SARTORIUS

Frequently Asked Questions (FAQ)

On the Chapter 2.1.7 "Balances for analytical purposes" of the European Pharmacopoeia (Ph.Eur.)

1. When does the new Chapter 2.1.7 "Balances for analytical purposes" come into effect and which weighing tasks are affected?

The new chapter was published in July, 2021 and becomes effective on the 1st of January, 2022. The new chapter is mandatory for any analytical weighing procedure described in a Ph.Eur. monograph.

2. What is the European Pharmacopoeia about and am I affected by this new chapter?

The Ph.Eur. is published by the European Directorate for the Quality of Medicines & Healthcare (EDQM) and is "a single reference work for the quality control of medicines in the signatory states of the Convention on its elaboration." It is a collection of monographs describing quality standards for ingredients, dosage forms, and methods of analysis for medicines for both human and veterinary use. These standards are defined to ensure the quality of the pharmaceutical products.

The Ph.Eur. is the legally binding reference for all pharmaceutical companies placing pharmaceutical products in the market of European member states. This means it is not only relevant for European pharmaceutical companies but for any producers of medicines and | or substances for pharmaceutical use who export into the European market. Chapter 2.1.7 affects companies in these industries if they use "balances for analytical purposes."

3. Are there any specific requirements to make a balance model compliant with Chapter 2.1.7 of the European Pharmacopoeia?

There is nothing that makes a particular balance model compliant or non-compliant with Chapter 2.1.7 of the Ph.Eur. There are however some general requirements listed in Chapter 2.1.7, such that it must be ensured "that the installation and operating conditions do not have a negative impact on the performance of the balance." The only specific requirement is that the balance must be grounded, which is however usually the case via the electrical supply for state-of-the-art models.

4. What is the meaning of "analytical purposes?" Are preparational weighings (e.g. preparing buffer solutions) also subject to the regulation?

The chapter specifies that "Any weighings performed as part of tests prescribed to establish compliance with a monograph of the Ph.Eur. must be carried out according to the principles outlined in this chapter." When determining whether a balance is affected, users should consider this statement and if in doubt, determine whether the result of the weighing is really relevant for the assessment of compliance with the corresponding monograph or not. It should also be noted that the preparation of a buffer solution can be affected by the new chapter of the European Pharmacopoeia.

5. What are the requirements of Chapter 2.1.7 concerning the calibration of a balance?

During calibration, a relationship is established between the known values of the test weights and the associated indicated values of the balance. Chapter 2.1.7 requires that "…instruments must be periodically calibrated […] by the user or by a suitable competent body."

There are three requirements stipulated in Chapter 2.1.7 of the Ph.Eur.:

a. Calibration must establish the traceability of measurement results to the SI units.
b. Calibration results must include an associated measurement uncertainty.
c. It is recommended to perform an "as found" calibration before any maintenance operation that significantly alters measurements and to perform a second calibration ("as left") afterwards. Significant operations according to Chapter 2.1.7 include repairs, transfer of the balance to another location, or mechanical adjustments.

We recommend having the calibrations conducted by an accredited calibration laboratory, as in this case, competence is ensured through the accreditation and the above requirements are fulfilled.

6. How does the Cubis® II support compliance with Chapter 2.1.7 of the European Pharmacopoeia?

The pharma software package available for Cubis® II balances helps customers successfully meet the requirements set by both the new Ph.Eur. Chapter 2.1.7 and the USP, chapter 41.

The USP Advanced QApp is used to check the performance of balances and offers a guided workflow to determine minimum weight acc. to USP chapter 41 or the new Ph.Eur. Chapter 2.1.7. The minimum weight application monitors the weight determined by the USP Advanced QApp and checks it against permitted ranges as per different guidelines. Both applications can be paired with add-on advanced software programs for determining and monitoring the measurement uncertainty.

7. Chapter 2.1.7 of the European Pharmacopoeia requires performance checks—what is the purpose?

Performance checks are carried out to evaluate the random and systematic error of a balance. These checks focus on repeatability and sensitivity.

8. What are the requirements on repeatability and sensitivity?

For the repeatability check, a single-piece test load is used that is not bigger than 5% of the maximum capacity of the balance, but at least 100 mg. This weight is placed at least 10 times on the weighing pan. Before each measurement the balance is set to zero. The repeatability is satisfactory if two times the standard deviation of the measured values divided by the smallest net weight defined by the user is not greater than 0.10%. In cases where the standard deviation (s) is smaller than $0.41 \times d$ (where d is the actual scale interval of the balance), s is replaced by $0.41 \times d$.

For the sensitivity check, a single-piece test load with a weight between 5% and 100% of the capacity of the balance is placed on the balance. The sensitivity is satisfactory if the difference between the indicated value of the balance and the nominal weight of the test load (or its conventional mass, see Question #15) is not more than 0.05%.

9. What is the smallest possible sample weight that can be weighed in compliance with Chapter 2.1.7 of the European Pharmacopoeia?

The smallest possible sample weight on a balance is limited by the minimum weight (m_{min}), which is 2000 times the standard deviation of the repeatability measurement. Thus, if the standard deviation s is, for example, 0.00015 g, the minimum weight is m_{min} = 0.3000 g = 300 mg.

The additional requirement of replacing the determined standard deviation with $0.41 \times d$ in cases where the standard deviation is less than $0.41 \times d$ (where d is the actual scale interval of the balance), sets the smallest possible minimum weight that can be weighed on a balance at $820 \times d$. For example, for a four-digit analytical balance with d = 0.0001 g, this means that the smallest possible minimum weight can never be less than 0.0820 g or 82 mg.

10. Can smaller samples be weighed on the balance when using a tare weight that is bigger than the minimum weight?

The mass of a tare vessel is not considered for the minimum sample weight. This means that the minimum weight applies to net loads over the entire weighing range of the balance, regardless of the tare load. Independent from the use of a tare vessel, the net weight of each sample must be equal to or greater than the minimum weight.

11. How do I define the smallest net weight?

The smallest net weight is defined by the user as the smallest net amount of substance that will be weighed on the balance. This means it should be defined based on the actual laboratory requirements.

It is generally not advisable to adjust the smallest net weight to the possible minimum weight value resulting from the repeatability measurement as the standard deviation is a statistical quantity and is subject to slight variations in each test. For example, if users obtain the standard deviation of $s = 5$ µg in a repeatability measurement and define the smallest net weight for their balance to $2000 \times s = 10$ mg accordingly, they bear the risk that in a subsequent repeatability measurement where the standard deviation changes to $s = 8$ µg, for example, the minimum weight will increase to $2000 \times s = 16$ mg. If after the first measurement, weighing was carried out down to the minimum weight, it would be questionable whether preceding weights between 10 mg and 16 mg complied with the requirements of the European Pharmacopoeia.

12. Are the Ph.Eur. Chapter 2.1.7 and the United States Pharmacopeia (USP) chapter <41> similar? What are the main differences between the two chapters?

There are differences in the applicability of the respective chapters, which is somewhat broader in the Ph.Eur. ("analytical purposes") as compared to the USP ("when substances must be accurately weighed").

- The Ph.Eur. explicitly requires the traceability of measurement results to the SI unit.
- The Ph.Eur. explicitly states that calibration of the balance must include a measurement uncertainty calculation.
- For the repeatability check, the Ph.Eur. requires a test load that is not bigger than 5% of the maximum capacity of the balance, but at least 100 mg, while the USP does not give any comparable restrictions.
- The "sensitivity" check of the Ph.Eur. is similar to the "accuracy" check of the USP, but the acceptable deviation of 0.05% in the Ph.Eur. is smaller than 0.10% in the USP.
- For both performance checks, the Ph.Eur. explicitly requires single piece test loads, while this is not the case in the USP.

13. Can I conduct the performance checks by myself or should they be done by an external service provider?

Generally, the performance checks can be carried out by the user. We recommend, however, having external service providers conducting the performance check additionally from time to time to have some independent external confirmation of their own results.

The Sartorius Ph.Eur. certificate documents compliance with the acceptance criteria as described in Chapter 2.1.7 of the Ph.Eur. This also includes the documentation of the minimum weight.

14. How often should performance checks be conducted?

Similar to USP <41>, the frequency is not defined within Chapter 2.1.7 of the Ph.Eur. and must be defined by the user, stating that "The frequency of the qualification and performance checks is defined in each user's quality management system." We recommend defining the test frequency based on the risk of the particular application.

15. Which weights are allowed for the "sensitivity" performance check?

Weights must comply with either OIML R-111 or ASTM E-617. The nominal weight value can generally be used if the maximum permissible error (MPE) of the particular weight is not bigger than one third of the test specification ($MPE \leq 0.05\%/3$). This is fulfilled for all weights ≥ 500 mg that are of Class F1 or better according to OIML R-111. For heavier weights, Class F2 or M1 may be sufficient, but the above criterion should be applied for the particular case.

Traceability of the weights is required for this test, which means that they have to be calibrated periodically with a recalibration interval that has to be defined by the user.

16. Which "Max" has to be considered for the choice of test loads for MR and MI devices?

Multi-range (MR) and multi-interval (MI) balances comprise more than one "Max" value, and are typically listed as "Max1 = 120 g | Max2 = 220 g" or "Max = 120 g | 220 g." When there is more than one Max value, the Ph.Eur. does not clearly define whether the "5% of Max" (as the upper limit for the repeatability test load and the lower limit for the sensitivity test load, respectively) applies to Max1 or Max2. In this situation, we recommend use of weights that fulfill the requirements for both Max values. For the example provided above, a test load of 5 g used in the repeatability test fulfills the requirement "≤ 5% of Max" for both Max values; similarly, a sensitivity test load of 100 g fulfills the requirement "≥ 5% of Max" for both Max values (and can still be used for both ranges as it is ≤ Max1).

For MR and MI balances, it should be sufficient to perform both performance checks in the first | finest range only.

17. Is it possible to cover the performance check requirements with a calibration certificate according to EURAMET cg-18?

Most accredited calibration laboratories perform calibrations of weighing instruments according to the "EURAMET cg-18" guidelines. Such calibrations include a repeatability measurement as well as a measurement of the error of indication. While the results of the latter can be used for an assessment of the sensitivity requirement, the repeatability measurement of such calibrations (as required by the calibration guideline) is usually performed with test loads of at least approximately 50% of Max, which contradicts the requirement "≤ 5% of Max" of Chapter 2.1.7.

18. I use a weighing vessel in my weighing process. Should it be taken into account as a tare load during performance tests?

Chapter 2.1.7 explicitly allows repeatability and sensitivity tests to be performed with the weighing vessel or a comparable tare load. By including the weighing vessel in the performance experiment, it is possible to determine its influence on the performance of the balance. Sartorius Service can consider a tare load when creating a test report in accordance with the Ph.Eur. The tare load will be noted in the test certificate.

Germany
Sartorius Lab Instruments GmbH & Co. KG
Otto-Brenner-Strasse 20
37079 Goettingen
Phone +49 551 308 0

USA
Sartorius Corporation
565 Johnson Avenue
Bohemia, NY 11716
Phone +1 631 254 4249
Toll-free +1 800 635 2906

For additional information,
visit www.sartorius.com

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