Concept of Weighing in the Japanese Pharmacopoeia *<G1-6-182>*

(日本薬局方における秤量の考え方〈*G1-6-182*〉)

In the section of balances and weights in "Measuring instrument, Appliances *<9.62>*" in General Tests of the JP, it is required that balances and weights in the JP shall be calibrated ensuring traceability to the international system of units (SI).

Traceability in metrological measurement is defined as follows: "property of a measurement result whereby the result can be related to a reference through a documented unbroken chain of calibrations, each contributing to the measurement uncertainty." [1)] The most significant sources of metrological traceability are the following basic units of the international system of units (SI): meter (length), kilogram (mass), second (time), ampere (electric current), kelvin (thermodynamic temperature), candela (light intensity), and mole (amount of substance). In the case of a balance, calibration that ensures traceability for mass should be performed. Factors of traceability include a) a series of continuous comparisons, b), measurement uncertainty, c) documentation, d) technical ability, e) reference to the international system of units (SI), and f) calibration, and f) is required in this section. In addition, for a balance used in the JP, the requirements for repeatability (intra-assay precision) and accuracy (trueness) are specified, as well as being specified to perform calibration that ensures traceability to the international system of units (SI). By meeting the requirements, weighing results can be traceable to the international system of units (SI).

On the other hand, for metrology in the JP, results traceable to the international system of units (SI) are not always required. This is clear because most reference standards and reference materials used in the JP is determined by the mass balance method, which is not traceable to the international system of units (SI). Analysis in the JP is performed in accordance with the predetermined regulations to judge whether the specification (value) is met.

In other words, if the specification for assay in each monograph is not less than 99.0%, when an analytical value is not less than 98.95% considering the number of significant digits and an analysis is performed according to the assay method specified in each monograph, it meets the JP. Therefore, it is important that accurate weighing up to the fourth significant digit is possible. It is known that a semimicrobalance, which can indicate up to the digit of 10 μg, generally has an error of not less than 130% (an error of not less than ± 13 μg) at the digit of the reading limit, even if it was calibrated in accordance with the above rules.[2)] Therefore, for example, if the semimicrobalance displayed 50.65432 g, including the tare weight, when about 0.1 g of a sample or a reference standard is weighed for the assay method, "3" at the digit of 100 μg is considered to be almost accurate, and therefore, it can be well used for weighing of samples and reference standards for the assay method. In most assay methods in the JP, the number of significant digits required is four at maximum, for example, for a water content of 0.10% and loss on drying of 4.0%, the number of significant digits required for the calculation is three, and for residue on ignition of 0.1%, it is two. Therefore, it is necessary to use a balance that satisfies these numbers of significant digits for analysis. In other words, in the JP, it is important to perform weighing in line with the concept suitable for the purpose (fit for the purpose). Therefore, when weighing 0.2 g of a drug used for the color reaction as an identification test or a purity test, two significant digits are enough for the balance used. On the other hand, when weighing about 5 mg of a reagent used for purity determination with quantitative NMR using an ultramicrobalance, for example, if 25.2345 mg, which includes the tare weight, is displayed, "4" at the digit of 1 μg is considered to be almost accurate. Because the number of significant digits used for the calculation of purity is three, the fourth digit is almost accurate as the weighed value of a reagent, and the balance can be used enough even if the tare weight is about 20 mg. In addition, even if only a micro balance is available, when weighing not less than 10 mg of a reagent, up to the fourth significant digit is considered to be almost accurate.

In addition, when weighing, it is important to understand what kinds of error occurs. Factors that cause errors during weighing with an appropriately calibrated balance include change in sensitivity, repeatability, linearity, and eccentricity, etc. Changes in sensitivity are caused by changes in gravitational acceleration applied to the place, temperature drift, and other factors. When a place where a balance is used is moved, sensitivity adjustment may be required because the gravitational acceleration applied to the place is different. In particular, an electronic balance displays mass being corrected according to the balance between the electromagnetic force and free fall acceleration (gravitational force). Therefore, the electronic balance, whose sensitivity was adjusted at the place before moving, displays mass that is different from the actual mass because the environment of the place after moving is different. In addition, displayed values change because of changes in the environment; therefore, the sensitivity must be adjusted using the balance's internal weight or external weight(s).

Repeatability is the degree of consistency of values displayed when the same sample was weighed on the weighing pan of a balance multiple times and is an essential characteristic for the performance evaluation of a balance that has a high display resolution allowing a reading up to the digit of 10 μg or less.

Based on the results obtained from the requirements for repeatability shown in the section on balances and weights of the general test "Measuring instruments, Appliance *<9.62>*" of the JP, the minimum weight of the balance at that time is estimated. To make the weighing traceable to the international system of units (SI), it is a standard to weigh a mass larger than the minimum weight for the balance.

Because the minimum weight is affected by the installation environment of the balance (presence or absence of vibration at the installation location, etc.), temperature changes during weighing, and other factors, it is important for accurate weighing to record the minimum weight value routinely. The minimum weight is an estimated value that shows the lower limit of weighing to ensure the accuracy of the balance, not including the tare, and it is necessary that repeatability to ensure the precision of the smallest net weight using the standard deviation obtained by the requirements of repeatability (intra-assay precision) is not more than 0.10%. In other words, it is necessary to weigh not less than the minimum weight when performing weighing traceable to the international system of units (SI). Factors that may affect repeatability (intra-assay precision) of a balance are as follows:

1) The minimum weight indicates the performance of a balance and may change depending on the change of environment or the elapse of time.
2) Methods for weighing may differ among analysts. In other words, the minimum weight determined may vary among analysts.
3) Note that the standard deviation for a limited number of replicates is an estimated value of the true standard deviation and cannot actually be identified.
4) Determination of the minimum weight may not be fully consistent with the established test method.
5) If the tare/container used affects mass depending on environment, it may affect the minimum weight.

Based on these factors, weighing must be performed over the minimum weight in most cases. In other words, the smallest net weight using a balance actually should be set larger than the minimum weight to some extent.

The error of linearity is the degree of deviation from the ideal straight line at each point, which divides the interval from the zero point to the maximum weight point almost evenly. The error of sensitivity is the degree of inclination of a straight line from the zero point, including the error of linearity. Generally speaking, an error becomes larger from the zero point to the maximum weight point, and becomes significant in conjunction with environmental changes. Therefore, for the requirements of accuracy (trueness), use a weight with mass near the upper limit of the weighing range, or slightly lower than the balance's capacity in order to confirm the allowable error of sensitivity. The error of eccentricity is the degree of change in the value displayed when a load is applied to a position distant from the center of the balance, and is less necessary to be taken into consideration unless a sample or sampling container has a special shape. Evaluation of accuracy (trueness) in a normal environment includes the three errors of sensitivity, linearity, and eccentricity, and the acceptance criterion, 0.10%, according to the error propagation rule (square root value of the sum of squares) satisfies the following equation.[2)]

$$0.10\% \fallingdotseq \sqrt{0.05\%^2[\text{err. of sen.}]+0.05\%^2[\text{err. of lin.}]+0.05\%^2[\text{err. of ecc.}]}$$

(err.=error, sen.=sensitivity, lin.= linearity, ecc.=eccentricity)

Therefore, in the requirements for accuracy (trueness), not more than 0.05% is required as the difference between the displayed value of a balance obtained by loading and unloading a weight once and the mass value of the weight. In other words, 0.05% each is allocated to the error of sensitivity and the error of linearity.

When the above-mentioned errors are considered, in the inspection of a balance, it is necessary to implement the requirements for repeatability (intra-assay precision) and the error of sensitivity (accuracy [trueness]) for the purpose of confirming at least the precision for a point near 5% of the balance's capacity and the accuracy (trueness) for a point near the balance's capacity (or a point near the maximum value of the range of use). For confirmation of repeatability (intra-assay precision), a weight with no change in mass is used, and for confirmation of accuracy (trueness), a weight with a calibration certificate traceable to the international system of units (SI) is used. If the requirements for accuracy (trueness) are not met, it is necessary to calibrate the balance, ensuring traceability with the value of uncertainty[3)].

References

1) ISO/IEC Guide 99: 2007, International vocabulary of metrology - Basic and general concepts and associated terms (VIM).
2) Reichmuth. A and Fritsch. K, Pharmaceutical Engineering 29(6), 46-58 (2009).
3) ISO/IEC Guide 98-3: 2008, Uncertainty of measurement Part 3: Guide to the expression of uncertainty in measurement (GUM:1995).