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Determination of the Working Range of the Laboratory Balance According To USP Chapter <41> With USP V2.0

White Paper

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Introduction

For more than 140 years Sartorius, now Sartorius Lab Instruments GmbH & Co. KG, has been providing high-quality weighing technology for laboratory and production environments. One of its key areas of expertise is the production of products specially tailored to the requirements of the pharmaceutical industry.

The balances in the Cubis® product range are designed for use in this very demanding environment based on the rules of "Good Manufacturing Practices" (GMP) and "Good Laboratory Practices" (GLP). Equipped with the "Advanced Pharma Compliance" (APC) design, function and service package, they use customer-friendly solutions to meet the process and quality requirements of the sector.

The United States Pharmacopeia (USP) is one of the central regulatory documents for pharmaceutical companies wishing to sell their products on the American market. Active ingredients and drugs which are imported into the USA must also comply with the regulations and standards of the USP. Chapter <41> Weights and Balances of the USP was considerably revised in summer 2013 after its content had remained unchanged for almost twenty years. The subject of this chapter is the requirements for the minimum accuracy of balances which are used for quantitative analyses. The requirements specified here and the, in some cases, unclear formulations had long been criticized.

The revised version was published on June 3, 2013 in the second appendix to USP 36-NF 3 and it came into force on December 1, 2013. The new, more balanced content particularly aims to ensure unprecedented levels of accuracy during weighing processes. There is a new description of reproducibility and accuracy tests for the balances and minimum quality standards for the reference weights that are used.

Compliance with the USP requirements is closely monitored worldwide by the American Food and Drug Administration (FDA). As a result of the revision of Chapter 41, manufacturers in the pharmaceutical industry are now faced with the challenge of meeting higher requirements for their measurement and weighing equipment.

For the balances in its Cubis® balance, Sartorius Lab Instruments GmbH & Co. KG offers user-friendly, convenient solutions of the highest pharmaceutical quality standards. These include, in particular, Q-App USP V2.0 and the SQmin function. These software applications automate the conduct of the necessary tests and therefore ensure a USP-compliant weighing process for the user.

Quality-Assured Weighing

Chapter 41 of the USP can be seen as the minimum quality standard for precise weighing. Among other things, it is necessary to determine the working range of the balance. This includes the determination of the starting point of the working range.

The starting point of the working range is comparable with what was previously the minimum initial weight. First, it is important to explain this term in more detail. The minimum initial weight was defined as the smallest sample quantity which could be weighed on a balance and which produced a reliable result in consideration of the measurement uncertainty. Patient safety in the pharmaceutical industry can be linked to the correct weighing of the smallest amounts, for example when using highly effective substances. In these applications, the dosage is often only very small and therefore only a minimal part of the balance's weighing capacity is used. However, given that the relative measurement uncertainty increases as the weighed amount decreases, knowledge of the minimum initial weight was crucial in ensuring that the tolerance limits of the quality management system were not exceeded.

Statistical data from multiple weighing processes was recorded in order to determine the minimum initial weight. In this case it was crucial to conduct this work at the installation location because it is influenced by ambient conditions. The calculation of the minimum initial weight involved the repeatability, the relative measurement uncertainty and an expansion factor. The reproducibility is expressed by the standard deviation (σ) of a defined number of the same weighing processes. It is dependent on the item being weighed, the relevant ambient conditions and the settings of the balance. The relative measurement uncertainty (U_{rel}), which can be tolerated in a weighing process, is either stipulated by standards and regulations (such as USP Chapter 41) or defined by the user. The expansion factor (k) describes the level of confidence with which it can be assumed that a measured value is actually in the specified range of values. Depending on the process, different values can either be selected by the user or the factor can be stipulated by regulations. With an expansion factor of k = 2, a confidence level of 95% is reached and with k = 3, 99% is reached. These parameters could be used to calculate the minimum initial weight (M_{min}). This initial weight resulted from the repeatability and expansion factor being divided by the relative measurement uncertainty.

$$M_{min} = \frac{\sigma^* k}{U_{rel}}$$

The rest of this document will deal with the current version of Chapter 41 of the USP, which no longer uses the term minimum initial weight.

The requirements of the new Chapter 41

In the revised version of Chapter 41 of the USP, the working range of a balance needs to be determined instead of the minimum initial weight. The upper end of the working range is limited by the maximum weighing capacity and the lower range begins from a starting point at which the repeatability is less than or equal to 0.10%.

In terms of content, this starting point corresponds to the previous minimum initial weight, but it is calculated according to an altered procedure which is detailed below. The repeatability and the accuracy need to be determined for this purpose.

In order to determine repeatability, a test weight must be weighed as least ten times and its standard deviation must be determined. The standard deviation is multiplied by the expansion factor 2 and divided by the nominal value of the test weight that is used. If the result does not exceed 0.10%, the repeatability is satisfactory. If the standard deviation is a value less than 0.41 d (where d is the scale interval/the readability of the balance), then in the calculation the standard deviation must be replaced with 0.41 d. In order to determine the starting point of the working range of the balance, twice the standard deviation is multiplied by 1000. Therefore, for example, in an analytical balance with a readability of 0.1 mg with a determined standard deviation of less than 0.41 d, this results in 82 mg as the starting point of the working range. The inclusion of the factor of 0.41 d is based on rounding processes during the quantification as part of digitalization (continuous uniform distribution: 0.29, 2 readings for loaded and unloaded $\rightarrow SD_{min} = \sqrt{2} \times 0.29 = 0.41$, according to equations 7.1.1-3a/3b and 7.1.1-6 of the Guideline "SIM Guidelines on the Calibration of Non-Automatic Weighing Instruments" of 2008).

In order to assess repeatability, according to Chapter 41 it is not necessary to use a small test weight. It is therefore recommended that a test weight should be used which is roughly half of the weighing capacity. This kind of weight is, firstly, easier to handle than a small test weight and, secondly, offers the option to combine the repeatability testing and the accuracy testing.

When determining the accuracy, according to USP <41> test weights should only be used which are between 5% and 100% of the weighing capacity. This is due to the fact that standard deviations cannot be assessed precisely enough with weights below 5%. If a test weight of half the maximum weighing capacity is now used in the repeatability testing, then it is easy to use a value from this for the accuracy testing. This describes a balance as sufficient if the deviation of the displayed weight value from the conventional mass of the test weight is less than 0.10%. In this case, conventional mass is understood to be the sum of the nominal value and the difference stated on the calibration certificate.

Finally, for reasons of completeness it is stated that a new formulation of the revised version of Chapter 41 of the USP indicates that a calibrated balance must be used if substances need to be "weighed accurately".

Support in Daily Laboratory Work from the Q-App USP V2.0 and SQmin

With the innovative Q-App USP V2.0 and the SQmin function, Sartorius Lab Instruments GmbH & Co. KG offers automated solutions for its balances in the Cubis® range which give the user optimum support in everyday laboratory work when it comes to compliance with the requirements of Chapter 41.

The software application Q-App USP V2.0 guides the user step by step through the necessary tests which ensure the fulfillment of the requirements of the new Chapter 41. Following determination, the identified starting point of the working range can be programmed into the balance. As the technical measurement limits of the balance are now known, it is recommended that the function SQmin should be routinely used in order to work securely within the working range. When this function is used, the measured value is compared with the previously saved starting value of the working range during the weighing process. If the starting value has not been reached, then an error will be reported and clear warnings will be shown on the balance display.

A central quality criteria in the pharmaceutical industry is documented proof of the suitability of measurement procedures. Sartorius Lab Instruments GmbH & Co. KG supports the validation of the mentioned applications, if necessary, with comprehensive informative material, detailed document templates and accompanying services, and therefore ensures effortless integration of these products into ongoing pharmaceutical operations. Q-App USP V2.0 has been developed in a quality assured manner and classified in category 3 according to GAMP (Good Automated Manufacturing Practices).

Synopsis

The requirements of the United States Pharmacopeia are binding for the pharmaceutical industry within the USA and around the world. Chapter 41 of the USP specifies the minimum quality standards for precise weighing.

A revision of this chapter was published on June 3, 2013 and the revised version provides for tests on accuracy and repeatability when determining the working range of the balance. In this context, the Q-App USP V2.0 from Sartorius Lab Instruments GmbH & Co. KG can provide valuable support in daily laboratory life because the user is systematically guided through the required determination of the working range. The function SQmin also guarantees that the starting point of the working range is always adhered to. These applications are an excellent way to achieve the high requirements for the pharmaceutical industry.

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