

Measurement Quality in Karl Fischer Analyses

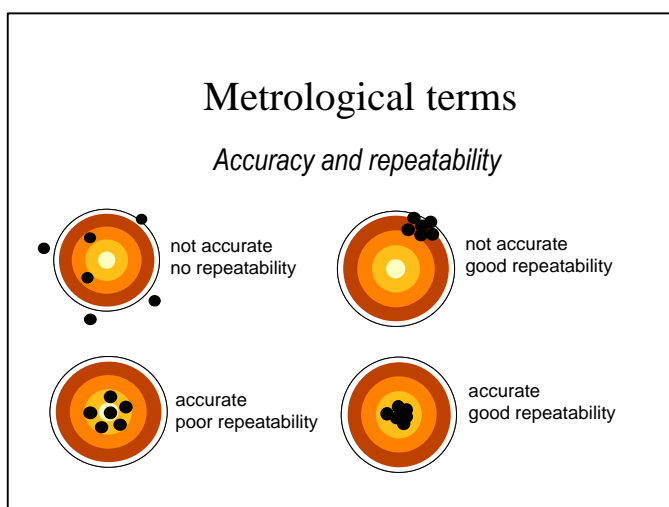
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In addition to information concerning traceability, Good Laboratory Practice requires pharmaceutical laboratories to express the quality of results obtained. This quality level is frequently expressed using the common Standard Deviation (SD) or Relative Standard Deviation (RSD). The aim of this article is to explain why a low SD or RSD does not necessarily correspond to a high level of result accuracy nor the result obtained correspond to the true value of your sample. To simplify the expression of measurement quality in Karl Fischer analyses, a new volumetric titration system from Radiometer Analytical offers automatic expression of the quality of your measurements and corresponding accuracy.

Key concepts

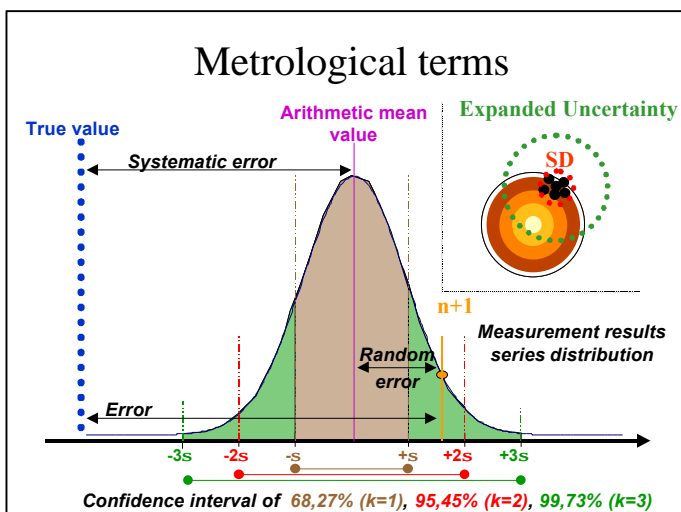
The science of measurement or **metrology** aims to express the true value of a measurement. To achieve this, we calculate the mean value associated with its expanded uncertainty and directly trace it to national or international standards (traceability). First of all, it is necessary to differentiate between repeatability and accuracy. To explain these terms, we could consider that shooting at a target is similar to making a perfect measurement with the "bull's eye" being the true value of your sample or value of a known reference standard. Each shot corresponds to one result.

The four targets in the picture illustrate the various possibilities: shots on or off the target, close to or far from the bull's eye, widely distributed etc., helping us clearly identify the meaning of accuracy and repeatability. Let us take the case of repeatable analyses that give a good SD with closely grouped shots. The question is how far are these shots from the bull's eye (true value)? It is impossible to say based only on the SD! It is therefore necessary to take into account **measurement errors** and introduce another parameter to express measurement quality and accuracy: the **Expanded Uncertainty**.



Errors and uncertainty

If a set of repeated measurements is made and the corresponding histogram is plotted, we may have a normal or Gaussian distribution. The top of the curve corresponds to the arithmetic mean value of the measurements. If we represent the "inaccessible" true value and if we select another measurement value (e.g. $n+1$), the difference between these two results corresponds to the error. The error consists of a systematic error and a random error. The systematic error corresponds to the bias, the deviation that can be known on some parameters of the

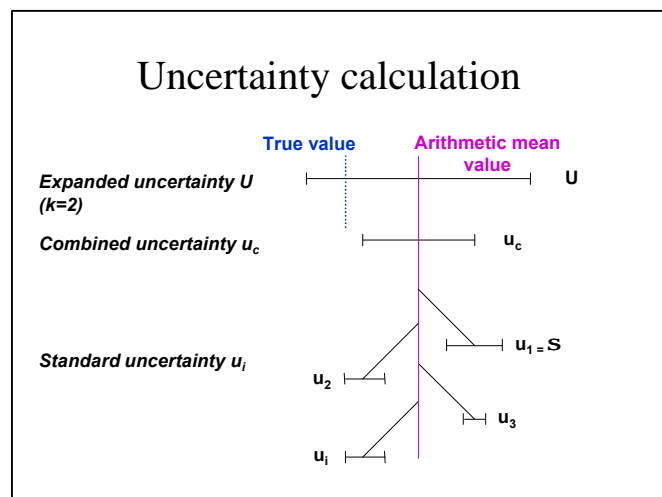


measurement, for instance instrument or sensor calibration. To reduce systematic errors, known corrections must be applied based on a calibration certificate. The random error is due to changing parameters during a series of measurements. Random errors may be due to the resolution of the instrument or changes in environmental conditions. Random errors are reduced by increasing the number of measurements and taking the average value because the sign of each error can be positive or negative and the average is close to zero. Plotted on this Gaussian curve, the confidential level can be expressed as being given by one, two or three times the standard deviation of the corresponding distribution. A corresponding coverage factor k equal to 1, 2 or 3 can be set, meaning there is respectively a 68.3%, 95.4% and 99.7% of chance of finding results in the specified interval. The difference between error and uncertainty should always be borne in mind. The error is the difference between the result and the true value. The uncertainty characterises the dispersion around the measurement result values of the measurand.

For example, the result of a measurement after correction can be very close to the unknown value of the measurand, even though it may have a large uncertainty.

Calculating measurement uncertainty

Uncertainty calculations must be considered in the context of the Guide to the expression of the Uncertainty in Measurement (GUM)*. This international standard defines the requirements for analysing and computing the uncertainty of a measurement. The first objective is to define the mathematical model of the measurement process. A result is always a function of one or several input parameters. The model gives the relationship between these inputs and the final result. With the model function, the uncertainty calculation is based on



the determination of the first order terms of its Taylor series. Computing the partial derivative of each input gives the sensitivity coefficient of the corresponding input. Each sensitivity coefficient is combined with the standard uncertainty “ u ” of each parameter, including SD “ σ ”, in a quadratic sum and this gives the expression of the combined standard uncertainty “ U_c ”. It is then possible to compute the expanded uncertainty “ U ” as it is the combined standard uncertainty “ U_c ” multiplied by the k factor (the coverage factor), usually equal to 2 which means a confidence level close to 95%. In other words, there is a 95% chance of having the true value included in the expression of the interval associated with your result (e.g. 5.023 ± 0.015 mg/l, $k=2$).

Taking the effort out of metrology

Following GUM requirements and calculating the expanded uncertainty for each of your results is both time-consuming and complicated on a day-to-day basis. **Radiometer Analytical S.A.** is the first company in the world to offer a volumetric titration system that includes the automatic expression of the quality of your measurements and corresponding accuracy by associating the expanded uncertainty with each result.

The **TIM550 Volumetric Karl Fischer Titrator** is entirely dedicated to water content determination in various pharmaceutical products. It is the first instrument of a new generation of Karl Fischer titrators, which offer a major breakthrough in the expression of measurement quality. Calibration data are also embedded and are automatically taken into account in the calculation of the systematic error, making your results even more accurate. You can enter the sample weight at any time during your analysis. Repeating measurements could not be easier and a simple binary choice helps operators minimise random errors.



Safety, minimum maintenance and ease of use are the key words of this instrument. The TIM550 guides the user during operating and maintenance procedures and ensures that results are obtained with the quality you are entitled to expect.

*GUM: ENV13005