Total error and uncertainty: Friends or foes?

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Guidelines ISO 17025 and ISO 15189 aim to improve the quality-assurance scheme of laboratories. Reliable analytical results are of central importance due to the critical decisions that are taken with them. ISO 17025 and ISO 15189 therefore require that analytical methods be validated and that laboratories can routinely provide the measurement uncertainty of the results of measurements. To evaluate the fitness of purpose of analytical methods, total error is increasingly applied to assess the reliability of results generated by analytical methods. However, the ISO requirement to estimate measurement uncertainty seems opposed to the concept of total error, leading to delays in laboratories implementing ISO 17025 and ISO 15189 and confusion for the analysts. This article therefore aims to clarify the divergences between total error and measurement uncertainty, but also to discuss their main similarities and emphasize their implementation.

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1. Introduction

ISO guidelines ISO 17025 [1] dedicated to the accreditation of testing laboratories and ISO 15189 [2] for medical laboratories were introduced to improve the quality-assurance (QA) schemes of these laboratories for international recognition of their analytical competence. In particular, these two documents require that analytical procedures should be validated and that laboratories should be able to provide measurement uncertainty linked to their results. For medical laboratories, the introduction of these two documents generated a conflict between the advocates of total error promulgated by Westgard and co-workers for three decades [3–5], and those following the metrological view of measurement uncertainty promulgated by the ISO GUM [6] {e.g., Dybkaer [7,8] or, more moderately, Kristiansen [9]}.

In parallel, for pharmaceutical and biopharmaceutical laboratories, awareness of the concept of total error (also called total analytical error or total measurement error) was recently reborn. For example, in Europe, a French working group, including industrialists, academics, and regulatory bodies from the pharmaceutical and agro-food industry, promoted use of total error for evaluating the validity of analytical methods [10–12]. Similarly, industrialists and regulatory agencies [e.g., US Food and Drug Administration (FDA)], in a recent summary of the 2006 Bioanalytical workshop, concluded with a new criterion, namely total error, to assess the validity of ligand-binding assays (LBAs) [13]. This recent application of total error in these sectors was made in order to meet the more demanding requirements of regulatory agencies on risk management, in particular, of consumer or client risks [14,15] (e.g., the risk of falsely declaring acceptable an unacceptable result). Nonetheless, in the pharmaceutical and biopharmaceutical industries, the concept of measurement uncertainty is rarely used to assess the reliability of results generated during routine applications (e.g., when releasing batches of pharmaceutical products to market).

Total error and uncertainty are not new concepts. They are both aimed at improving the quality of the results generated by laboratories and are part of a larger QA scheme. However, due to the evolution of national and international guidelines dedicated to the quality of
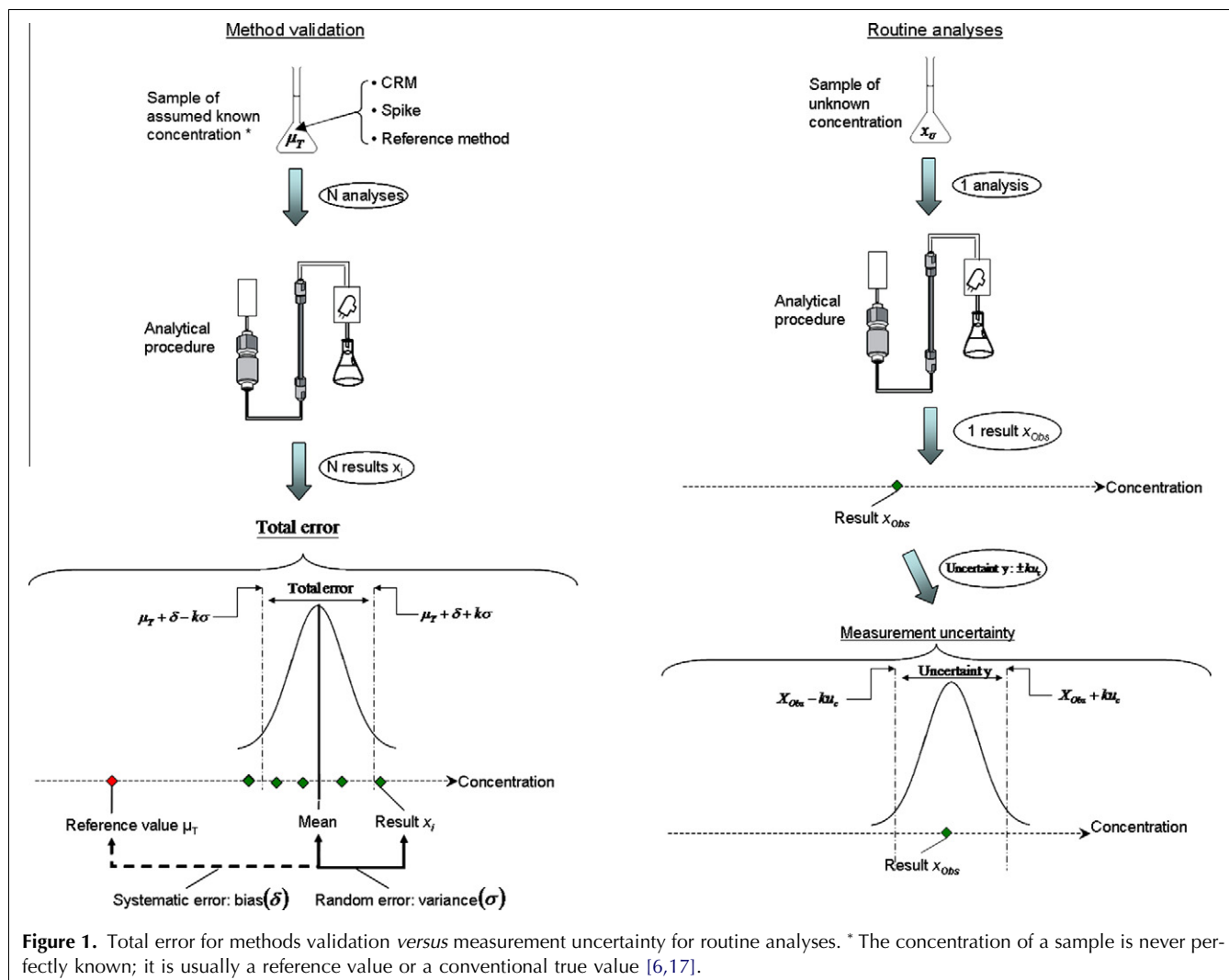
analytical results generated by analytical procedures, these concepts seem contradictory [3–5,7–9,16]. The difficulty of laboratories implementing them is therefore increased, so having a generally negative effect on the global quality of analytical laboratories.

The main aim of this article is to highlight some of the differences between the two concepts of total error and uncertainty but also to stress their main similarities. The first two sections summarize the concepts of error and measurement uncertainty. The subsequent sections focus on the differences and the similarities between total error and measurement uncertainty as well as the essentials for their implementation.

2. Types of error

Typically, two main types of error are recognized in analytical chemistry: systematic and random, as shown in Fig. 1 [17–19]. To estimate random error, variances, standard deviations or relative standard deviations are computed based on replicate measurements of the same sample. To estimate systematic error, the first step is to compute the mean of several replicate measurements of the same sample. This last sample has an additional essential attribute: the concentration of the analyte of interest is known, or is considered as known and is generally a reference or conventional value. This is commonly achieved by preparing spiked samples with certified reference substances, through the analysis of a certified reference material (CRM), or, finally, the analysis of the sample by a reference method or reference laboratory. Finally, the difference between the mean result and the reference value allows us to estimate the method bias or systematic error, as illustrated in Fig. 1. These two elements of analytical error are easily estimated when several replicates of a sample with a reference or conventional true concentration value are analyzed. The separate evaluation of these two parts is much applied in methods validation, transfer and comparison studies. Finally, some authors have proposed to subdivide these two main categories of errors in order to

Figure 1. Total error for methods validation *versus* measurement uncertainty for routine analyses. * The concentration of a sample is never perfectly known; it is usually a reference value or a conventional true value [6,17].