U* calculated using a coverage factor $k = 2$ (….). The following form is recommended: (Result): (x ± *U*) (units) [where] the reported uncertainty is [an expanded uncertainty as defined in the International Vocabulary of Metrology - Basic and General Concepts and Associated Terms, 3rd ed., BIPM 2012, calculated using a coverage factor of 2, [which gives a level of confidence of approximately 95%].
- Terms in parentheses [] may be omitted or abbreviated as appropriate. The coverage factor should, of course, be adjusted to show the value actually used.

What is the flow to compute and evaluate measurement uncertainty?

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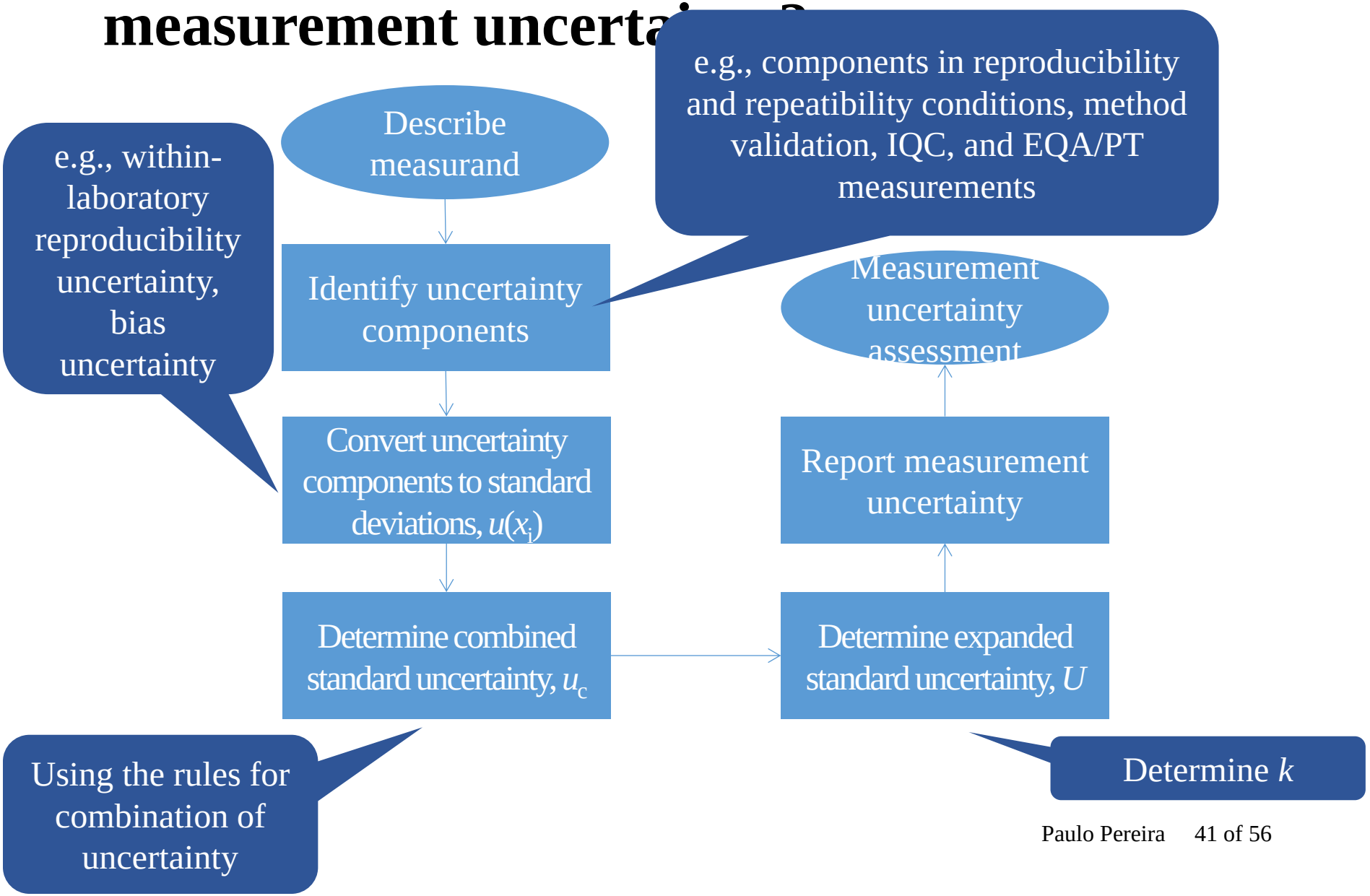
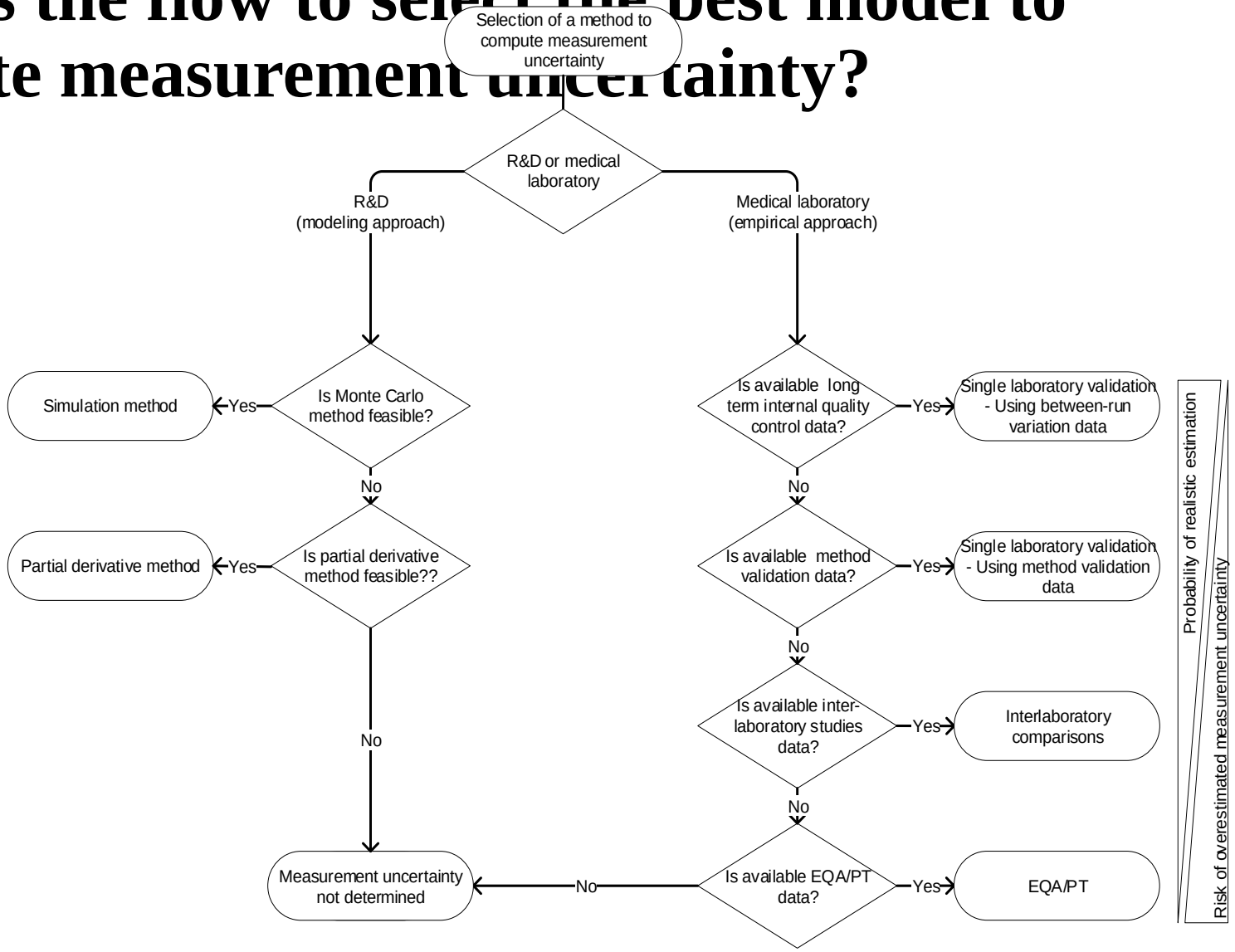


What is the flow to select the best model to compute measurement uncertainty?

What is the flow to select the best model to compute measurement uncertainty?

- Flowchart to select a model to the determination of measurement uncertainty in a medical laboratory



Cases

Empirical approach

- CASE 1: measurement uncertainty of alanine aminotransferase (IU/L) (quantitative test)
- Method: Single laboratory validation using data from between-run variation
- s_{Rw} = 1.833 UI/L - computation based on CLSI EP5-A3 combining reproducibility s_{I} and repeatability s_{r} conditions over 20 days
- $u_{\mathrm{bias}} = \sqrt{b^2 + (s_b/\sqrt{m})^2 + u_{c_{\mathrm{ref}}}^2} = \sqrt{0.003 + \left(0.329/\sqrt{16}\right)^2 + 0} =$ $0.082\ \mathrm{UI/L}$

Note: Previously bias is corrected using Passing-Bablok equation; u_{bias} compute the uncertainty arising from the remaining bias

Empirical approach

- CASE 1: measurement uncertainty of alanine aminotransferase (IU/L) (quantitative test)
- $u_{\mathrm{c}}(y) = \sqrt{s_{\mathrm{Rw}}^2 + u_b^2} = \sqrt{3.544 + 0.007} = 1.885\ \mathrm{UI/L}$
- $U = k \cdot u_{\mathrm{c}} = 2 \cdot 1.885 = 3.770 \cong 3.8\ \mathrm{UI/L} = 3.8/60 \cdot 100 = 6.34\%$
- Challenge: measurement uncertainty assessment - unavailable tables

Empirical approach

- CASE 2: screening immunoassay for anti-HCV (s/co)
- Method: Single laboratory validation using data from between-run variation
- $s_{\mathrm{Rw}} = \sqrt{s_{\mathrm{r}}^2 + s_{\mathrm{I}}^2} = \sqrt{14.4\%^2 + 8.5\%^2 = 16.5\%}$
- computation based on CLSI EP15-A3 combining reproducibility s_{I} and repeatability s_{r} conditions over 5 days with 3 replicates per day
- $u_{\mathrm{bias}} = \sqrt{b^2 + (s_b/\sqrt{m})^2 + u_{c_{\mathrm{ref}}}^2} = \sqrt{6\% + \left(11.87\%/\sqrt{370}\right)^2 + 0} = 6.03\% \cong 6\%$

Empirical approach

- CASE 2: screening immunoassay for anti-HCV (s/co)
- $u_c(y) = \sqrt{s_{Rw}^2 + u_b^2} = \sqrt{16.5\%^2 + 6\%^2} = 17.8\%$
- $U = k \cdot u_c = k \cdot 17.8\% \cong 36\%$
- Compute the decision limit ("gray zone") based on the model: $1.65 \cdot u_c = 1.65 \cdot 18\% = 30\%$
- So, if results are ≥ 0.70 they are in the "rejection zone" and the corresponding blood components are declared not compliant and rejected
- If the results are < 0.70 they are in the "acceptance zone" and the corresponding blood components are in compliance with the intended use of results, and are acceptable

Empirical approach

- CASE 3: measurement uncertainty of alanine aminotransferase (IU/L) (quantitative test)
- Method: Single laboratory validation using data from between-run variation
- s_{Rw} = 1.833 UI/L - computation based on CLSI EP5-A3 combining reproducibility s_I and repeatability s_r conditions over 20 days
- $u_{\text{bias}} = \sqrt{b^2 + (s_b/\sqrt{m})^2 + u_{c_{\text{ref}}}^2} = \sqrt{0.033 + \left(0.900/\sqrt{12}\right)^2 + 0} = 0.260$ UI/L

Empirical approach

- CASE 3: measurement uncertainty of alanine aminotransferase (IU/L) (quantitative test)
- $u_c(y) = \sqrt{s_{Rw}^2 + u_b^2} = \sqrt{3.544 + 0.068} = 1.900\ \text{UI/L}$
- $U = k \cdot u_c = 2 \cdot 1.900 = 3.770 \cong 3.8\ \text{UI/L} = 3.8/60 \cdot 100 = 6.34\%$
- Challenge: measurement uncertainty assessment - unavailable tables

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