Review Article

Abdurrahman Coskun*, Berrin Berçik İnal and Muhittin Serdar

Measurement uncertainty in laboratory medicine: the bridge between medical and industrial metrology

Laboratuvar tıbbında ölçüm belirsizliği: Tıp ve endüstriyel metroloji arasındaki köprü

https://doi.org/10.1515/tjb-2019-0170
Received April 22, 2019; accepted April 22, 2019; previously published online May 30, 2019

Abstract: Uncertainty is an inseparable part of all types of measurements, that is, in metrology a measurement without uncertainty is not possible. Calculation of uncertainty increases the awareness of the certainty of measurement results. Reporting measurement uncertainty is mandatory in almost all industrial sectors but not in laboratory medicine. Test results without analytical uncertainty increases the diagnostic uncertainty, causing errors that could seriously affect patients health. To improve diagnostic certainty, we should calculate and upon request report measurement uncertainty to laboratory users (ISO 15189). In this mini-review, we summarized the theoretical perspective of uncertainty concept, its relation to Six Sigma and finally compared it with Total Error Method.

Keywords: Allowable total error; Measurement uncertainty; Metrology; Quality control; Six Sigma.

Öz: Belirsizlik, tüm ölçümlerin ayrılmaz bir unsurudur. Belirsizliğin olmadığı bir ölçümü gerçekleştirmek mümkün değildir. Belirsizliğin hesaplanması ölçüm sonuçlarının kesinliği hakkında farkındalığı artırmaktadır. Hemen hemen tüm endüstriyel sektörlerde yapılan ölçümlerin belirsizliğini raporlamak zorunlu olduğu halde laboratuvar tıbbında böyle bir zorunluluk yoktur. Analitik belirsizlik olmadan raporlanan test sonuçları teşhiste de belirsizliğe neden olup hasta sağlığına olumsuz etkide bulunabilir. Doğru teşhis için ölçümü yapılan testlerin ölçüm belirsizliğinin hesaplanıp gerektiğinde raporlanması önerilir (ISO 15189). Bu mini derlemede belirsizlik kavramının teorik yönünü ve Altı Sigma ile ilişkisini özetleyip laboratuvar tıbbında kullanılan Toplam Hata Metodu ile karşılaştırdık.

Anahtar Kelimeler: Altı Sigma; Kabul edilebilir toplam hata; Kalite kontrol; Metroloji; Ölçüm belirsizliği.

Introduction

In one of the most important scientific events of 2018, metrologists redefined the four basic SI units: ampere, kilogram, Kelvin, and mole. These four units were redefined using fundamental constants of nature instead of some physical objects or abstract definitions [1]. The kilogram, for example, used to be defined by a chunk of platinum-iridium, stored in a vault near Paris; however, now it is defined using the Planck's constant [2]. These redefinitions will increase the level of precision without losing the accuracy, helping to deliver one of the main purposes of the redefinition process, that is, to decrease the uncertainty of measurements [3]. Uncertainty is unavoidable in measurements as illustrated in Vocabulary International Measurements (VIM) [4]: *'Metrology includes all theoretical and practical aspects of measurement in all sectors including routine measurement. It applies in analytical science, biological and clinical measurement whatever the relative magnitude of the measurement uncertainty'*.

***Corresponding author: Abdurrahman Coskun,** Acıbadem Mehmet Ali Aydınlar University, School of Medicine, Department of Medical Biochemistry, Atasehir, Istanbul, Turkey, Phone: +90 532 744 66 83, Fax: +90 216 576 51 20, e-mail: coskun2002@gmail.com. https://orcid.org/0000-0002-1273-0604
Berrin Berçik İnal: Istanbul Training and Research Hospital, Department of Clinical Biochemistry, Istanbul, Turkey, e-mail: drberrininal@gmail.com. https://orcid.org/0000-0002-9098-4140
Muhittin Serdar: Acıbadem Mehmet Ali Aydınlar University, School of Medicine, Department of Medical Biochemistry, Atasehir, Istanbul, Turkey, e-mail: maserdar@hotmail.com. https://orcid.org/0000-0002-3014-748X

Using uncertainty in laboratory medicine will facilitate the integration of medical metrology to universal metrology such as traceability, harmonization of SI units in laboratory medicine worldwide, etc.

Uncertainty is an inseparable part of all measurements [4], that is, a measurement without uncertainty is not possible. In medical laboratories, myriad quantities and activities are measured and to omit measurement uncertainty (MU) would mean reporting incomplete and unreliable results [5]. Calculation of uncertainty increases the certainty of the measurement results. For example, patients reported glucose level of 100 mg/dL does not mean that the glucose level is exactly 100 mg/dL. To make such a claim, we must prove that all digits after the decimal point of the result are zero, i.e. 100.00….00 ∞. Such claims make no sense and cannot be proved in theory or practice. Patient test results should be reported with MU to ensure reliable and non-suspicious results. This practice ensures that the results are clear and understandable, easing the decision-making process for physicians, particularly when the results lie near the cut-off points defined for clinical decision-making. Reporting test results without analytical uncertainty increases the diagnostic uncertainty, causing errors that could seriously affect patient health.

Reporting MU is mandatory in almost all industrial sectors. Measurements with uncertainty have a stronger position in the competitive market because it clarifies results and increases the reliability of data. Despite this reality, to the best of our knowledge, medical laboratories are not mandated to report results with uncertainty. Although results are reported by laboratorians they are interpreted by physicians who want to be certain about test results used for diagnosis. Because test results without reported uncertainty increase diagnostic uncertainty, pragmatic approaches are needed to minimize such problems.

1. Physicians should be made aware that test results without uncertainty are infact incomplete and might not be sufficient for the diagnosis and monitoring of patients.
2. Laboratorians should be convinced that uncertainty calculations are not as complex as claimed by some laboratory scientists.

Laboratory consultation [6] and active communication between physicians and laboratorians is essential to increase awareness of the benefits of uncertainty with test results [7, 8]. A positive shift will take time because the widespread use of uncertainty requires a cultural change. Engineers are taught the concept of MU through their education, but unfortunately, most of medical doctors are not familiar with the MU when they graduated from school of medicine; postgraduate education and workshops can help physicians to use MU effectively.

Just like physicians, laboratorians ought to be familiar with the calculation of MU. Most laboratorians think that the calculation of MU is complex and cannot be applied to all tests performed in the laboratory. They prefer to use easily computable and practical parameters such as allowable total error (TEa). As stated by Albert Einstein ‘everything should be made as simple as possible, but not simpler’. Effectively using MU guidelines prepared by experts will make their calculation simple and understandable.

Guidelines of measurement uncertainty

The literature contains plenty of information about how to calculate the MU. Although the information is useful and often points out some interesting issues in MU, it is advisable to follow a guideline to calculate MU, especially if one is inexperienced. However, correct guideline selection is imperative, because it is similar to a road map, which if not used correctly, could cause troubles. Some of these guidelines are summarized below:

1. *GUM, Evaluation of measurement data – Guide to the expression of uncertainty in measurement*
   This is a reference guide prepared by the Joint Committee for Guides in Metrology (JCGM) [9]. ISO collaborated with IUPAC (International Union of Pure and Applied Chemistry), IUPAP (International Union of Pure and Applied Physics), OIML (International Organization of Legal Metrology), IFCC (International Federation of Clinical Chemistry and Laboratory Medicine), IEC (International Electrotechnical Commission), BIPM (Bureau International des Poids et Mesures) to establish general principles and rules for calculating MU, applicable to a broad spectrum of measurements. Although IFCC supported the preparation of this guide, the presented principles are not specific to MU in medical laboratories.
2. *Quantifying Uncertainty in Analytical Measurement*.
   This document was prepared by Eurachem and gives detailed guidance for the expression and calculation of MU particularly in quantitative chemical analysis [10]. Based on the main approaches taken in the GUM, it is a general guide applicable at all levels of measurements, from routine to complex research chemical analysis.

3. *EP29, Expression of Measurement Uncertainty in Laboratory Medicine*
   This is the main guideline prepared by CLSI (Clinical and Laboratory Standards Institute) specifically for MU in the field of clinical laboratory medicine [11]. The recommendations given in this document are consistent with GUM.
4. *ISO TC 212/WG 2, Medical laboratories – Practical guide for the estimation of measurement uncertainty*
   As one of the newest guideline prepared by ISO, it considers the requirements of MU in the ISO 15189 standard [12], which states that MU should be reported by the laboratory upon request. However, this guideline has not been used widely in laboratory medicine and new updates may be necessary depending on the users' feedbacks.

Components of uncertainty

MU may comprise many components depending on the type of methods using in measurements, see Figure 1 [10]. We use this figure when we prefer to use bottom-up approach to calculate MU. It should be noted that it is not necessary to include all uncertainty components for the calculation of all analytes. We can simplify this figure by neglecting some components and including only the major components, which have a significant contribution to the total uncertainty.

Different approaches to calculate the uncertainty in laboratory medicine

Estimation of MU can be performed in two ways: bottom-up (Type A) and top-down (Type B) [10]. The bottom-up approach suggests that the possible sources contributing to MU are identified and quantified. This approach is more useful particularly during method development. Figure 1 exemplifies the use of the bottom-up approach and the combined uncertainty is calculated using the uncertainty of each component as shown in Eq. 1. However, it may not be possible to regularly determine all possible sources, particularly in automated systems such as autoanalyzers. In this case, it is more practical to employ a top-down approach that can be used widely in laboratory medicine [13]. Long-term QC data such as internal quality control (QC) and interlaboratory comparisons (PT or EQAS) are routinely collected and can be used to obtain a combined standard uncertainty [13, 14].

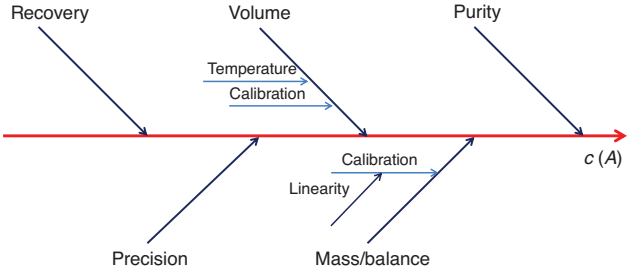

Figure 1: Cause and effect diagram of some components used in calculation of measurement uncertainty in bottom-up approach.

Calculation of uncertainty

In brief, the uncertainty of a measurand in bottom-up (Type A) method can be calculated and reported in five steps:

- Step 1. Define the major components contributing to the uncertainty of the measurand and draw an appropriate fishbone, as shown in Figure 1.
- Step 2. Calculate the SD (Standard Deviation) or RSD (relative standard deviation) of each component. Instead of SD, it is better to use RSD (or CV).
- Step 3. Combine all RSDs using the Gaussian approach to obtain the combined standard uncertainty (U_{cs}) as shown in Eq. 1:

$$U_{cs} = \sqrt{\mathrm{RSD}_1^2 + \mathrm{RSD}_2^2 + \mathrm{RSD}_3^2 + \ldots\ldots \mathrm{RSD}_n^2} \quad (1)$$

- Step 4. Use a suitable coverage (c) factor, such as 2, to calculate the expended uncertainty (U_e).

$$U_e = c \times U_{cs} \quad (2)$$

- Step 5. Combine the expanded uncertainty with patient test results such as *Test result* $\pm$ U_e.

Using these five basic steps facilitates the uncertainty calculations of the main tests performed in laboratory medicine. The details of MU calculation can be found in the guidelines developed by CLSI and ISO.

A detailed calculation methods of MU in Top-down approach with numerical examples was recently published by Ćelap et al. [15]. Alternatively, the guideline prepared by The Royal College of Pathologists of Australasia recommends the use of CV% of at least 30 sets of internal QC data to calculate of MU in laboratory medicine [16].

The uncertainty level at different regions of the measurement range

At the limit of quantitation (LOQ) there are more uncertain parameters and therefore higher uncertainty [17, 18]. Quantitative data measured here is acceptable, but it does not fully comply with the quality performance criteria. Thus, the background noise of the device, the effect of the "blank" used and the undesirable effect of the interference will add more to the uncertainty compared to the normal linear range.

Six Sigma and measurement uncertainty

It has been reported that the quality of test results reported in laboratory medicine is lower than the quality of various products produced by high technologies [19, 20]. Sigma metric (SM) can be accepted as an indicator of product quality and services given by various sectors. The SM of the aviation sector ranks the highest, expected at above 6 sigma [21]. On the other hand, the SM of various tests produced in laboratory medicine is around 3–4. In Six Sigma language this is not an acceptable score. The quality of data and products affecting our health should not be so low.

It should be noted that the real SM of data and products related to laboratory medicine is not as low as reported by various papers. In laboratory medicine, the equation used to calculate SM (Eq. 3) is different from the equation used in industry (Eq. 4); moreover, Eq. (3) usually gives a lower SM level than the actual [22, 23].

$$SM = \frac{TE_a - Bias}{SD} \quad (3)$$

The universal equation used to calculate the SM is given as below:

$$SM = \frac{TL}{SD} \quad (4)$$

The SD is obtained from precision data.

The second important point is that we should integrate the medical metrology with the universal metrology and strictly enforce the metrological rules. Uncertainty can be used as a strong link between medical metrology and universal metrology.

Decreasing uncertainty is not as easy as expected; it requires effort and new technologies. On the other hand, the degree of uncertainty can be accepted as an indicator of the quality of technology used in measurements.

$$SM = \frac{TL}{MU} \quad (5)$$

Using MU instead of SD is more realistic in the calculation SM. MU represents various parts of variation effecting the total variability of test results.

Allowable total error and measurement uncertainty

The TEa concept was developed by Westgard and coworkers and has been popular in laboratory medicine for more than two decades [24]. Recently, the TEa concept has been subjected to numerous criticisms [25, 26]. TEa was a useful parameter in the 1980s and 1990s because at that time, QC in the field of laboratory medicine was not widely used so consequently the tolerance for imprecision and bias of laboratory tests were higher. Historically, it was a very practical way to combine bias and imprecision using a simple statistical approach as given in Eq. (5):

$$TEa = Bias + 1.65 \times CV \quad (6)$$

Although TEa was a very practical and simple parameter, it cannot solve the main problems related to test results and, based on previous experiences, we can say with confidence that the TEa concept will not be able to solve such problems.

The main drawback of the TEa concept is the incorrect estimation [27] and discrepancies related to the combination of TE with patients' results. MU can be combined with results in the form of *Test results* ± *MU*. However, total error cannot be combined with test results as given for MU. In other words, it is not an appropriate way to report patients test results such as *Test results* ± *TE*. Recently, it has been proposed to use TEa for proficiency testing and MU for patients test results [25].

Conclusion

Reporting reliable data is essential for all clinical laboratories and physicians make their decisions based mainly on these data. The main question is then: how can we increase the reliability of these data? To answer this question, we must first check the experimental protocols

and examine the nature of the data. The best available methods, reagents, and instruments should be used. However, even if all the equipment, reagents and methods are perfect, we cannot be certain that the reported result is error free. To improve diagnostic certainty, we should calculate and report analytical uncertainty. Implementing uncertainty reporting in laboratory medicine will facilitate the integration of medical metrology with universal metrology.

Conflict of interest: All authors have no conflict of interest.

References

1. Gibney E. New definitions of scientific units are on the horizon. Nature 2017;550:312–3.
2. Quinn T. From artefacts to atoms – a new SI for 2018 to be based on fundamental constants. Stud Hist Philos Sci Part A 2017;65–66:8–20.
3. Fischer J. Low uncertainty Boltzmann constant determinations and the kelvin redefinition. Philos Trans R Soc A Math Phys Eng Sci 2016;374:20150038.
4. Prichard E, Magnusson B, Patriarca M, Superiore di Sanità I, Elizabeth Prichard I, Andersen J, et al. Terminology in Analytical Measurement-Introduction to VIM 3 First Edition 2011 Editors Vicki Barwick (LGC, UK). 2011.
5. Farrance I, Frenkel R. Uncertainty of measurement: a review of the rules for calculating uncertainty components through functional relationships. Clin Biochem Rev 2012;33:49–75.
6. Coskun A. Six Sigma and laboratory consultation. Clin Chem Lab Med 2007;45:121–3.
7. Bal C, Serdar MA, Güngör OT, Çelik HT, Abuşoğlu S, Uğuz N, et al. Calculation of measurement uncertainty of biochemical parameters. Turk J Biochem 2014;39:538–43.
8. Ozturk O, Serdar MA, Ozturk M, Kurt I. Calculation of uncertainty for glucose: may it affect the diagnosis of gestational diabetes? Turk J Biochem 2012;37:68–72.
9. JCGM. Evaluation of measurement data – guide to the expression of uncertainty in measurement. JCGM 100:2008.
10. Ellison Secretary US, Bettencourt da Silva R, Poland Fodor EP, Kaarls R, Germany Magnusson EB, Robouch IP, et al. EURACHEM/CITAC Guide Quantifying Uncertainty in Analytical Measurement. 2009.
11. CLSI EP29-A. Expression of Measurement Uncertainty in Laboratory Medicine; Approved Guideline. 2012.
12. ISO 15189:2012. Medical laboratories – requirements for quality and competence. Geneva, Switzerland: International Organization for Standardization, 2012.
13. Ceriotti F. Deriving proper measurement uncertainty from Internal Quality Control data: an impossible mission? Clin Biochem 2018;57:37–40.
14. Magnusson B, Ossowicki H, Rienitz O, Theodorsson E. Routine internal- and external-quality control data in clinical laboratories for estimating measurement and diagnostic uncertainty using GUM principles. Scand J Clin Lab Invest 2012;72:212–20.
15. Ćelap I, Vukasović I, Juričić G, Šimundić A-M. Minimum requirements for the estimation of measurement uncertainty: recommendations of the joint Working group for uncertainty of measurement of the CSMBLM and CCMB. Biochem Medica 2017;27:030502.
16. The Royal College of Pathologists of Australasia. Uncertainty of measurement. Guideline No 2/2004.
17. Armbruster DA, Pry T. Limit of blank, limit of detection and limit of quantitation. Clin Biochem Rev 2008;29(Suppl. 1):S49–52.
18. Uhrovčík J. Strategy for determination of LOD and LOQ values – some basic aspects. Talanta 2014;119:178–80.
19. Oosterhuis WP, Coskun A. Sigma metrics in laboratory medicine revisited: we are on the right road with the wrong map. Biochem Medica 2018;28:020503.
20. Coskun A, Serteser M, Ünsal I. Sigma metric revisited: true known mistakes. Biochem Medica 2019;29:010902.
21. Panagopoulos I, Atkin C, Sikora I. Lean Six-Sigma in aviation safety: an implementation guide for measuring aviation system's safety performance. J Saf Stud 2016;2:30.
22. Coskun A, Serteser M, Kilercik M, Aksungar F, Unsal I. A new approach to calculating the Sigma Metric in clinical laboratories. Accred Qual Assur 2015;20:147–52.
23. Coskun A, Serteser M, Serdar M, Aksungar F, Kilercik M, Unsal I. Z transformation is the gold standard for computing the sigma metric. Clin Biochem 2016;49:732–3.
24. Westgard JO. Assuring analytical quality through process planning and quality control. Arch Pathol Lab Med 1992;116:765–9.
25. Oosterhuis WP, Bayat H, Armbruster D, Coskun A, Freeman KP, Kallner A, et al. The use of error and uncertainty methods in the medical laboratory. Clin Chem Lab Med 2018;56:209–19.
26. Theodorsson E. Uncertainty in measurement and total error. Clin Lab Med 2017;37:15–34.
27. Oosterhuis WP. Gross overestimation of total allowable error based on biological variation. Clin Chem 2011;57:1334–6.