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Use of laboratory balances in the pharmaceutical industry

Chapters <41> and <1251> of the United States Pharmacopeia (USP) Chapter 2.1.7. of the European Pharmacopoeia (Ph. Eur.)

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Abstract

Pharmacopoeias are collections of recognized and binding quality regulations that specify, among other things, test requirements and methods for the analysis of drugs. Both the European Pharmacopoeia (Ph. Eur.) and the United States Pharmacopeia (USP) contain specific chapters that deal with the use of laboratory balances. The chapters emphasize the criticality of weighing samples accurately in pharmaceutical analytical processes.

The aim of this white paper is to present the testing requirements for laboratory balances as described in the relevant chapters of the pharmacopoeias and the associated certificates offered by Sartorius Service.

United States Pharmacopeia (USP) requirements

The United States Pharmacopeia Convention is a scientific and non-governmental organization through which standards for drugs and related products are set in the United States. The United States Pharmacopeia (USP) (1), published annually, is the official pharmacopeia for the United States of America. It deals with the use of laboratory balances in two places. Firstly in Chapter <41> "Balances", and secondly in Chapter <1251> "Weighing on an Analytical Balance".

The requirements of Chapter <41> are mandatory for weighing applications where "accurate weighing" is required. Compliance is checked as part of cGMP audits by the Food and Drug Administration (FDA). Failure to comply will result in audit discrepancies.

Chapter <1251>, on the other hand, like all USP chapters from 1000 to 1999, is informal in nature, i.e., it provides important suggestions. However, the implementation of the recommendations made on the testing and use of balances is voluntary.

Chapter <41> of the United States Pharmacopeia

Chapter <41> describes specific criteria for all balances used for the "accurate sample weighing" of materials. The objective of Chapter <41> is to ensure that the error introduced by the weighing application for "accurately weighed" material is reduced to an acceptable or negligible level, thereby ensuring that the effect on the total error remains manageable. The respective chapters on the manufacture of medicinal products or ingredients explicitly state if and which substances must be "accurately weighed" within the meaning of the USP and thus if the corresponding balance must comply with the requirements set out in Chapter <41>.

USP Chapter <41> contains three specific requirements for balances. Firstly, balances must be calibrated over the entire working range. In addition, they must meet tolerance requirements for testing repeatability and accuracy. The repeatability test is used as a basis for checking if the "desired smallest net sample weight" can be made within the tolerance requirements of the USP.

Calibration
USP Chapter <41> requires that accurate weighing of samples must be performed only on balances that are calibrated over the entire working range. However, how and in which cycles the calibration has to be performed is not more closely defined. Sartorius recommends regular calibration in every case, based on the criticality of the application (see also the separate white paper "Test intervals and tolerances" (2)). The calibration result should be documented in every case in a calibration certificate.

Calibration certificates from accredited providers offer the greatest possible security here, as they have a high level of international recognition and ensure traceability of the measurement results to national standards. See also the separate white papers "Calibration certificates from accredited suppliers" (3), "The calibration certificate according to EURAMET cg-18" (4) and "Calibration guideline EURAMET cg-18" (5).

Repeatability and minimum sample weight
The repeatability requirement limits the weighing range to a usable working range by defining a minimum sample weight. Weighing must not be carried out below the minimum sample weight.

Repeatability testing is performed by weighing a test weight at least ten times. The weight of the test weight must be within the working range of the balance, but does not have to be calibrated according to Chapter <41>. Similarly, repeatability as per USP Chapter <41> does not explicitly require the use of a small weight because it is assumed that repeatability is independent of the test load used. Chapter <41> only requires that the test load be within the working range (i.e. not less than the minimum sample weight). For practical reasons (as for all repeatability measurements), Sartorius still recommends selecting a one-piece test load here if possible. On this point, the requirement set out in USP Chapter <41> differs from the recommendation in Chapter <1251>. Here it is recommended that the size of the test weight for the repeatability test should not exceed a few percent of the weighing range of the balance.

Repeatability is considered satisfactory if two times the standard deviation of the measured values divided by the smallest net weight to be weighed on the balance ("desired smallest net weight") is not greater than 0.10%. The standard deviation as the result of the repeatability measurement is therefore set in relationship to the desired smallest net sample weight. If the USP requirement is fulfilled for the "desired smallest net sample weight", this ensures that the USP tolerance requirement for repeatability is also fulfilled for each initial sample weight above this value, since the relative error becomes smaller and smaller as the sample weight increases. The general rounding rule of the USP should be noted in this context: The result is first rounded to the number of digits of the acceptance criterion. With the acceptance criterion of 0.10% specified here, a result of e.g. 0.1049% is rounded down to 0.10%, so the repeatability test is therefore considered to have been passed in this case. On the other hand, if the result is 0.1050%, the balance is rounded up to 0.11%, so that in this case the balance does not pass the repeatability test.

The repeatability test therefore restricts the working range of the balance downwards (see also separate white paper on the subject of minimum sample weight (6)). The smallest possible sample weight on a balance, or minimum sample weight (M), is 2000 times the standard deviation of the repeatability measurement; it represents the start of the working range of the balance. Thus, if the standard deviation s is, for example, s = 0.00015 g, the smallest possible sample weight M is M = 0.3000 g = 300 mg.

USP chapter <41> defines another criterion if a standard deviation s is very small. This relates to the scale interval (d) of the balance and states that if the standard deviation $s < 0.41\ d$, the minimum load is 2000 x 0.41 d. The minimum sample weight is therefore limited to the smallest possible value of 820 d. For a four-digit analytical balance with d = 0.0001 g, for example, this means that the minimum sample weight can never be less than 0.0820 g or 82 mg.

Since the repeatability is significantly influenced by the conditions at the place where the balances are installed, the test must be performed at the place of installation and should be checked regularly.

It is generally not advisable to adjust the "desired smallest sample weight" to the minimum sample weight value resulting from the last repeatability measurement; instead, this should always be defined on the basis of the actual laboratory requirements. As standard deviation is a statistical quantity and is subject to slight variations in each test, setting the "desired smallest sample weight" to the minimum sample weight would mean that the sample weight that can be determined on a balance would change with each test. For example, if users obtain the standard deviation of s = 5 µg in a repeatability measurement and set the minimum sample weight for their balance to 2000 x s = 10 mg accordingly, they run the risk that in a subsequent repeatability measurement where the standard deviation changes to, say, s = 8 µg, the minimum sample weight will increase to 2000 x s = 16 mg. If, after the first measurement, weighing was carried out down to the minimum sample weight, it would be questionable whether preceding weights between 10 mg and 16 mg complied with the requirements of the USP. It is therefore recommended, as also described in USP Chapter <41>, that the "desired smallest net sample weight" be determined by the user according to laboratory requirements and validated during repeatability testing.

On balances used under USP regulations, the validated "minimum desirable net sample weight" should be clearly marked. Some Sartorius balances allow you to enter this in the service menu. Net sample weights below the "minimum desirable net sample weight" are then displayed with a warning symbol.

It should also be reiterated here that the mass of the tare vessel is not taken into account for the minimum sample weight. This means that the minimum sample weight applies over the entire weighing range of the balance, regardless of the tare load. As such, placing a weighing vessel on the balance precludes weights below the minimum sample weight; rather, the net weight of each sample must be equal to or greater than the minimum sample weight, regardless of the tare weight.

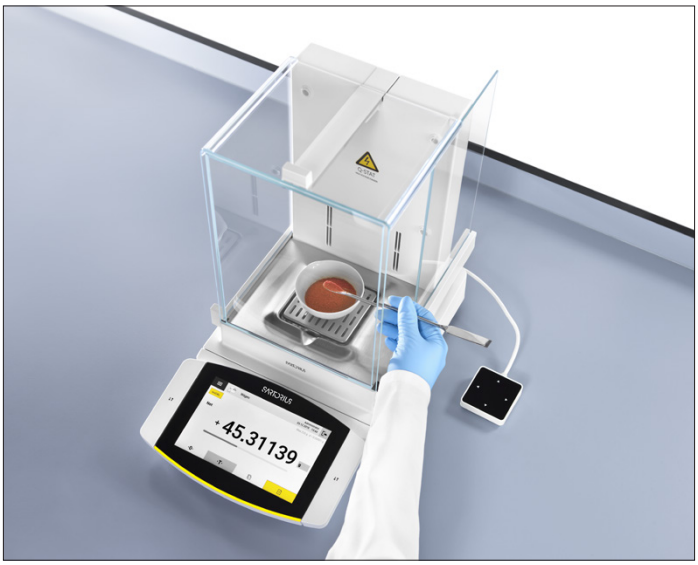

Figure 1: Analytical weighing on a Cubis II balance.

Accuracy

The accuracy requirement from Chapter <41> is a general requirement, i.e. if the requirement for accuracy is not met, the balance in its current state is not suitable for the accurate weighing of sample substances.

According to USP Chapter <41>, the accuracy of a balance is sufficient if the weight value indicated by the balance is within 0.10% of the "true" test weight value when tested with one or more suitable weights.

A test weight is suitable if it has a mass between 5% and 100% of the maximum load for the balance, and if the maximum permissible error (MPE) of the test weight does not exceed one third of the applied test limit for the accuracy test (i.e. 0.033%). The test weight requirement is independent of the scale interval (*d*) of the balance. Specifically, for example, for a 5 g test weight, the requirement means that the error must not exceed 0.00167 g (1.67 mg). According to the error limits of OIML R111, test weights of accuracy class F_2 still meet this requirement (for weights ≥ 1 g). Here, an MPE of ± 0.5 mg applies for a test weight of 5 g. According to ASTM E-617 tolerances, test weights of accuracy class 4 safely meet the requirements (here, a 5 g weight of accuracy class 4 has a permissible MPE of ± 0.36 mg). Since the USP requirement for test weights is formulated in relative terms, the requirements for small test weights are very strict. However, for test weights of ≥ 0.5 g, weights of classes E_2 and F_1 can be used without any problems. For practical reasons, Sartorius recommends selecting a one-piece test load here as well, if possible.

Sartorius USP <41> certificate

With a Sartorius USP <41> certificate, you receive a certificate showing equipment testing to USP Chapter <41>. On the first page, in addition to the customer and equipment data, the calibration status of the balance is listed with the last calibration date and calibration certificate number, if this information is known.
The outcome of the repeatability and accuracy check is also clearly displayed in one block of results. Whether the customer's "desired smallest net sample weight" has been met is specified. In addition, the working range of the balance (minimum sample weight to maximum load) is listed.
The test location is named on the second page. The important thing to note here is that the measurement is only valid at this location. When changing the location of the device, it is mandatory to repeat the test as described above. Also listed on the second page are the test equipment used and the accuracy class according to OIML R111 or ASTM E-617. Furthermore, all measured values and the evaluation are documented here again.

On the third page, the working range of the balance and the desired smallest net sample weight are graphically displayed in a double-logarithmic diagram. This makes it possible to identify quickly and easily whether the desired smallest net sample weight is within the working range defined by the USP requirements. If the desired smallest net sample weight is within the working range, the sample can be weighed safely under USP conditions.
Note: Premium balances from the Cubis series support the verification of the minimum sample weight according to USP <41>, using a dedicated APP.

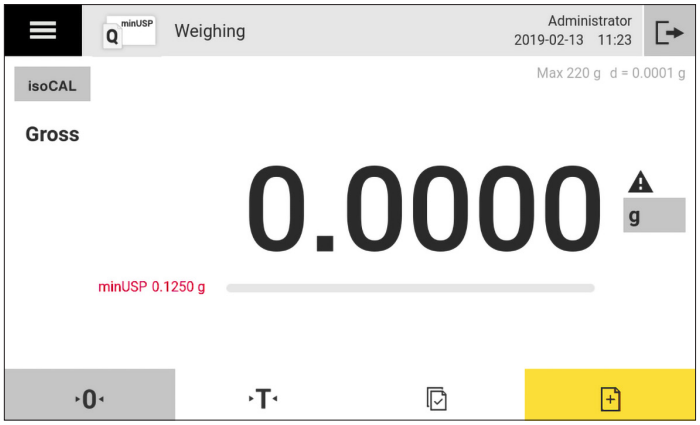

Figure 2: Indication of the minimum sample weight for a Cubis series balance.

Chapter <1251> of the United States Pharmacopeia

Chapter <1251> of the USP is entitled "Weighing on an Analytical Balance" and contains detailed information on the qualification and operation of electronic balances.
In the introduction, it is explicitly stated that the recommendations are not only valid for balances on which "accurate sample weighing" is performed, but for all balances used in settings where analytical procedures are performed.

Many of the recommendations mentioned in chapter <1251> are of a rather general nature, as also described in the Sartorius white paper "Reliable Weighing Results" (7). The following, therefore, focuses specifically on the recommended "Performance Qualification" test.

Performance Qualification

The "Performance Qualification" section sets out specific metrological tests and tolerances against which balances should be tested on a regular basis. The test frequency should be based on the criticality of the application, i.e. it should be risk-based (see also the separate white paper "Test intervals and tolerances" (2)).

Specifically, four performance tests are recommended for evaluating a balance:
- Sensitivity
- Linearity
- Eccentricity error
- Repeatability

Sensitivity, linearity, and eccentricity errors all contribute to the systematic deviation of a balance, thus limiting its accuracy. The testing of these parameters represents general requirements, i.e. if the set requirements are not met, the balance is not suitable for use. Provided that accurate weighing is carried out on balances in accordance with USP Chapter <41>, an acceptance criterion of 0.05% applies to the above tests. For weighing in other applications, the acceptance criterion can be defined by the customer.

As in Chapter <41>, the maximum permissible error (MPE) of the test weight must not exceed one-third of the applied test limit (i.e. 0.016% in this case), which specifically means that for test weights of ≥ 0.5 g, tests can be performed with weights of accuracy classes F_2 (OIML R111) or better. When using test weights of < 0.5 g, the requirement may not be met.

The fourth recommended repeatability test, like the repeatability test in Chapter <41>, restricts the working range of the balance downward to a minimum sample weight.

The general rounding rule of the USP must also be observed for these tests, in which the result is first rounded to the number of digits of the acceptance criterion and only then is the comparison made with the acceptance criterion.

Sensitivity
Before testing the sensitivity, a balance should always be calibrated (if possible with an internal calibration weight).

When testing sensitivity, a test weight is placed on the balance once. If possible, the test should be performed with a one-piece weight in the range of the maximum load. The Sartorius recommendation here is to use a test weight with min. 80% of the maximum load. For a balance with a maximum load of 120 g, this means a test with a 100 g test weight.

The deviation between the weight value of the test weight and the displayed value of the balance must not exceed the acceptance criterion (0.05% for balances on which accurate weighing is performed). For the above example with a 100 g test weight, the display rounded to two decimal places must therefore be between (and including) 99.95 g and 100.05 g for the test to be passed.

Eccentricity
In the eccentricity test, a test weight is placed on the weighing pan, first in the center and then in four off-center positions. If possible, the test should be performed with a one-piece weight at a minimum of 30% of the max. The test is performed in the same way as for the calibration according to EURAMET-cg-18 (see separate white paper): "Calibration Guideline EURAMET cg-18 (5)).

The largest deviation of the weight value in an off-center position from the center load must not exceed the acceptance criterion (0.05% for balances on which accurate weighing is performed). This means, for example, no more than 0.025 g when using a 50 g test weight.

Linearity
When testing linearity, a load value is applied to the balance at several points over the entire weighing range. Linearity describes the proportionality between the applied loads and the displayed values. The test is performed in the same way as for the drafting of a balance test report and is set out in the separate white paper "Testing and evaluating balances against different tolerance requirements" (8).

The deviation from the linearity characteristic curve must not exceed the acceptance criterion (0.05% for balances on which accurate weighing is performed) at any test point during this test. This test is therefore sensitive, especially in the lower weighing range of the balance.

Repeatability
The repeatability test under Chapter <1251> is identical to the repeatability test under Chapter <41>. However, there is a difference in the choice of the test weight. Chapter <1251> explicitly requires a small test weight here (<10% of max). Sartorius recommends a one-piece test weight here. For critical applications, a typical tare object (container, vessel, etc.) can be placed on the weighing pan as a pre-load for testing.

Sartorius USP <1251> certificate
The Sartorius USP <1251> certificate documents compliance with the acceptance criteria as described in chapter <1251> of the USP.

Requirements from chapter 2.1.7. of the European Pharmacopoeia

The European Pharmacopoeia (Ph. Eur.) (9) contains standards for the quality control of medicinal products. In the *"Convention on the Composition of a European Pharmacopoeia," the contracting states undertake "to take the necessary measures to ensure that the monographs adopted on the basis of Articles 6 and 7, which will constitute the European Pharmacopoeia, constitute official standards applicable within their territories."*

Chapter 2.1.7. entitled "Balances for analytical purposes", which first appeared in Supplement 10.6 (07/2021) to the Ph. Eur., describes principles for the use of balances used in analytical procedures. In explicit terms, weighing procedures performed as part of tests designed to determine compliance with a monograph must be performed in accordance with the principles set forth in this chapter.

Many of the recommendations are of a general nature, as also described in the Sartorius white paper "Reliable Weighing Results" (7).

Equipment Performance

Balances must be calibrated regularly in accordance with Chapter 2.1.7. and checked by conducting performance tests between calibrations to ensure compliance with predefined requirements. The user must define the frequency of calibrations and tests in the quality management system. Sartorius recommends matching the frequency to the criticality of the application (see also the separate white paper "Test intervals and tolerances" (2)).

Calibration

Calibration by the user or a suitable service provider must be performed regularly according to Chapter 2.1.7. The aim of calibration is to ensure the traceability of the measurement results to national standards. In this case, Sartorius recommends calibration by a calibration laboratory accredited to ISO | IEC 17025, as its calibration certificates are internationally recognized as proof of traceability (see also the white paper "Calibration certificates from accredited providers" (3)).

To ensure traceability of the measurement results after maintenance or adjustment work, repairs or a change of location of the balance, performing an input (as found) calibration is explicitly required before this work. Sartorius offers input (as found) calibrations for all calibrations. Both the input (as found) and output (as left) calibrations are documented in a calibration certificate. See also the separate white papers "The calibration certificate according to EURAMET cg-18" (4) and "Calibration guideline EURAMET cg-18" (5).

Performance testing

The purpose of performance testing is to determine the random and systematic error of a balance and thus verify the precision and accuracy of the balance. Two performance tests are required in this context as per Chapter 2.1.7: firstly, repeatability, to check the precision of the balance, and secondly, sensitivity, to check the accuracy of the balance. Before testing the sensitivity, a balance should always be adjusted (if possible with the internal adjustment weight).

For the tests according to Ph. Eur., the result is first rounded to the number of digits of the acceptance criterion and only then is the comparison with the acceptance criterion made.

Repeatability

When weighing small quantities, the measurement uncertainty of the balance is determined in particular by the random error. This is estimated by specifying the standard deviation. The repeatability test from Chapter 2.1.7. is largely identical to the repeatability test described in USP Chapter <41>. The only significant difference is the test load to be used. In accordance with Chapter 2.1.7. of the Ph. Eur., this should be ≤ 5% of max but at least 100 mg.

When determining the standard deviation, the test weight is weighed at least ten times in succession, with the balance set to zero between each weighing.

Balance type	Scale interval (readability), *d*
Precision balances	= 10^{-1} g to 10^{-3} g = 100 mg to 1 mg = 0.1 g to 0.001 g
Analytical balances	≤ 10^{-4} g = 0.1 mg = 0.0001 g
Semi-micro balances	= 10^{-5} g = 10 µg = 0.01 mg = 0.00001 g
Micro balances	= 10^{-6} g = 1 µg = 0.001 mg = 0.000001 g
Ultra-micro balances	= 10^{-7} g = 0.1 µg = 0.0001 mg = 0.0000001 g

Table 1: Balance types according to Chapter 2.1.7. of the European Pharmacopoeia (9).

As in USP Chapter <41>, repeatability is considered satisfactory in European Pharmacopoeia Chapter 2.1.7. if two times the standard deviation of the measured values divided by the smallest net weight (m_{snw} = smallest net weight) to be weighed on the balance is not greater than 0.10%.

$$\frac{2 \times s}{m_{snw}} \times 100 \leq 0{,}10$$

In the case of a standard deviation of < 0.41 *d*, the standard deviation is also replaced here by 0.41 *d*, so that even under the European Pharmacopoeia the minimum sample weight m_{snw} on a balance cannot go below 820 *d*.

Sensitivity

The accuracy of the balance is checked when testing the sensitivity. Since accuracy is also affected by linearity and eccentricity, an acceptance criterion of 0.05% applies to sensitivity testing, while linearity and eccentricity testing may be omitted.
As with the accuracy test in USP Chapter <41>, the sensitivity test is a general requirement, i.e. if the requirement is not met, the balance is not usable in its current state.

During the test, a one-piece test weight of ≥ 5% of the max is placed on the balance once. If the deviation is in the range of ≤ 0.05%, the test is considered to have been passed. The accuracy requirements for the test weight are identical to the requirements of Chapter <41> of the USP, i.e. test weights of accuracy classes F_1 (according to OIML R111) or Class 4 (according to ASTM E-617) are generally sufficient here as well.

Use of internal test weights

Chapter 2.1.7. of the European Pharmacopoeia explicitly recommends the use of internal calibration/adjustment equipment, which most modern laboratory balances have today. Their use can reduce the frequency of sensitivity tests with external reference weights. This explicitly specifies that when using internal calibration/adjustment equipment, a daily sensitivity check using an external reference weight is not required. Nevertheless, Chapter 2.1.7. recommends performing a sensitivity test with an external test weight on a regular basis in order to detect possible problems with the integrated weights.

Sartorius Ph. Eur. 2.1.7. certificate

A certificate documenting compliance with the acceptance criteria according to Ph. Eur. 2.1.7. will be available from mid-2021.

Figure 3: Weighing out the smallest amounts of substances on a microbalance.

Sartorius Recommendation

- Balances used in the pharmaceutical field for analytical procedures must be checked according to the provisions of Chapter <41> of the USP or Chapter 2.1.7 of the European Pharmacopoeia.
- Balances must be calibrated regularly. Accredited calibration, which allows traceability of the weighing results to national standards, is strongly recommended.
- Determine a minimum sample weight that is also adhered to with the following provisions and have it checked regularly.
- The smallest sample to be weighed on the balance should be clearly documented on the balance.
- Performance tests should be carried out regularly by the user between calibrations. These should be based on the criticality of the application.

This white paper is part of the white paper bundle "Best Practice Guide: Lab Weighing". To be able to dynamically add updates and corrections and at the same time giving users as clear a reference as possible, for example in their QM documentation, versions are provided.

Version history

Version	Date	Changes
1.0	March 2021	Initial version
1.1	October 2021	Correction of typos

Bibliography

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