This article introduces a scientific methodology to selecting and testing weighing instruments within an integrated qualification approach (Good Weighing Practices). Based primarily on the user’s weighing requirements and prevailing weighing risks, it provides a state-of-the-art strategy to reduce measurement errors and to ensure reliable weighing results. The understanding of weighing process requirements and important balance and scale properties as minimum weight is essential to select an appropriate weighing system in the framework of the design qualification. The performance qualification takes into account these requirements and risks to establish a specific routine testing scenario for the instrument. The higher the impact in case of inaccurate weighings, and the more stringent the weighing accuracy requirements are, the more frequently user tests have to be carried out. However, for less risky and stringent applications, testing efforts can be reduced accordingly. Risk- and life cycle management form an integrated part of the overall strategy of Good Weighing Practices to bridge the gap between regulatory compliance, process quality, and cost consciousness.

Out of Specification results and their consequences
Out of Specification results have had a significant impact in the pharmaceutical industry for many years but especially since the Barr Labs court ruling in 1993. In this case, the court ruled in favor of Barr Labs which upheld their view that an OOS result does not necessarily constitute a batch failure but it should be investigated to determine if there are other causes such as a laboratory error. In October 2006, the FDA revamped their guidance concerning how to handle OOS results and how to perform a proper investigation. Since then, the FDA has issued a significant number of 483 Observations concerning poor investigations. A recent three-part article concerning OOS investigations by Lanese begins by saying:

"Out of Specification. It’s a term that brings the fear of the gods to the laboratory."
It causes gridlock, finger pointing, and delays in the normal workflow."

It seems that even 5 years after the guidance and 18 years after the Barr ruling, we still have a lot of work to do in this area.

Furthermore, in the abovementioned guidance, the FDA states that

“Laboratory errors should be relatively rare. Frequent errors suggest a problem that might be due to inadequate training of analysts, poorly maintained or improperly calibrated equipment, or careless work.”

Since we are seeing a significant number of FDA 483 Observations on poor investigations, the rarity of a laboratory error may not be as rare as we would like. Unfortunately, there is no published data that shows for every OOS result generated there were many more minor errors that didn't lead to an OOS result. These errors may be classified as a “Note to Record”; or simply noted in the laboratory notebook as an error. Many companies don’t investigate these errors even though they are probably symptoms of more serious future issues with the analysis method or process.

Weighing is a key activity in most laboratories, however its understanding is not always at a sufficient level, and its complexity often underestimated. As the quality of weighing strongly influences the quality of the final result, USP specifically requires in its General Chapter <41> highly accurate weighing results used for quantitative analysis.

"Unless otherwise specified, when substances are to be "accurately weighed" for Assay, the weighing is to be performed with a weighing device whose measurement uncertainty [...] does not exceed 0.1% of the reading. Measurement uncertainty is satisfactory if three times the standard deviation of not less than ten replicate weighings divided by the amount weighed, does not exceed 0.001."

Such a stringent requirement is not implemented for other instruments, where quite often the analytical development group sets the method requirements.

Compared to the laboratory, the importance of weighing results is most of the time underestimated in the production environment.

A scale is considered a production tool that is submitted to external factors such as corrosion, risks of fire or explosion, health and safety of the operator or productivity. In the current practice of selection and operation of a scale, all these factors are regarded as higher in priority than mere metrological needs. The metrological criteria are thus insufficiently taken into consideration.

More than often the level of qualification of operators in a production environment is lower than that of a laboratory technician. As a consequence manipulation errors are more frequent in production than in a laboratory. Therefore one can expect a higher frequency of Out of Specification in the production than in the laboratory.

Another frequent practice is to recycle existing instruments for a different purpose than the one they had been acquired for. Here too, though, the principle “what you see is what you get” (WYSIWIG) is applied.

In this environment of misconception, scales are the last suspected part of the production chain in case of OOS. OOS become then a necessary evil. But it must not.

Measurement Uncertainty and Minimum Weight

State-of-the-art strategies for adhering to consistently accurate and reliable weighing processes comprise of scientific methodologies on instrument selection and testing. Within these methodologies, typical misconceptions on weighing that are very widespread in the industry are also described.

One of them is that many users believe "what you see is what you get". What do we mean by that? Let us make an example: A user weighs a product on an industrial floor scale and gets a reading of 120.000kg which he believes is the true amount of material that he was weighing. However, this reading might not exactly reflect the amount weighed, in other words, the amount weighed might differ slightly from the indication. This is due to the so-called measurement uncertainty which is applicable to every instrument you might think of.

Measurement uncertainty of instruments is determined in calibration, and the results issued in appropriate calibration certificates. In general, measurement uncertainty of weighing systems can be approximated by a positive sloped straight line – the higher the load on the balance, the larger gets the (absolute) measurement uncertainty, as shown in Figure 1. Looking at the relative measurement uncertainty, which is the absolute measurement uncertainty divided by the load, and usually indicated in per cent, we clearly see that the smaller the load is, the larger the relative measurement uncertainty gets. If you weigh at the very low end of the instrument's measurement range, the relative uncertainty can become so high that the weighing result cannot be trusted anymore.

It is good practice to define accuracy (tolerance) requirements for every weighing process. For quantitative analysis this is even stipulated by USP General Chapter <41>. Weighing in the red area as indicated in the figure will result in inaccurate measurements, as here the measurement uncertainty of the instrument is larger than the required accuracy of the weighing process. Consequently, there is a
specific accuracy limit for every weighing instrument – the so-called minimum sample weight, or short, minimum weight, and one has to weigh at least this amount of material in order to have an uncertainty that satisfies the specific weighing accuracy requirement.

While measurement uncertainty is described in much detail in the respective weighing accuracy requirement. To have an uncertainty that satisfies the specific weight at least this amount of material in order to determine at calibration. For standard weighing processes, a safety factor of 2 is commonly used, provided you have reasonably stable environmental conditions and trained operators. For very critical applications or a very unstable environment, an even higher safety factor is recommended.

Another frequent misconception that we briefly want to mention is prevalent in the industry: Many companies wrongly believe that the weight of the tare vessel also accounts for the adherence to the minimum weight requirement. In other words, they believe that if the tare weights more than the minimum weight, the balance will only play a relatively small role in the effort of weighing small loads on analytical and microbalances.

While measurement uncertainty is described in much detail in the respective literature**, we want to emphasize that for weighing small loads on analytical and microbalances the dominant contribution factor to the uncertainty stems from repeatability (expressed as the standard deviation of a series of weighings). Samples and standards that are typically weighed on these balances usually are small loads as compared to the capacity of the balance. This finding is also reflected in USP General Chapter <41>.

Scales follow the same principles as balances with some additional constraints that arise from the technology used and from the size of the instrument. Most scales are using strain gauge weighing cells that lead to a lower resolution than balances. In some cases the rounding error may be predominant, but for scales of higher resolution the repeatability becomes a decisive contributor to the measurement uncertainty in the lower measurement range of the instrument.

Linearity deviation is often considered a large contributor too, but it can normally be neglected when weighing small samples. Considering that the relative measurement uncertainty is getting small when weighing larger samples, we can conclude that linearity will only play a relatively small role in the effort of maintaining measurement uncertainty of the instrument below the required process tolerance. Same as for laboratory balances, we need to focus our attention on the repeatability to define the critical limit of a high-resolution industrial scale.

It is important to state that the minimum weight of balances and scales is not constant over time. This is due to changing environmental conditions that affect the performance of the instrument, as for example vibrations, draft, wear and tear or temperature changes. The operator himself also adds variability to the minimum weight, as different people might weigh differently or with a different skill level on the instrument. In order to ensure that you always weigh above the minimum weight as determined at calibration (at a particular time with particular environmental conditions by a qualified service technician), it is highly recommended applying a safety factor. The safety factor describes that you would only weigh sufficiently above the minimum weight as determined at calibration. For standard weighing processes, a safety factor of 2 is commonly used, provided you have reasonably stable environmental conditions and trained operators. For very critical applications or a very unstable environment, an even higher safety factor is recommended.

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Just recently we encountered another misconception with a dispensing application and the measured minimum weight of the very scale being around 100kg. The company stated that they dispense 20kg at a time, however, would always leave more than 100kg of substance in the container in order to adhere to the minimum weight requirement. They did not understand that they would have to dispense at least 100kg – instead of 20kg – in order to comply with their own accuracy requirement.

Routine Testing of Weighing Instruments

“Measuring equipment shall be calibrated and/or verified at specified intervals [...] against measurement standards traceable to international or national measurement standards.”

ISO9001:2008, 7.6 Control of Monitoring and Measuring Devices

“Automatic, mechanical or electronic equipment [...] shall be routinely calibrated, inspected or checked according to a written program designed to assure proper performance.”

21 CFR Part 211.68 (a), US GMP for Pharma

The statements cited above delegate the responsibility for the correct operation of equipment to the user. This also applies for weighing instruments. Statements like these are usually formulated vaguely, as they are meant as general guidelines. Therefore, they cannot be put to work for daily routine. Questions like “How often should I test my weighing instrument?” emerge in situations where guidance is needed to design standard operating procedures to assure the proper functioning of the instrument that neither are too exhaustive, and thus costly and time consuming, nor too loose, and thus not adequate to assure proper functioning. The right balance between consistent quality and sufficient productivity must be found.

The following test procedures for weighing instruments are recommended in the framework of the performance qualification:

1. Calibration in-situ by authorized personnel, including the determination of measurement uncertainty and minimum weight under normal utilization conditions; the aim is to assess the complete performance of the instrument by testing all relevant weighing parameters of the instrument, made transparent to the user by a calibration certificate. Calibration also is an important step within operational qualification after the instrument is installed and the necessary functional tests performed.

2. Routine test of the weighing system, to be carried out in-situ by the user; only those
3. Automatic tests or adjustments, where useful test to assess weighing accuracy, whereas the linearity test that does not constitute a necessary to conduct that many user tests, and based approach would reveal whether it is really weights (a so-called linearity test). A proper risk-

It is assumed that the more stringent the accuracy requirements of a weighing process are, the higher the probability becomes that the weighing result will not meet the accuracy requirements. In this case, the test frequency is increased. Similarly, if the severity of the impact increases, the tests should be performed more frequently. That way, a higher impact is offset by more frequent tests, thereby lowering the likelihood of occurrence of the impact, and hence, offsetting the increase of risk that otherwise would occur – see Figure 2 on page 3. If the malfunction of the weighing instrument is easily detectable, the test frequency is decreased. The frequencies for the test of all properties extend from daily for risky applications (user or automatic tests), over weekly, monthly, quarterly, twice a year to yearly (e.g., calibration by authorized personnel).

Our experience is that many Pharmaceutical companies tend to test their balances very frequently, in many cases on a daily basis, and partly involving a whole set of different test weights (a so-called linearity test). A proper risk-based approach would reveal whether it is really necessary to conduct that many user tests, and whether testing efforts can be reduced without compromising on the quality of the weighing data. Furthermore, the applied test procedures might not always be appropriate as in the case of the linearity test that does not constitute a useful test to assess weighing accuracy, whereas the importance of the repeatability test is very frequently underestimated.

Surprisingly, the practice in the production is different. More than often, only rudimentary or no procedures at all are in place. This leads to inconsistent quality and to OOS. Only a few companies have understood the importance of establishing a robust routine testing scheme. For these conscious users, the practice is often to reproduce in the production what they have implemented in the laboratory. This is of course not appropriate because probability, severity and detectability differ significantly.

A sound understanding of the instrument’s functionality and its weighing parameters, combined with the necessary understanding of the process-specific weighing requirements allows for eliminating these misconceptions, and helps preventing critical weighing errors that might result in Out of Specification results, both in the laboratory and the production environment.

Conclusion
By implementing Good Weighing Practices as a methodology to provide a risk-based life cycle approach for evaluation, selection, and routine testing of balances and scales, measurement errors can be reduced and reliable weighing processes can be realized.

The key issue to be considered for a successful operation of weighing instruments is that the minimum weight for the required accuracy must be smaller than the smallest amount of material expected to be weighed by the user. Furthermore, it is recommended to apply an appropriate safety factor to compensate for the fluctuations of the minimum weight due to variability in the environment and different operators working with the instrument.

An understanding of the weighing process requirements together with an understanding of the basic principles of balance and scale properties as measurement uncertainty and minimum weight enables the user to realize an integrated qualification strategy as a basis for achieving qualified weighing processes. Furthermore, an important source for Out of Specification results is eliminated, both in the laboratory and the production environment.

Appropriate and meaningful routine tests enable the user to test exactly what is needed to adhere to the specific weighing requirements, and to avoid unnecessary – and costly – testing. Risk- and life cycle management thereby form an integral part of an overall strategy to bridge the gap between regulatory compliance, process quality, and cost consciousness.

REFERENCES

European Pharmaceutical Review
Mettler-Toledo AG – White Paper

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