

Estimation of uncertainty of measurement in medical laboratories

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Introduction:

This EDMA position paper is intended to act as a guide for medical laboratories that want to determine the measurement uncertainty of the results obtained with in-vitro diagnostic medical device procedures. The need to comply with accreditation requirements is also a key factor in the desire of laboratories to calculate the uncertainty of measurement.

Measurement uncertainty and its estimation is already referenced in standards and other documents. These standards and documents are briefly described in this position paper together with more details of the generic model that can be used for the calculation of uncertainty of measurement. Work on how to evaluate and report uncertainty of laboratory values is in progress, including projects to develop guidance documents and standards by the Clinical and Laboratory Standards Institute (CLSI) and the Technical Committee 212 of the International Organization for Standardization.

Responsibilities of the manufacturer:

The IVD manufacturer is responsible for the provision of information regarding calibration traceability and method imprecision in the instructions for use. The manufacturer's responsibility for metrological traceability begins with the selection of available reference materials and/or reference methods and ends with assignment of values to product

calibrators. In addition to documenting the higher order basis for a calibration, the IVD manufacturer is also responsible for determining the uncertainty of values assigned to product calibrators.

Uncertainty in accreditation standards:

Accreditation standards already ask medical laboratories to calculate the uncertainty of laboratory results. These standards include ISO 17025: 2005 and ISO 15189: 2003.

ISO 17025:

5.4.6.2. Testing laboratories shall have and shall apply procedures for estimating uncertainty of measurement

5.4.6.3. When estimating the uncertainty of measurement, all uncertainty components which are of importance in the given situation shall be taken into account using appropriate methods of analysis.

NOTE 1: Sources contributing to the uncertainty include, but are not necessarily limited to, the reference standards and reference materials used, methods and equipment used, environmental conditions, properties and condition of the item being tested or calibrated, and the operator.

NOTE 3: For further information, see ISO 5725 and the Guide to the Expression of Uncertainty in Measurement.

ISO 15189:

5.6.2. *The laboratory shall determine the uncertainty of results, where relevant and possible. Uncertainty components, which are of importance, shall be taken into account. Sources that contribute to uncertainty may include sampling, sample preparation, sample portion selection, calibrators, reference materials, input quantities, equipment used, environmental conditions, condition of the sample and changes of operator.*

Uncertainty measurement:

The Guide to the Expression of Uncertainty in Measurement (GUM) represents a master document on uncertainty evaluation and calculation of its estimate. Several working parties have issued various recommendations and standards in support of the implementation of uncertainty determination: EA, Eurachem, Eurolab, AFNOR and ISO / TC 69 / SC 6. A basic requirement of the GUM is to use a model for the evaluation of uncertainty. Developing such a specific model for every testing procedure in the medical laboratory is prohibitive and not realistic. Furthermore the GUM encourages the evaluation of uncertainty based on the evaluation of the variability of the measurement procedure from all the available information (e.g. previous measurement data, experience, manufacturer's specifications, data provided in calibration and other certificates).

Three elements contribute to total uncertainty:

- the calibration system (working calibrators, primary and secondary calibrators, reference measurement procedures...)
- the procedure (reagents, instruments, laboratory staff ...)
- the sample

The estimation of the uncertainty in measurement results obtained in the

medical laboratories preferably should be based on the information already existing in the particular laboratory for the routine measurement procedures (no special scientific research should be required from the laboratories). Data from manufacturers and existing experimental data can be appropriately used (e.g. quality control charts, validation data).

Uncertainty is a parameter that is associated with every single quantitative result that is produced by a laboratory and is specific to each result. Since this parameter cannot be evaluated for each component in each sample, this paper proposes a protocol that can be applied easily for every quantitative IVD and MD testing procedure in the medical laboratory.

Generic model:

To estimate the uncertainty of a measured value, a generic mathematical model can be applied by splitting the process into four elements and using data available from different sources. The measurement uncertainty is evaluated from the 'analytical procedure imprecision', the 'calibrator assigned value uncertainty component', the 'sample effects' and from the contribution of 'other' analytical effects.

- The analytical procedure imprecision component (umethod) includes the effect of:
 - the intra-laboratory variation for the routine measurement procedure, i.e. replication within the same procedure, variation due to different lots of reagents or calibrators, different operators etc. and,
 - the variation between different laboratories pertaining to the same measurement procedure (method).

Data can be obtained from, for example, the overall repeatability and reproducibility estimates from a given

measurement procedure in a collaborative study.

- the calibration component (u_{cal}) includes the contribution of :
 - the uncertainty of the values assigned to calibrators.

Estimates of uncertainty of values assigned to calibrators can be obtained on request from the manufacturers (according to the requirements of the Directive 98/79/CE and the supporting standard, EN ISO 17511). The uncertainty of a calibrator's assigned value provides an indication of the degree of traceability of a particular measurement procedure to a reference method or reference material.

- the sample effects components (u_{sample}) include :
 - pre-analytical effects and
 - intra- and inter-individual variations (biological variations).

Data may be available from the literature for a limited number of analytes.

- the other component (u_{other}) represents various effects such as interferences that may be present in certain samples.
 - This contribution to overall uncertainty applies only to specific samples and/or under specific conditions.

Estimates of this variance component may be available in the literature in exceptional cases, but are not typically readily available for most methods.

The overall expression of uncertainty is therefore:

$$u_{result} = \sqrt{u_{cal}^2 + u_{method}^2 + u_{sample}^2 + u_{other}^2}$$

Sources of data:

1. For the estimation of the analytical procedure imprecision:

1.1. If the medical laboratory staff is interested only in measurement

uncertainty estimates of its own routine measurement procedures, the within laboratory reproducibility estimates based on routine quality control data will provide sufficient data to support an estimate of measurement uncertainty.

1.2. Another approach is to use the data coming from a collaborative study aiming to estimate the overall imprecision (reproducibility) of one particular routine measurement procedure. In this protocol several instruments, laboratories, reagents lots and operators have to be involved over a substantial period of time to be sure to include all the potential source of imprecision.

1.2.1. In some cases, these data may be available from the manufacturer as part of technical file of the product. The advantage of this approach is that it does not involve any experimental work.

1.2.2. Data may also be obtained by participating in collaborative peer-group comparison studies (i.e. EQAS). Such studies can be performed with quality control specimens, including a significant number of laboratories over a substantial period of time (allowing the use of several lots of reagent). This approach represents the whole combined among-labs imprecision of the analytical procedure in routine practice. The advantage of this approach is that it uses data available in many laboratories. It does reduce the creation of additional experimental data

1.3. A surrogate approach is to use a modified precision model (e.g. according to CLSI protocol EP5-A). In this experimental setup frozen human material is used (homogeneity and stability of the samples must be assured);

- over a period of three months,
- involving at least three reagent lots per analyte,
- involving at least three different instruments and operators,
- over at least 10 different days per lot,
- two replicates per day are analyzed,
- at least 60 results will be generated per instrument and the data will be evaluated according to the CLSI protocol.

Note: This protocol can be modified by using quality control samples instead of frozen human material. This may be more applicable to the specific situation in the laboratory. A potential drawback is that, due to the lack of specificity and selectivity of some analytical methods, the use of control material may introduce artifacts, i.e. bias: however, the effect is usually negligible on the precision of the methods.

2. For the estimation of the uncertainty of the calibration component :

2.1. The uncertainty of the value assigned to the calibrator (ucal) is supplied, on request, by the manufacturer and depends on the mathematical model that is used to determine the assigned values. As the concentration of the samples for which the uncertainty shall be estimated may differ from the concentration of the calibrators, the uncertainty of the calibrators should be adjusted by interpolation or extrapolation to the concentration level in question (sample concentration). This

calibrator standard uncertainty is reported as ucal.

3. For the estimation of the sample effects components :

3.1. Intra-individual biological variation data for a limited number of parameters are available in publications such as: C. Ricós et al. Scand. J. Clin. Lab. Invest, 1999, 59, 491-500.

3.2. Pre-analytical effects shall be evaluated by the laboratory in relation with its own organization and practices (e.g. The stability of the sample is important). Information for a limited number of parameters is available in publications such as: W. Guder, et al.: Samples from the Patient to the Laboratory.

Conclusion:

1. Today the determination of measurement uncertainty is mainly required by standards supporting accreditation of medical laboratories.
2. The medical community is not yet familiar with this new concept. Training and explanations will be necessary to introduce it into routine practices.
3. Currently the measurement uncertainty cannot be reported together with test results to physicians, since physicians are not fully aware of the interpretation and value of this new statistic associated with a given laboratory result.
4. This EDMA position paper is a first step in helping the medical community and the medical laboratories to understand the uncertainty of results reported by in-vitro diagnostic medical devices and how to evaluate this statistic.
5. The manufacturers have a role in traceability and overall measurement uncertainty, and they will provide the uncertainty of the assigned values for product calibrators upon request.

Bibliography:

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EN ISO/CEI 17025: General requirements for the competence of testing and calibration laboratories

ISO 5725: Accuracy (trueness and precision) of measurement methods and results (6 parts)

EN ISO 17511: In vitro diagnostic medical devices – Measurement of quantities in biological samples – Metrological traceability of values assigned to calibrators and control materials

Directive 98/79/EC of the European Parliament and of the Council of 27 October 1998 on in vitro diagnostic medical devices

EA-4/16: Eurachem Accreditation Guidelines on The expression of uncertainty in quantitative testing – January 2003

GUM: Guide to the expression of uncertainty in measurement – BIPM, IEC, IFCC, ISO, IUPAC, IUPAP, OIML - 1995

Eurachem /CITAC Guide CG4: Quantifying Uncertainty in Analytical Measurement – Second Edition, 2000

AFNOR – FD X 07- 021 : Métrologie et application de la statistique – Aide à la démarche pour l'estimation de l'incertitude des mesures et des résultats d'essais

ISO/TS 21748:2004 Guidance to the use of repeatability, reproducibility and trueness estimates in measurement uncertainty estimation.

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Ricós C, Alvarez V., Cava F., Garcia-Lario J.V., Hernandez A., Jimenez C.V., Minchinela J., Perich C., Simon M., Current databases on biological variations: pros, cons and progress. Scand J Clin Lab Invest 1999, 59, 491-500

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AACB Australasian Association of Clinical Biochemists: Uncertainty of measurement in quantitative medical testing – a laboratory implementation guide. Clin Biochem 2004, 25 (iv), 207. Authors Graham HW and Farrance I.

EDMA Guidance Documents:

- [Interpretation of the CEN/ISO Standards prEN ISO 17511 and prEN ISO 18153 on metrological traceability of values assigned to calibrators and control materials](#), September 1995, revised March 2001

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