White Paper

# Weighing According to US Pharmacopeia

## General Chapters 41 and 1251

**Content**



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# 1 Introduction

Weighing is one of the key activities carried out in every QC laboratory. Usually it is one of the first parts of a whole analysis chain, such as when a sample or a standard is prepared for subsequent dilution and HPLC or qNMR analysis. As any weighing errors have the potential to propagate through the whole analysis and deliver an inaccurate final result, the United States Pharmacopeia (USP) has set stringent requirements for balances used for weighing analytes for quantitative measures. These requirements should ensure that weighing errors are small or even negligible within the analysis.

This white paper details the weighing requirements of the United States Pharmacopeia, and provides advice on how to put these requirements into practice to ensure consistently high quality of weighing results. Besides the mandatory General Chapter 41 "Balances" which sets three key requirements that balances need to fulfill when weighing analytes for quantitative measures, USP provides detailed guidance on the state-of-the-art strategy for qualification and operation of balances in its informational General Chapter 1251 "Weighing on an Analytical Balance".

While presenting all information of General Chapter 1251 would go beyond the scope of this white paper, dedicated topics reflecting user routine testing of the equipment are included, as they are crucial to ensure that the instrument works continuously according to the requirements and is "fit for its intended purpose".

# 2 Role of Pharmacopeias

A central document for the pharmaceutical industry is the pharmacopoeia (or pharmacopeia), which is a collection of published standards describing requirements for testing chemical and biological drug substances and dosage forms, as well as methods of analysis for medicines. These standards are defined to ensure pharmaceutical products are of the appropriate identity, as well as strength, quality, purity and consistency. While pharmacopeias describe requirements for testing drug substances and dosage forms, they do not apply for manufacturing of the respective products.

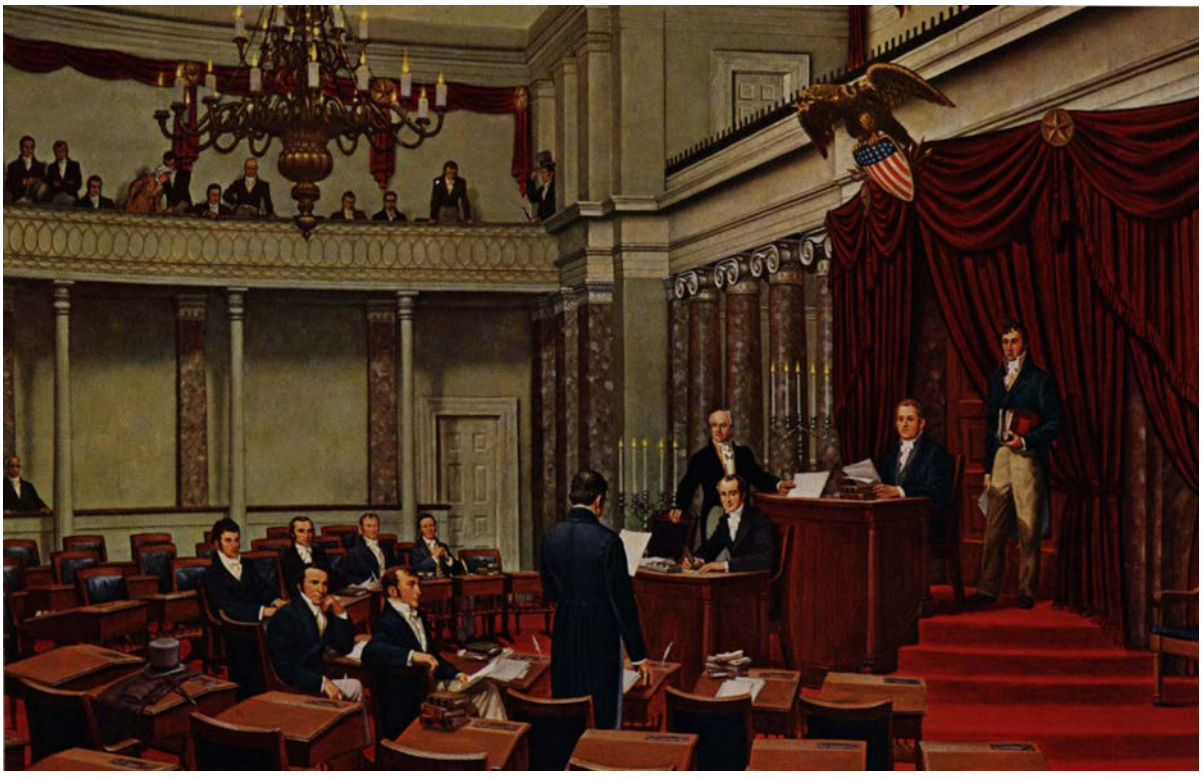


Figure 1: Foundation of the United States Pharmacopeial Convention on January 1, 1820 in the Old Senate Chamber of the U.S. Capitol (11 of the 16 delegates – all physicians – present) [1]. The first USP was published on December 21, 2020. Artist: Robert Thom. Painting commissioned by USP, 1957

In the United States, the "United States Pharmacopeia" (USP) was published the first time 1820 and was one of the first pharmacopeias worldwide. Today, many national and some international pharmacopoeias exist, such as the International Pharmacopoeia of the World Health Organization (WHO), the European Pharmacopoeia (Ph. Eur.) or the Japanese Pharmacopeia (JP). However, the U.S. Pharmacopoeia is quite often considered as a de facto world standard and its monographs and methods are regularly adopted by other pharmacopoeias and used in more than 140 countries. Considerable cooperation and scientific exchange between the individual pharmacopeias have been established over the years. As one of the most important programs, the three most influential pharmacopoeias (USP, European and Japanese Pharmacopeia) have set up a program to achieve harmonized standards across the three organizations through a formal, step-wise process (Pharmaceutical Discussion Group PDG).

In most countries, the respective national pharmacopoeia is a legally binding document, and the pharmacopeial organizations are governmental. USP, however, is not a government entity but is ruled by a Board of Trustees that is elected by the USP Convention. The USP Council of Experts makes the scientific and standards-setting decisions. The status of being a de facto law is achieved through the U.S. Federal Food, Drug, and Cosmetics Act that designates the U.S. Pharmacopeia and the National Formulary (USP-NF) as official compendia for drugs marketed in the United States. The U.S. Food and Drug Administration (FDA) enforces the implementation of the applicable General Chapters and monographs during their GMP inspections. USP itself has no role in law enforcement.

USP-NF is a combination of two compendia, the United States Pharmacopeia (USP) and the National Formulary (NF). Monographs for drug substances, dosage forms, and compounded preparations are featured in the USP. Monographs for dietary supplements and ingredients appear in a separate section of the USP. Excipient monographs are in the NF. USP-NF is published three times a year. The full title shows the revision number that is not the same for USP and NF. As an example, in 2019, "USP 42-NF 37" is official, i.e. the 42$^{nd}$ revision of the USP and the 37$^{th}$ revision of the NF, and in 2020, "USP 43-NF 38" will be the official compendia. Two supplements per year amend the revisions.

A monograph includes the name of the ingredient or preparation; the definition, packaging, storage, and labelling requirements; and the specification. The specification consists of a series of tests, procedures for the tests, and acceptance criteria. These tests and procedures require the use of official USP Reference Standards. Medicinal ingredients and products will have the stipulated strength, quality, and purity if they conform to the requirements of the monograph and relevant General Chapters. Tests and procedures referred to in multiple monographs are described in detail in the USP-NF General Chapters. The General Notices and Requirements section provides definitions for terms used in the monographs, as well as information that is necessary to interpret the monograph requirements. Note that the General Notices as well as the General Chapters numbered below 1000 and above 2000 describe applicable mandatory requirements, while General Chapters numbered 1000 to 1999 are for informational purposes only. They present best practice and are quite often recognized or implemented by the industry but are not legally enforced by the U.S. FDA.

# 3 Weighing Requirements in USP

Of central importance about weighing applications is the USP General Chapter 41 "Balances" [2] that describes specific criteria for the balance performance when used for quality control activities carried out in the laboratory. It is important to refer to the USP General Notices and Requirements to understand the exact scope of applicability of General Chapter 41. They contain two important paragraphs that need to be taken into account.

Section 6.50.20 "Solutions" states:

"[…] Solutions for quantitative measures shall be prepared using accurately weighed or accurately measured analytes (see section 8.20 About)."

Section 8.20 "About" stipulates:

"'About' indicates a quantity within 10%. If the measurement is stated to be 'accurately measured' or 'accurately weighed', follow the statements in Volumetric Apparatus ⟨31⟩ and Balances ⟨41⟩, respectively."

With these two requirements, it is evident that whenever a monograph requires material to be "accurately weighed", the balance on which the weighing process is carried out needs to comply with the requirements described in General Chapter 41. Furthermore, as a rule applicable for all monographs, analytes used for quantitative measures need to be weighed on a balance which fulfills the requirements of General Chapter 41.

It needs to be stated again that USP, as well as other pharmacopeias, set requirements only for **testing** of chemical and biological drug substances and dosage forms, as well as methods of analysis for medicines. In other words, they are not applicable for the **production** of active pharmaceutical ingredients, excipients or finished pharmaceuticals.

General Chapter 41 is supported by General Chapter 1251 "Weighing on an Analytical Balance" [3] that presents additional information and state-of-the-art concepts about analytical weighing. As discussed earlier, all General Chapters numbered 1000 to 1999 are for informational purposes only and are not enforced by the U.S. FDA during GMP audits. However, many companies implement these concepts on a voluntary basis in order to achieve a high level of quality that can easily be referred to in management handbooks, and during internal and external audits.

# 4 USP General Chapter 41 "Balances"

## 4.1 Accuracy and Precision

As stated previously, the United States Pharmacopeia (USP) has set stringent requirements for balances used for weighing analytes for quantitative measures. These requirements should ensure that weighing errors are small or even negligible within the analysis. General Chapter 41 sets three distinct requirements used for materials that must be accurately weighed in order to accomplish this objective (citation re-formatted for clarity).

"The weighing shall be performed using a balance that is
- calibrated over the operating range and meets the requirements defined for
- repeatability and
- accuracy."

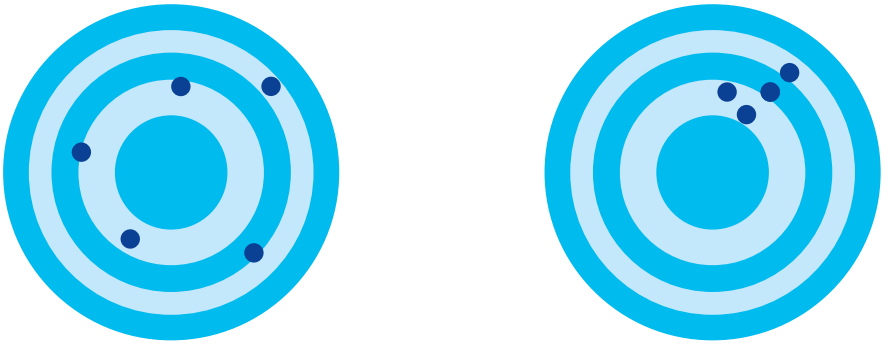
Before we analyze in detail the three requirements on calibration, repeatability and accuracy, it is important to understand how accuracy is defined in USP. USP defines accuracy in its General Chapter 1225 "Validation of Compendial Procedures" as [4]:

"The accuracy of an analytical procedure is the closeness of test results obtained by that procedure to the true value. The accuracy of an analytical procedure should be established across its range. [A note on terminology: The definition on accuracy in this chapter and ICH Q2 corresponds to unbiasedness only. In the International Vocabulary of Metrology (VIM) and documents of the International Organization of Standardization (ISO), "accuracy" has a different meaning. In ISO, accuracy combines the concept of unbiasedness (termed "trueness") and precision.]" [5, 6, 7]

In other words, the accuracy requirement described in USP General Chapter 41 stipulates a test that assesses systematic deviations, the bias, of the balance. This concept is called "trueness" in all other fields of metrology.

The repeatability test, on the other hand, assesses the precision of the balance. Precision is defined in a similar way in the Pharmaceutical Industry and in VIM/ISO. USP General Chapter 1225 states for precision:

"The precision of an analytical procedure is the degree of agreement among individual test results when the procedure is applied repeatedly [...]. The precision of an analytical procedure is usually expressed as the standard deviation or relative standard deviation (coefficient of variation) of a series of measurements. [...]."



a. Accurate, but not precise

b. Precise, but not accurate

Figure 2: a) Results which are accurate (true) but not precise (repeatable), showing a wide spread but around the central point; b) Results which are precise but not accurate (true), showing tightly clustered results but not around the central point.

In simple words, the two tests stipulated by USP General Chapter 41 are intended to assess the random and the systematic error of the balance. By defining specific acceptance criteria for both tests, it ensures that both random and systematic errors of the instrument are controlled. As will be elaborated upon later, both acceptance criteria are expressed as relative limit values, 0.10%. From a practical perspective, this requirement is quite stringent and ensures that the weighing error is usually small, if not negligible, compared to errors in the subsequent process steps described in the individual monographs when drug substances are tested (e.g. dilution, HPLC analysis, etc.).

It should be noted that the meaning of the term "accurately weighed" is different from the meaning of "accuracy" as per the definition above: "accurately weighed" takes into account all the three requirements, a calibrated balance and a balance that fulfills the specific requirements on its random ("precision") and systematic ("accuracy") error.

## 4.2 Calibration

Calibration is one of the key activities that must be performed periodically when instruments are used for quality relevant measurements. Internationally, there are many standards, which stipulate this requirement, e.g. ISO 9001, Good Laboratory Practice (GLP) and Good Manufacturing Practice (GMP) regulations. Almost everybody working in quality control (QC) and quality assurance (QA), either in the laboratory or in the production environment, is familiar with the applicable requirements stipulated in these documents. However, there is no common understanding on the definition, implementation, or specific activities that comprise calibration. Let us therefore establish a common platform on what calibration is.

Calibration is a set of activities carried out on a measuring instrument to understand its behavior. This is done by establishing a relationship between known values (measurement standards) and the associated measured values (indications) of the instrument being calibrated. This relationship consists of deviations and their associated uncertainties. The International Vocabulary of Metrology (VIM) provides this definition of calibration:

"Operation that, under specified conditions, in a first step, establishes a relation between the quantity values with measurement uncertainties provided by measurement standards and corresponding indications with associated measurement uncertainties and, in a second step, uses this information to establish a relation for obtaining a measurement result from an indication."

It is evident that the relationship between the known and the measured values can only be established if the associated measurement uncertainties are derived. Unfortunately, in practice there is a widespread misconception about calibration, as many users outside of the calibration laboratory do not consider measurement uncertainty when "calibrating" an instrument. Measurement uncertainty is defined in the Guide to the Expression of Uncertainty in Measurement (GUM) [8] as:

"Parameter, associated with the result of a measurement that characterizes the dispersion of the values that could reasonably be attributed to the measurand."

Basically, measurement uncertainty quantifies how far away from the true value a measurement result might reasonably be with a certain likelihood. The measurement results, along with the associated uncertainty, are documented in calibration reports or certificates.

If the "measurement standards" used in the calibration process are metrologically traceable (preferably to SI units) and the measurement uncertainty is evaluated properly, then the calibration establishes metrological traceability of the values of the calibrated instrument, provided that recognized methods are used by a competent laboratory.

The ISO/IEC 17025 standard [9] specifies the general requirements for the competence of laboratories to carry out tests and/or calibrations. Accreditation by an accreditation body is the formal process that confirms that a laboratory is competent and fulfils the requirements stipulated by ISO/IEC 17025. It is appropriate to note, at this point, that there is some misconception over what constitutes calibration from an accredited provider. Accreditation is awarded across a fixed scope, with defined capabilities, for each discipline of calibration. Accreditation is not "carte blanche" to carry out all calibrations for an instrument user who requires the service of an accredited calibration laboratory. A calibration certificate by an accredited laboratory is usually accepted without any further necessity of auditing the laboratory. This is due to international multilateral agreements among the accreditation organizations, e.g. ILAC Mutual Recognition Arrangement (MRA). ILAC is the International Laboratory Accreditation Cooperation.

About non-automatic weighing instruments (balances and scales), many calibration guidelines exist on national levels, most of them based on the concepts described in the GUM. While these guidelines are generally quite similar, they differ in details, which makes it difficult if not impossible to develop and use one single calibration guideline on a global level. There are recent activities in the scientific community to address this issue by creating a harmonized approach for calibration of non-automatic weighing instruments that is based on an internationally recognized calibration guideline. This process is driven by EURAMET, with their calibration guideline EURAMET cg-18 "Calibration of Non-Automatic Weighing Instruments" developing to become the most widespread guideline in this field on a global level [10]. It acts in most of the European countries as a basis for accrediting calibration laboratories according to ISO/IEC 17025 and was furthermore transposed into a SIM guideline (SIM is the Inter-American Metrology System) and thus is very frequently applied in the Americas [11]. However, it has been, until very recently, virtually unknown in Asia. This is about to change as the first calibration laboratories have now been granted accreditation based on EURAMET cg-18 in Japan, Thailand, Malaysia, Singapore, India and Indonesia. It is to be expected that the guideline will extend further in Asia, thus closing the gap to become an industry standard that is used on a global level.

The value of EURAMET cg-18 is further substantiated as it not only describes how to derive the uncertainty at the time of calibration, but also how to estimate the so-called uncertainty of a weighing result, characterizing the performance of the instrument during day-to-day usage. This approach has significant practical importance as it facilitates the assessment of the equipment's performance against user specific weighing tolerance requirements.

At this point it is relevant to introduce another misconception about calibration – that is, besides being calibrated, an instrument can also be adjusted. Adjustment is defined in the VIM as:

"Set of operations carried out on a measuring system so that it provides prescribed indications corresponding to given values of a quantity to be measured."

In other words, when adjusting an instrument, its indications are modified in a way so that they correspond – as far as possible – to the quantity values of the measurement standards applied. Unfortunately, many users apply the words calibration and adjustment interchangeably, incorrectly, or even randomly [12]. Quite often, they talk about calibrating a weighing instrument when they mean adjusting it. The VIM also emphasizes this by stating:

"Adjustment of a measuring system should not be confused with calibration, which is a prerequisite for adjustment. After an adjustment of a measuring system, the measuring system must usually be recalibrated."

This statement highlights another important aspect of calibration; before an instrument is adjusted, it must be first calibrated in order to understand – and document – its behavior. This is specifically important in order not to break the calibration history of preceding measurements on the instrument. After an adjustment, the instrument must be recalibrated. Quite often, users talk about an "as found" calibration, i.e. a calibration before any modification (adjustment) is carried out, and about an "as left" calibration, i.e. a calibration after any necessary adjustment and/or repair has been carried out.

To summarize, USP General Chapter 41 requires the use of a calibrated balance. Usually, the calibration results are documented in a calibration certificate along with the estimation of measurement uncertainty. This formal process is required from a quality management perspective and stipulated by both ISO and GLP/GMP. It provides the basis for two specific assessments – repeatability and accuracy - that are presented in the following chapters.

## 4.3 Repeatability Requirement – Minimum Weight

USP General Chapter 41 states:

"Repeatability is assessed by weighing one test weight not less than 10 times. [...] Repeatability is satisfactory if twice the standard deviation of the weighed value, divided by the desired smallest net weight (i.e. smallest net weight that the users plan to use on that balance), does not exceed 0.10%. [...]."

This requirement defines a specific test with an acceptance criterion that the balance shall meet. At this point it is important to understand the specific rounding rules that are applied throughout all USP chapters. The General Notices and Requirements section states in paragraph 7.20:

"The observed or calculated values shall be rounded off to the number of decimal places that is in agreement with the limit expression. Numbers should not be rounded until the final calculations for the reportable value have been completed. [...]. When rounding is required, consider only one digit in the decimal place to the right of the last place in the limit expression. If this digit is smaller than 5, it is eliminated and the preceding digit is unchanged. If this digit is equal or greater than 5, it is eliminated and the preceding digit is increased by 1."

Note that USP uses the term "limit expression" as a synonym for acceptance criterion.

In other words, the mathematical rounding rules are applied when the observed or calculated values are rounded to the number of decimal places of the limit expression. Example: with a given acceptance criterion of 0.10%, a standard deviation of 0.1049% would be rounded to 0.10%. With this value, the balance would pass the repeatability test. A standard deviation of 0.1050% would be rounded to 0.11%, and the balance would fail the repeatability test. Note that this rounding procedure is significantly different from rounding rules in all other fields of applied and legal metrology where the formatting of any given limit value has no effect at all on the rounding of a measurement result.

Independent from any test results, a lower limit of the repeatability of $0.41d$ is prescribed, where $d$ is the scale interval of the balance, also called readability. This limitation accounts for the rounding error of a digital indication. General Chapter 1251 provides the explanation for the lower limit of the standard deviation:

"The lower limit of $0.41d$ for the standard deviation results from the rounding error of the digital indication of a weighing instrument. The rounding error that is allocated to a single reading is calculated as $0.29d$. Note that a weighing always consists of two readings, one before and one after placing/removing the sample on/from the pan, with the difference between the two indications being the net sample weight. The two individual rounding errors are usually added quadratically, leading to $0.41d$. Taring the instrument after placing the tare container on the pan does not affect the rounding error as the zero indication is also rounded."

A very important consequence of the repeatability requirement is the concept of minimum weight that has already been described for many years in the informational General Chapter 1251. During a minor revision of USP General Chapter 41 that comes into effect from August 1, 2019, the description of minimum weight has been added in this mandatory chapter. While the repeatability test and assessment do not change in this revision, the importance of minimum weight for the practical application of the balance in day-to-day use is thereby enforced.

The revised General Chapter 41 states:

"The repeatability measurement establishes the smallest net amount of material that may be weighed on the balance in conformance with the 0.10% limit."

With the standard deviation $s$ and the repeatability acceptance criterion $\frac{2 \times s}{smallest\ net\ weight} \leq 0.10\%$ ,

all masses equal or larger than $\frac{2 \times s}{0.10\%}$ conform with this requirement. The smallest mass that satisfies this

criterion is called minimum weight:

$$m_{\text{min}} = \frac{2 \times s}{0.10\%} = 2{,}000 \times s$$

It is expressed in the revision to General Chapter 41 that the smallest acceptable standard deviation is $0.41d$, based on the rounding of a digital indication. Therefore, the smallest possible minimum weight on a balance with a readability d is $2{,}000 \times 0.41d = 820d$. As an example, on a semi micro balance with a readability of 0.01 mg the smallest possible minimum weight is 8.2 mg. Usually, minimum weight is higher than this threshold.

$$m_{\text{min}} \gg 820 \times d$$

As an example, when the standard deviation of ten repeated measurements on a semi micro balance is 0.007 mg, then the minimum weight would be calculated as 2,000×0.007 mg=14 mg. This example underlines that in all cases the minimum weight needs to be determined experimentally. Depending on the installation location and on the instrument itself, the standard deviation varies. Therefore, it cannot be derived from specifications that are published in data sheets, and the assumption of applying the smallest possible minimum weight of $820d$ is not valid.

As stated in the repeatability requirement, the smallest net weight is defined as the smallest quantity that the user wants to weigh on the device on a day-to-day basis. The smallest net weight is a user requirement and

should not be confused with the minimum weight that is a property of the instrument and which is calculated as described above. With these two definitions, the following statement applies: When the smallest net weight (the user wants to weigh) equals or is larger than the minimum weight (as calculated from the repeatability of the balance), then the repeatability criterion of General Chapter 41 is satisfied.

It must be stated again at this point that the mass of the tare vessel must not be considered when weighing a sample of the balance. This is made evident by the sentence in General Chapter 41 that clearly refers to the net amount of material:

"The repeatability measurement establishes the smallest net amount of material that may be weighed on the balance in conformance with the 0.10% limit."

Furthermore, General Chapter 1251 states:

"The minimum weight applies to the sample weight, not to the tare or gross weight."

Equally, when different samples are weighed into the same tare container, the mass of each individual sample must be equal or larger than the minimum weight.

Let us now highlight another important statement in the repeatability section of General Chapter 41:

"The test weight must be within the balance's operating range, but the weight need not be calibrated. Because the standard deviation is virtually independent of sample mass within the balance's capacity, use of a small test weight, which may be difficult to handle, is not required."

It is important to explain what the balance's operating range is: This is the range of the balance where stipulated requirements on its performance are adhered to. In this case, it is the range of the balance where the repeatability criterion is fulfilled. With the concept of minimum weight, the operating range of the balance starts with the minimum weight and ends at the upper end of the measurement range, at its maximum capacity.

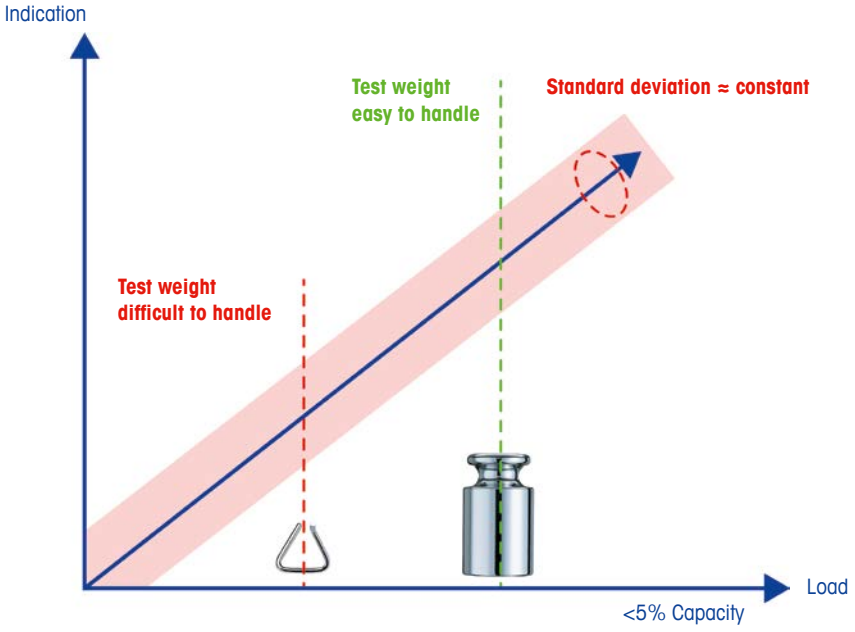



Figure 3: For repeatability testing, the test weight does not need to be selected at the working point of the balance. It is suggested by USP General Chapter 1251 that the test weight should be a few percent of the capacity of the balance, e.g. close to but below 5% of the balance capacity.

An important implication of the statement above is the fact that it is not necessary to select a test load at – or close to – the working point of the balance. As an example, on a semi micro balance with an expected minimum weight of around 20 mg it is not required to use a test weight of 20 mg for the repeatability test. The requirement states that the test weight shall be in the operating range of the balance, in this case between around 20 mg and the maximum capacity of the balance. USP General Chapter 1251 suggests in its Table 1 to take a test load of a few percent of the nominal capacity of the balance, e.g. a 10 g load for a balance with a nominal capacity of 200 g. A test load that is sufficiently larger than the expected minimum weight is easier to handle and avoids handling errors being introduced during the repeatability test that could negatively influence the assessment of the instrument's performance.

## 4.4. Accuracy Requirement

Further to repeatability, USP General Chapter 41 stipulates a specific test with an acceptance criterion for accuracy.

"The accuracy of a balance is satisfactory if its weighing value, when tested with a suitable weight(s), is within 0.10% of the test weight value. A test weight is suitable if it has a mass between 5% and 100% of the balance's capacity."

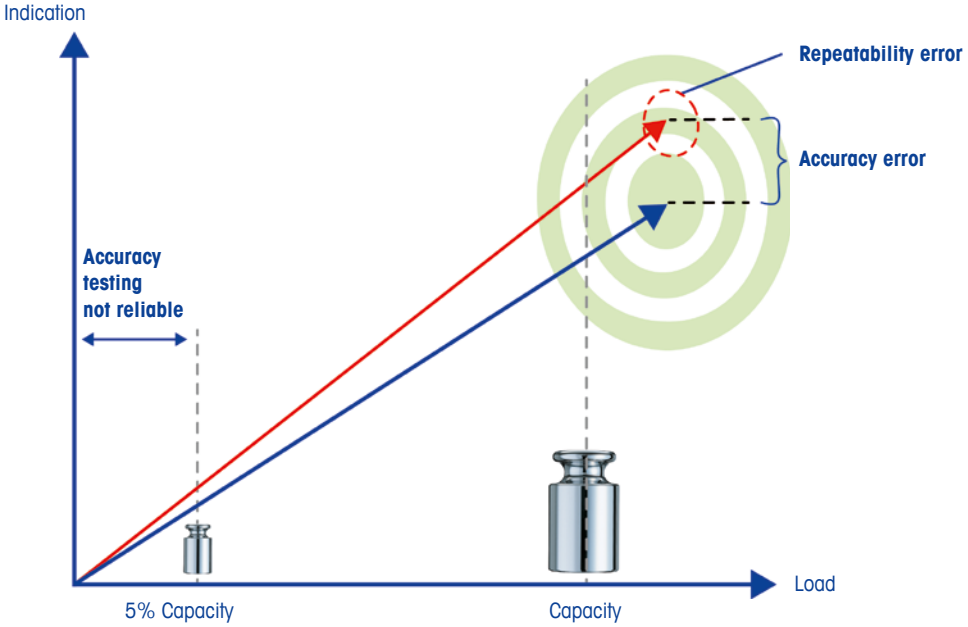



Figure 4: For accuracy testing, the test weight shall be between 5% and 100% of the balance capacity.

This accuracy test describes an assessment of the systematic error of the instrument. It needs to be noted that at the lower end of an analytical balance's measurement range, repeatability is the most dominant contribution factor to balance errors. Therefore, it is not meaningful to assess accuracy with small test weights as a potential systematic error would be masked entirely by the limited precision of the instrument, expressed by its repeatability. To avoid using small loads for testing systematic deviations, USP General Chapter 41 stipulates that the mass of the test load shall be at least 5% of the balance's capacity. To fulfill the accuracy requirement, the use of one single test weight is sufficient, made evident by the wording "[…] when tested with a suitable weight(s) […]". It is not a requirement to use multiple test weights to assess accuracy across the whole measurement range of the instrument.

As expressed by USP General Chapter 41 it is sufficient to use one test load to assess the accuracy of the balance. This is commensurate with a risk-based approach that is also described in General Chapter 1251 which states that performance qualification activities should take into account the criticality of the balance properties for the performance of the instrument. Usually, sensitivity is the most critical balance property when assessing the systematic error of the balance, so in practice very often only a sensitivity test is carried out to satisfy the accuracy test stipulated by General Chapter 41. As per General Chapter 1251, a typical sensitivity test load is at or sufficiently close to the capacity of the balance.

USP General Chapter 41 also stipulates a requirement for the accuracy of the test loads used for the test.

"The test weight's maximum permissible error (mpe), or alternatively its calibration uncertainty, shall be not more than one third of the applied test limit of the accuracy test."

If the test weight conforms to an mpe requirement (stated in a valid calibration certificate), it is sufficient to consider only the nominal mass value of the test weights for the accuracy test. Then, the user must ensure that the maximum permissible error does not exceed one third of the acceptance criterion. Alternatively, if the calibrated value (conventional mass value, stated in a valid calibration certificate) of the test load is considered, its calibration uncertainty shall not exceed one third of the acceptance criterion. If the acceptance criterion is set to 0.05% as per the information provided in USP General Chapter 1251, the maximum permissible error or alternatively the calibration uncertainty of the test weight shall not exceed 0.016%. Note that the acceptance criterion of 0.05% is explained later in Chapter 5.1 Performance Qualification.

The weight requirement is not very stringent, and in many cases weights of an OIML accuracy class of $F_1$ or $F_2$ or alternatively of an ASTM accuracy class 3 or 4 are sufficient. Let us make one example: A micro balance with a capacity of 20 g is tested with a 20 g test weight according to General Chapter 1251, thereby using its nominal mass value. The maximum permissible error of this 20 g test weight shall not exceed 0.016% of 20 g, i.e. 3.33 mg. A 20 g test weight of an OIML accuracy class $F_2$ has an mpe of ±0.8 mg (see OIML R111-1, Table 1 [13]), so it is more than sufficient to satisfy the weight accuracy requirement of General Chapter 41.

# 5 USP General Chapter 1251 "Weighing on an Analytical Balance"

USP General Chapter 1251 provides detailed information regarding qualification and operation of the instrument. While the chapter is specifically written for analytical balances, most of the information presented can also be applied for balances of higher capacity, such as precision balances or bench scales. Within this white paper, only two of the most important aspects of USP General Chapter 1251 are highlighted; which are performance qualification and safety factor.

## 5.1 Performance Qualification of Balances

As per USP General Chapter 1058 "Analytical Instrument Qualification" [14], performance qualification is the "documented collection of activities necessary to demonstrate that an instrument consistently performs according to the specifications defined by the user, and is appropriate for the intended use". It is evident from the definition that performance qualification is not a one-time activity but should be carried out periodically.

Calibration is a key activity during performance qualification and also required by USP General Chapter 41. However, USP General Chapter 1251 does not provide details on calibration but focuses on the remaining activities that are usually carried out by the user between calibrations, which are often referred to as user routine testing or simply, routine testing. It is recommended to carry out a risk analysis to assess the criticality of the weighing application for which the balance is used. Based on this risk analysis, the type and frequency of routine testing can be defined. Usually, sensitivity, linearity, eccentricity and repeatability are weighing parameters that could be considered in the risk analysis. But typically, only the weighing parameters that have a significant influence on the performance of the instrument are tested.

General Chapter 1251 provides further details on suggested performance tests for assessing the accuracy of the balance:

"Sensitivity, linearity, and eccentricity all account for systematic deviation; i.e. they limit the accuracy of the balance [. . .]. Because deviations are largely independent from each other, it is not likely that all deviations occur simultaneously and have the same algebraic sign. Therefore, the arithmetic addition of all individual deviations to assess the balance accuracy would constitute a rather conservative approach. A quadratic addition of the individual deviations is a more realistic approach. By allocating 50% of the weighing tolerance budget to the acceptance criteria of the individual properties, e.g. sensitivity, linearity, and eccentricity, analysts ensure adherence to the required weighing tolerance. Therefore, the acceptance criteria for the individual properties that account for the systematic deviations are set to the weighing tolerance divided by 2. These properties – or a subset of them – also can be taken to fulfill the accuracy requirement described in ⟨41⟩. In this case the acceptance criteria thus allow a maximum deviation of 0.05% for sensitivity, linearity, and eccentricity."

This statement explains why it is good practice to set the acceptance criterion of a sensitivity test to 0.05% instead of 0.1%, which is the acceptance criterion as per General Chapter 41 when the overall accuracy of the instrument ("the sum of all systematic deviations") is considered.

Because of the importance of routine testing for the day-to-day performance of the instrument, let us provide some more information on testing the individual weighing parameters.

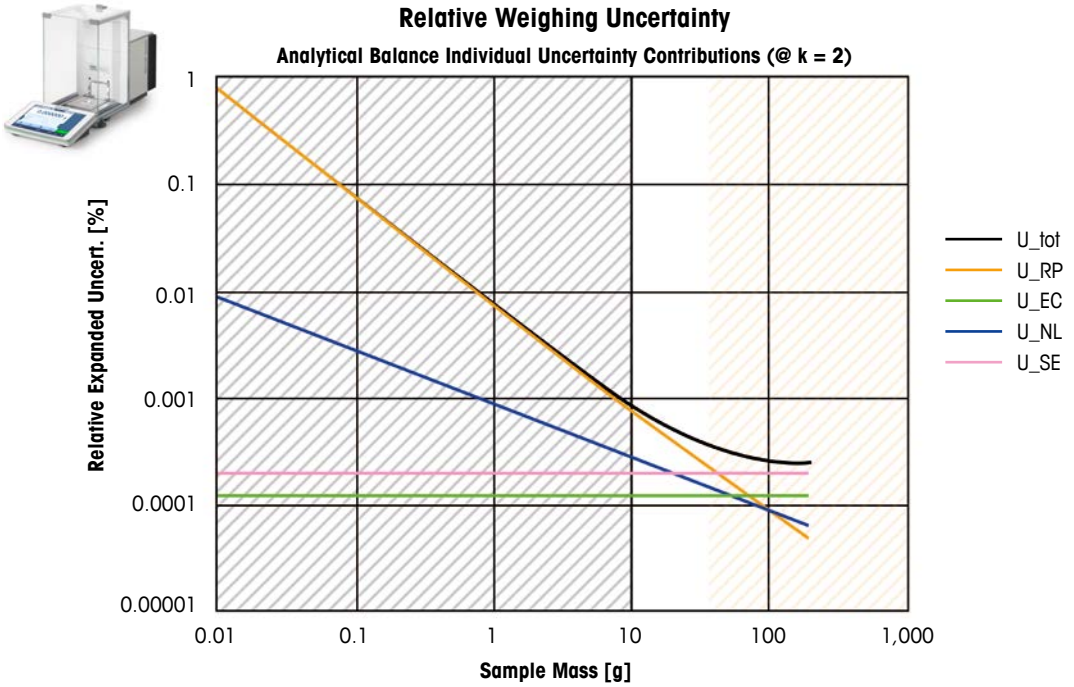



Figure 5: Relative expanded measurement uncertainty versus sample mass of an analytical balance with a capacity of 200 g (U_tot, thick black curve). The contributing components to uncertainty are also shown: repeatability (U_RP, orange), eccentricity (U_EC, green), nonlinearity (U_NL, blue) and sensitivity offset (U_SE, pink). Uncertainties are expanded with a factor of k = 2. Repeatability dominates uncertainty in the grey shaded region (at low sample mass). Sensitivity and eccentricity are the dominating factors in the orange shaded region (at high sample mass).

**a. Repeatability**

On laboratory weighing instruments, the majority of all samples being weighed, especially for quantitative analysis, satisfy the condition of being "small samples", i.e., samples with a net mass considerably smaller than the capacity of the weighing instrument. The measurement uncertainty of weighing instruments at the low end of the measurement range is governed by repeatability, see Figure 4. Consequently, with the majority of weighing processes, repeatability is the most significant contributor to uncertainty, and thus should

be tested by the user periodically. Repeatability is assessed preferably with a mass of a few percent of the maximum capacity. It is recommended to use the next available single weight denomination according to the OIML or ASTM classification which is smaller than or equal to 5% of the capacity of the weighing instrument. As repeatability is essentially constant for small sample masses (see Figure 3), this test can be considered representative for the whole lower capacity range. For critical applications on analytical and micro balances where small quantities are weighed, it is recommended to put an application-typical tare object (container, vessel, flask, etc.) on the weighing pan as a pre-load, especially if it has a large surface area. The tare object may increase the repeatability due to air currents and convection effects interacting with its surface [15] and thus the test with a realistic tare produces a more realistic result for repeatability.

**b. Sensitivity**

The sensitivity test is another important user test, which should be carried out regularly. The sensitivity deviation is linear with the load, and typically limits the accuracy of the instrument in the upper part of the weighing range, see Figure 5. Therefore, the sensitivity test is performed with a mass close to maximum capacity, preferably with one single test load. It is recommended to use the next available single weight denomination according to the OIML or ASTM classification [13, 16] which is smaller than or equal to the capacity of the weighing instrument. It is still widespread practice across many industries to test weighing instruments for systematic deviations at the so-called working point, i.e. with a load that reflects the amount of substance weighed or the object in a typical application. This practice is appropriate for working points in the upper part of the measuring range, however, it is not meaningful if the working point is in the lower part of the measuring range, due to the dominant influence of repeatability.

**c. Eccentricity**

An eccentricity deviation can also influence the performance of weighing instruments. Usually eccentricity deviations occur more frequently with weighing instruments in the production area due to different construction principles, high exposure of the device to mechanical stress or damage, and the higher likelihood that an object is placed non-centrally on the platform. Therefore, user tests for eccentricity are in general more important in the production area than in the laboratory. However, if relevant for the weighing application, the eccentricity test can be carried out with the same weight as for sensitivity testing.

**d. Linearity**

Linearity deviation tests usually have a smaller relevance, as the influence of linearity on weighing uncertainty is hardly dominant with any model of electronic weighing instruments, see Figure 5. Linearity is usually only tested when the weighing instrument is calibrated, rather than in routine testing between calibrations.

**e. Use of built-in weights**

In addition to testing weighing instruments with external weights, it is accepted practice and adjust the instruments by means of built-in reference weights. Such practice allows reducing the frequency of sensitivity tests with external reference weights [3, 17, 18].

At this point it is appropriate to comment on a very frequent misconception that has been prevalent in the industry for decades. Almost everybody in the pharmaceutical industry who works in quality control, talks about a "daily balance test" which usually assesses the accuracy of the balance (not the repeatability). It is anchored in the mindset of generations of people working with balances, who believe that it is mandatory test the balance on a daily basis. This dates back to the age of mechanical balances where - due to wear, tear and abrasion of critical mechanical components - a daily check was advisable. This is no longer the case with electronic balances, and specifically for electronic balances with a built-in weight, a daily test of sensitivity with an external reference weight is outdated practice. USP General Chapter 1251 and other references [17] now focus on a risk-based approach for testing. In fact, one state-of-the-art reference document [18] explicitly states:

"Historically the advice has been to perform daily checks however, as is the case for calibration, the frequency of these checks should be determined on the basis of the risk associated with the weighing application."

USP General Chapter 1251 also comments: "The frequency of the balance check depends on the risk of the application and the required weighing tolerance."

## 5.2 Consideration of a Safety Factor

The performance of a balance is influenced by a variety of factors (environmental changes, different operators, different tare vessels, etc.) and will therefore change over time. Periodic user tests are recommended by USP General Chapter 1251 to ensure that the balance is continuously fulfilling the stipulated requirements, i.e. that it is "fit for its intended purpose". One parameter that is specifically sensitive is repeatability, especially when weighing small amounts of substances on analytical or micro balances. In addition to the user routine tests, it is accepted practice for any kind of measurement instrument to apply a so-called safety factor. With regards to balances, the application of a safety factor is done by weighing only amounts of material that have sufficiently more mass than the minimum weight which was determined at a specific time, under environmental conditions present at that time by one authorized technician or user. As the minimum weight is calculated from repeatability, and repeatability is particularly sensitive to changes of the environment and user handling, it will fluctuate over time. By setting the smallest net weight to a value which is sufficiently higher than the minimum weight determined at one specific time under the prevalent environmental conditions it ensures that the instrument is "fit for purpose" irrespective of variations of the instrument performance. In other words, the smallest net weight the user would like to weigh during the normal usage of the balance should be sufficiently higher than the minimum weight that was determined at a specific time.

USP General Chapter 1251 states:

"Factors that can influence repeatability while the balance is in use include:

1. The performance of the balance and thus the minimum weight can vary over time because of changing environmental conditions.
2. Different operators may weigh differently on the balance—i.e., the minimum weight determined by different operators may be different.
3. The standard deviation of a finite number of replicate weighings is only an estimation of the true standard deviation, which is unknown.
4. The determination of the minimum weight with a test weight may not be completely representative for the weighing application.
5. The tare vessel also may influence minimum weight because of the interaction of the environment with the surface of the tare vessel.

For these reasons, when possible, weighings should be made at larger values than the minimum weight, i.e., the desired smallest net weight that the users plan to use on that balance should be larger than the minimum weight."

This concept is quantified with a safety factor. For applications within the scope of USP General Chapter 41, where minimum weight is calculated based on the standard deviation, the safety factor is defined as the quotient between smallest net weight and minimum weight. As an example, if the user wants to weigh 30 mg on a semi micro balance (i.e. when the smallest net weight is 30 mg), and the minimum weight was determined to be 15 mg, the safety factor is 2.

At this point it should be noted that the definition of the minimum weight as per USP General Chapter 41 and the concept of the safety factor as described above is a special scenario only valid for applications within the scope of this chapter. More generally, minimum weight can be calculated from the measurement uncertainty of a weighing instrument that is reported in the calibration certificate. In calibration, all relevant contributions to measurement uncertainty are included where repeatability is only one, though the most significant one for analytical and micro balances at the lower end of the measurement range. In other words, the calculation of

minimum weight based on USP General Chapter 41 is an approximation of the true minimum weight that can be derived from the measurement uncertainty of the device. However, for analytical and micro balances that are used for the applications within the scope of USP, the simplified approach stipulated by USP General Chapter 41 is valid due to the dominance of repeatability as compared to other uncertainty contributions.

Therefore, it must be stressed that for applications outside the scope of USP General Chapter 41, especially when precision balances or scales are considered, the calculation of minimum weight should not be done with the formula given by General Chapter 41 but the calculation should be done based on the measurement uncertainty of the device instead. It is beyond the scope of this White Paper to elaborate in detail on this topic, and we would like to refer to the respective literature [19].

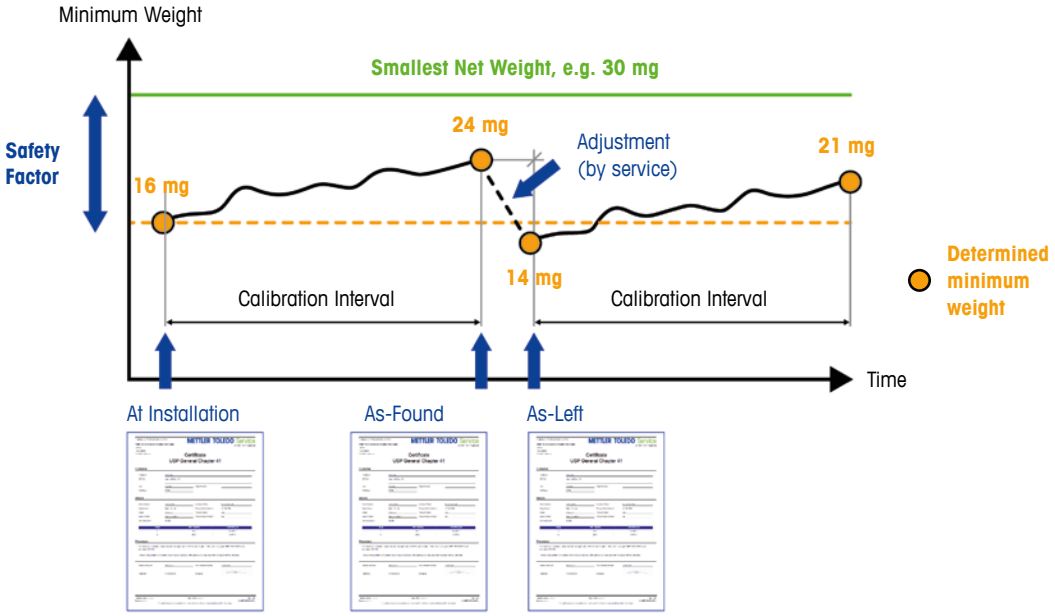



Figure 6: Variability of the minimum weight over time due to changing environmental conditions. The orange dots represent the minimum weight values as derived during determination of repeatability. In order to ensure that the smallest net weight of the weighing application is always larger than the minimum weight at the time of weighing, a safety factor should be applied. To ensure traceability of the weighing results, an as-found calibration is carried out before servicing/adjusting the instrument.

# 6 Summary

Accurate weighing is key for any quality relevant weighing application. USP has defined in its General Chapter 41 clear requirements that should ensure that any weighing application within the scope of USP does not significantly contribute to the overall error of the analysis. Besides using a calibrated balance, requirements for repeatability and accuracy are established and characterized by an assessment against a specified tolerance (0.10%). As an important consequence of the repeatability test, the minimum weight can be calculated which establishes the smallest amount of net substance that must be weighed in order to comply with the tolerance requirement. USP General Chapter 1251 elaborates more on the routine tests on the balance by applying a risk-based approach to performance verification activities. Furthermore, it elaborates on the variability of the balance's performance over time which leads to the concept of the safety factor. Applying the requirements of USP General Chapter 41 and the best practice from General Chapter 1251 ensures that the user can rely on the accuracy of the instrument over time.

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