Use of laboratory balances in the pharmaceutical industry

SARTORIUS

Taube A, Hage E, Haller J, Ludolph N

Introduction

Pharmacopeias set out pharmaceutical regulations, including rules for testing and analysing drugs. The European Pharmacopoeia (Ph. Eur) and United States Pharmacopeia (USP) both have chapters addressing the use of laboratory balances.

Requirements from Chapter 2.1.7 of the European Pharmacopoeia

The European Pharmacopoeia (Ph. Eur.) contains standards for the quality control of pharmaceutical products.

Chapter 2.1.7, 'Balances for analytical purposes' first appeared in Supplement 10.6 (07/2021), providing principles for use of balances in analytical procedures. The new chapter is mandatory for any analytical weighing procedure described in a Ph. Eur. monograph from **January 1, 2022.**

Equipment performance

- According to Chapter 2.1.7, balances must be calibrated regularly and additionally be checked through performance tests between calibrations.
- The user must define the frequency of calibrations and tests in the quality management system.

Calibration

- Regular calibration is required to ensure traceability of the measurement results to national standards.
- 'As found' calibration should be carried out before significant operations like maintenance, adjustment, relocation or repair of the balance.

Performance testing

- Performance testing helps define the random and systematic error of a balance – verifying precision and accuracy.

Chapter 2.1.7 requires two performance tests:

1. **Repeatability**
2. **Sensitivity**

Repeatability

When weighing small quantities, measurement uncertainty is dominated by the random error (estimated by specifying standard deviation).

Repeatability tests in Chapter 2.1.7 and USP Chapter<41> are largely identical. One exception is test load – Ph.Eur. specifies this should be no more than 5 % of the maximum capacity but at least 100 mg.

10x

To determine standard deviation, the test weight is weighed at least ten times in succession.

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.

Repeatability is considered satisfactory if two times the standard deviation of the measured values divided by the smallest net weight (m_{snw}) to be weighed is not greater than 0.10 %. If the standard deviation is ≤ 0.41 **d*, this is replaced by 0.41 **d*. This means that the minimum weight cannot fall below 820 *d*.

$$\frac{2 \times s}{m_{snw}} \times 100 \leq 0.10$$

SENSITIVITY

- Sensitivity testing confirms balance accuracy. An acceptance criterion of 0.05 % applies. Linearity and eccentricity testing may be omitted.
- If sensitivity requirements are not met, the balance is not usable.
- A one-piece test weight of ≥5 % of the maximum is placed on the balance. If the deviation is 0.05 % or less, the test is passed. Requirements on the test weights match those in Chapter <41> of the USP.

USE OF INTERNAL TEST WEIGHTS

Chapter 2.1.7 of the Ph.Eur. recommends regular sensitivity testing with an external test weight, but the frequency of this can be reduced by the use of internal calibration/ adjustment equipment.

Requirements from USP Chapters <41> and <1251>

The United States Pharmacopeia Convention is a scientific non-governmental organization which publishes the USP each year. Laboratory balances are covered in two places: Chapters <41> and <1251>.

Chapter 41: Balances

Compliance is mandatory where 'accurate weighing' is required and will be checked by the FDA during audits. The most recent update has been effective since August 1, 2019.

What does it cover?

Chapter <41> describes specific criteria for balances used for 'accurate sample weighing' of materials.

BALANCE REQUIREMENTS

1. Balances must be calibrated over the entire working range
2. Balances must meet tolerance requirements for testing repeatability and accuracy
3. The repeatability test should be used as the basis for checking if the 'desired smallest net sample weight' can be made within USP rules

CALIBRATION

Accurate weighing of samples must be performed only on balances that are calibrated over the entire working range.

Calibration certificates help to provide security and confirm that measurement results comply with national standards.

REPEATABILITY AND MINIMUM SAMPLE WEIGHT

Weighing must not be carried out below a minimum sample weight.

Repeatability testing involves weighing a test weight (within the working range of the balance) at least ten times.

While the repeatability test according to Ph.Eur. chapter 2.1.7 has to be carried out with a one-piece test load of ≤ 5% of max, USP <41> makes no specifications here. The repeatability test can be performed at any point over the entire weighing range of the scale.

Repeatability is considered satisfactory if two times the standard deviation of the measured values divided by the smallest net weight to be weighed is not greater than 0.10 %.

The smallest possible sample weight on a balance is 2000 times the standard deviation of the repeatability measurement, representing the lowest point of the balance's working range.

If the standard deviation of a balance is less than 0.41 **d*, the minimum load is 2000x 0.41 **d* (*d* being the scale interval). E.g. for a 4-digit analytical balance with *d* = 0.0001 g, the minimum sample weight can never be less than 0.0820 g.

Tests must be performed regularly at the place of installation. Desired smallest net sample weights should be determined according to laboratory requirements and validated during repeatability testing.

ACCURACY

- If a balance does not meet the USP accuracy requirement, it is not suitable for accurate weighing of sample substances.
- USP Chapter <41> states that 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 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 weight does not exceed one third of the applied test limit for the accuracy test.
- The test weight requirement is independent of the scale interval of the balance.
- Weights of classes E_2 and F_1 can be used. A one-piece test load is recommended.

Chapter <1251>: Weighing on an Analytical Balance

Chapter <1251> is not mandatory, but contains information on the qualification and operation of electronic balances.

Performance Qualification

Sets out metrological tests and tolerances for testing balances. Testing frequency is determined by the criticality of the application.

Four performance tests are recommended:

- Sensitivity
- Linearity
- Eccentricity error
- Repeatability

If requirements for sensitivity, linearity and eccentricity are not met, the balance is not suitable for use. An acceptance criterion of 0.05 % applies.

Repeatability restricts the working range of the balance down to the minimum sample weight.

Maximum permissible error of the test weight must not exceed one third of the applied test limit.

The USP rounding rule is observed for these tests.

Sensitivity

- The test involves placing a test weight on a calibrated balance.
- Test weight should be at least 80 % of the maximum load.
- Deviation between the weight value of the test weight and the displayed value must not exceed 0.05 %.

Linearity

At least three test loads are applied to the balance at several points over the entire weighing range. The deviation from a straight line must not exceed the acceptance criterion (usually 0.05 %) at any test point.

Eccentricity

Test weight placed in the centre then four off-centre positions of the weighing pan. A one-piece weight of at least 30 % of the maximum weight should be used.

Repeatability

Repeatability tests are the same for Chapters <1251> and <41> but Chapter <1251> requires a small test weight of no more than 10 % of the maximum. A typical tare object can be placed on the weighing pan as a pre-load.

Further guidance

For further guidance on laboratory balances, see:

Sartorius Wall Chart Sartorius Cubis eBook

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