BIO-METROLOGICAL UNCERTAINTY IN CLINICAL LABORATORY SCIENCES

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The International Federation of Clinical Chemistry and Laboratory Medicine (IFCC) and the International Union of Pure and Applied Chemistry (IUPAC) recommend that the uncertainty of measurement of patients' results obtained in clinical laboratories should be known (1). Moreover, the standard ISO 15189 (2) try to implement the use of the uncertainty of measurement in the real life of clinical laboratories seeking for accreditation. However, many clinical laboratories and their clients - physicians and surgeons - are reluctant to add to the clinical laboratory report the uncertainty of measurement of each result; they argue that such a practice does not bring any added value to this report. But if a more "clinical" uncertainty is used instead of the merely metrological uncertainty (uncertainty of measurement) the above inconvenient may disappear.

The uncertainty of measurement is, of course, a metrological concept. But in clinical laboratory sciences there are other two types of uncertainties affecting the measurement results: the pre-metrological uncertainty and the biological uncertainty. The former directly derives from the fluctuations of the processes done in the pre-metrological (pre-analytical, pre-examination) phase, and the latter directly derived from the intra-individual (within-subject) biological variation and is usually bigger than the uncertainty of measurement. The uncertainty derived from the combination of the pre-metrological uncertainty, the metrological uncertainty and the biological uncertainty may be called "bio-metrological uncertainty".

The bio-metrological uncertainty may facilitate the interpretation of a change in two consecutive results of the same quantity in the same patient, as an alternative to the reference change proposed by Harris and Yasaka (3); thus, it would be appropriate for clinical laboratories to move from metrological uncertainty to bio-metrological uncertainty.

For many biological quantities, the interpretation of a change in two consecutive results in the same patient is especially relevant; the concentration of cholesterol in plasma is a good example.

Thus, let me estimate the bio-metrological uncertainty of a hypothetical patient's result of this biological quantity.

In this example the substance concentration (subst.c.) cholesterol in plasma (P) is measured using an enzymatic procedure. The measurement system is calibrated daily with a calibrator traceable to the SI unit for substance concentration. Let a patient's result [according to IFCC-IUPAC recommended presentation (4)] be:

P-Cholesterol; subst.c. = 5.17 mmol/L

In order to estimate the uncertainty of measurement in our example, we assume that the sources of uncertainty are: premetrological variability, uncertainty of the calibrator assigned value, day-to-day imprecision, and endogenous influence quantities.

Uncertainty of the value assigned to the calibrator. - According the manufacturer's information, the value of the calibrator has been assigned with a primary measurement procedure using isotope dilution-mass spectrometry, and the standard uncertainty of this value is 0.048 mmol/L.

Premetrological variability. - For blood quantities the premetrological phase begins when the needle is first inserted into the vein and lasts until the sample enters into the measurement system. The coefficient of variation observed in this phase for the quantity measured is 1.2% (5), which in our example corresponds to a standard deviation, or standard uncertainty, of 0.062 ?mol/L.

Day-to-day imprecision. - The measurement procedure of this example has a day-today coefficient of variation (at physiologic concentration) equal to 1.9 %. This imprecision applied to the patient's result (5.17 mmol/L) expressed as standard deviation, or standard uncertainty, is 0.098 mmol/L.

Endogenous influence quantities. - The reagent manufacturer's criterion for deciding if a potential influence quantity should be declared as an interference is that the relative systematic error produced by the influence quantity must be > +/-10 %. In spite of this criterion being presented as a symmetric interval (+/-10 %), the changes of the value of the measure, and that may provoke a particular influence quantity will be within the interval [0 %; 10 %] or [-10 %; 0 %]. As it is more likely that an endogenous interference will not be present than the opposite, the effect of a possible influence quantity probably will be closer to 0 % than 10 % or -10 %. In these cases, the systematic errors that may produce an influence quantity follow a triangular (right angled triangle) distribution (6,7) and the standard uncertainty *(u)* is:

$$u = [(b - a)^2/18]^{0.5}$$

where a and b are, respectively, the lower and upper limits of the interval. Applying it to our example:

$$u = [(10 - 0)^2/ 18]^{0.5} = 2.4 \%$$

This percentage applied to the patient's result (5.17 mmol/L), corresponds to 0.124 mmol/L. But, as there are three influence quantities studied by the reagent manufacturer, the estimated standard uncertainty should be multiplied by 3:

$$u = [3 \cdot (0.124)^2]^{0.5} = 0.215 \text{ mmol/L}$$

When the standard uncertainties of every uncertainty component have been estimated, the combined standard uncertainty (u_c) due to all these components may be estimated (8,9):

$$(u_c) = (0.048^2 + 0.062^2 + 0.098^2 + 0.215^2)^{0.5} = 0.249 \text{ mmol/L}$$

Finally, we will estimate the expanded uncertainty (U) with a confidence level $1 - \alpha \approx 0.95$ multiplying the combined standard uncertainty by a coverage factor (k) equal to 2 (8,9):

$$U = u_c \cdot k = 0.249 \cdot 2 = 0.498 \text{ mmol/L}$$

Thus, the complete (under a metrological point of view) patient's result, after rounding the value of the expanded uncertainty as is usually done for the measurement result, will be:

P - Cholesterol; subst.c. = (5.17 +/- 0.50) mmol/L

If the biological uncertainty is included, the final expanded bio-metrological uncertainty will be higher but more realistic.

I*ntra-individual biological variation.* - The coefficient of variation corresponding to intra-individual biological variation 5.3 % (10), which in our example (5.17 mmol/L) corresponds to a standard deviation, or standard uncertainty, of 0.274 mmol/L.

Now we can add the standard uncertainty due to intra-individual biological variation to the combined uncertainty estimated above:

$$u_c = (0.048^2 + 0.062^2 + 0.098^2 + 0.215^2 + 0.274^2)^{0.5} = 0.370 \text{ mmol/L}$$

and:

$$U = u_c \cdot k = 0.370 \cdot 2 = 0.740 \text{ mmol/L}$$

and finally:

P - Cholesterol; subst.c. = (5.17 +/- 0.74) mmol/L

Numerical results accompanied with an estimation of the bio-metrological uncertainty may help requesting physicians and surgeons in decision-making about the significance of changes between two consecutive results: if the interval of the above example overlaps with a previous one, the difference between the two results may be considered negligible; on the contrary, non-overlapping means that the two results are really different.

Using this bio-metrological approach, the estimation of uncertainty in clinical laboratory reports may be to better understood and accepted by the clinical laboratory and medical community.

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