The Impact of Weighing Accuracy and Data Integrity for qNMR Applications

Abstract

One of the major sources for measurement uncertainty in quantitative NMR applications is weighing of reference and analyte. Weighing has a strong bearing on the final qNMR results. A balance must be consistently accurate, which is achieved by calibrating the device periodically and by determining the minimum weight and the safe weighing range. Weighing sample sizes in the safe weighing range reduces the measurement uncertainty of the weighing process below a predefined threshold. Further to accurate weighing, data integrity of plays a fundamental role in regulated environments. With automated transfer of weighing data and associated metadata the traceability of the weighing process is established and operator errors can be avoided.

The significance of measurement uncertainty and minimum weight

Weighing is a critical step for qNMR analysis. It strongly and directly influences the accuracy of the final result because the weight of the net sample and of the reference standard have a direct correlation on the determination of sample purity or content. To ensure that weighings are accurate, laboratory managers often rely on quality management systems to define a weighing process. This includes proper recording criteria, calibration of the instrument and determination of measurement uncertainty.

To better understand minimum weight, it is important to recognize that the stand out prerequisite for traceable and accurate weighing is the effective calibration of weighing instruments, which must include an estimation of measurement uncertainty. Historically, many laboratories have set up their own calibration procedures due to the lack of nationally or globally recognized calibration guidelines. Based on international cooperation from subject matter experts in the field of metrology, efforts have been made to globally harmonize the methodology of calibration of weighing instruments[1].

The benefit of these harmonization activities is that the state-of-the-art calibration concepts not only stipulate how to estimate measurement uncertainty at the time of calibration, but provide guidance for estimation of uncertainty during the day-to-day usage of the instrument. This concept leads to the calculation of the minimum sample weight, often referred to as the minimum weight. This is the smallest amount of net substance that must be weighed in order to achieve a specified degree of accuracy.

All weighing instruments act in a similar manner across the weighing range - as the sample size decreases, the relative measurement uncertainty increases. Eventually, with a small enough mass, the relative weighing uncertainty can become high enough that the weighing result is no longer accurate. The measurement uncertainty then becomes larger than the specified threshold. This accuracy limit is the minimum weight (*Figure 1*). Based on the risk associated with the weighing process, it is also recommended to apply a safety factor to this value. This factor increases the minimum amount that should be weighed on a particular balance and defines the starting point of the so-called safe weighing range. The safety factor accounts for performance fluctuations caused by environmental factors (air drafts, temperature, vibrations, and different user techniques) that can affect the balance during normal use between calibrations.

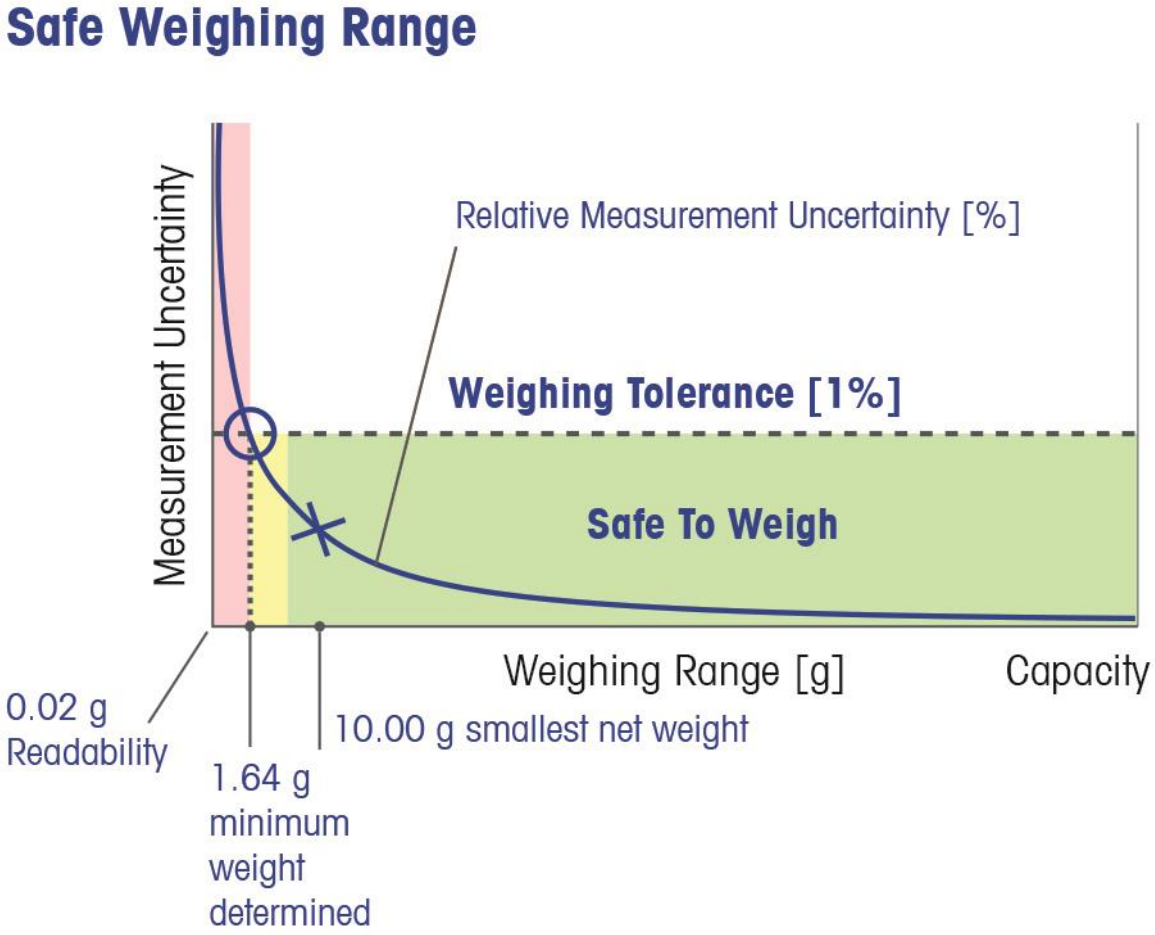

Figure 1: *Typical behavior of measurement uncertainty across the weighing range of a balance*

The minimum weight is an extremely important characteristic when performing quantitative NMR analysis because small sample sizes are often used for the purpose of minimizing costs or limited valuable amount of samples. The associated weighings of the samples and standards have a direct impact on the analysis results. Therefore, weighing above the minimum weight under consideration of an appropriate safety factor, i.e. weighing in the safe weighing range of the instrument, is extremely critical.

With the benefit of measurement uncertainty and the resulting minimum weight defined, it is important to realize that typical calibration certificates only contain measurement uncertainty values. An Accuracy Calibration Certificate (ACC) contains both components, the measurement uncertainty and the minimum weight for the required weighing tolerance. Therefore, it links the performance of the weighing instrument to the weighing process tolerances required by the user for their specific application. Based on the defined safety factor, the ACC allows the safe weighing range to be determined for each particular balance. This level of detail from a calibration enables balance users to improve the quality of their weighing, increase confidence in the weighing results and avoid weighing errors.

Ultimately, understanding and implementing a quality system that adheres to weighing sufficiently more substance than the minimum weight and thus working in the safe weighing range of the

balance, ensures instrument accuracy and minimizes the risk of errors that could affect the correctness of analysis results.

Avoiding incomplete data and achieving compliance

To help comply and meet the requirements on data integrity, especially in the regulated environment like pharmaceutical laboratories, it is also important to understand the benefits of incorporating the components of the weighing process in an integrated data management system. In recent years, an increasing number of assessments and FDA warning letters have revealed incomplete data, the lack of audit trails, and falsification of results. The problems with data integrity could be eliminated by first focusing on the sample file generated from the sample during the course of analysis. Many labs have turned toward LIMS systems with the idea of replacing the manual workflow. These systems are designed primarily to aggregate result data from an array of analytical tests, rather than to automate and document bench top workflows or bind instrument metadata to the measurement.

With respect to measuring instruments, many regulations and guidelines now require ***complete data derived from all tests...***[2]. This includes the raw data generated through the course of an analysis and the associated metadata. Metadata is the contextual information required to understand data[3].

An example of the use of metadata in an everyday situation is shown in Figure 2. If a car speeds through a traffic enforcement camera and the only information captured is the image, the speed of the automobile, and the associated unit of measure, there isn't enough information to link the car to the speed. However, if the date, time, color of the car, unique picture identifier, and location is included, the necessary contextual information is then available to link the car with the speed.

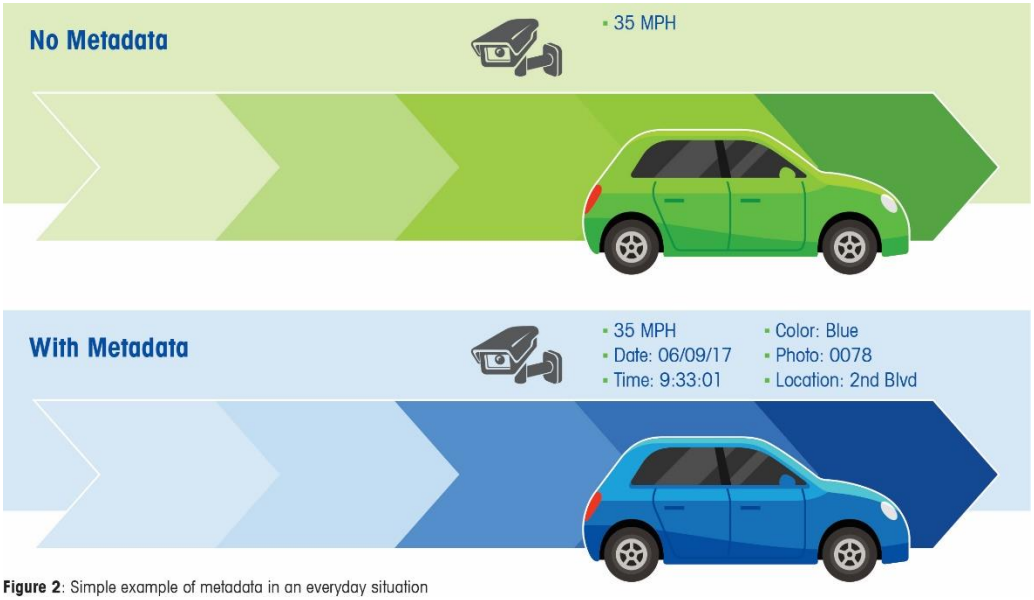

Figure 2: Simple example of metadata in an everyday situation

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When the same principle is applied to the regulated laboratories , every critical weight measurement that is recorded should not only include the weight and unit of measure, but the additional metadata necessary to be considered "complete data" (*Figure 3*).

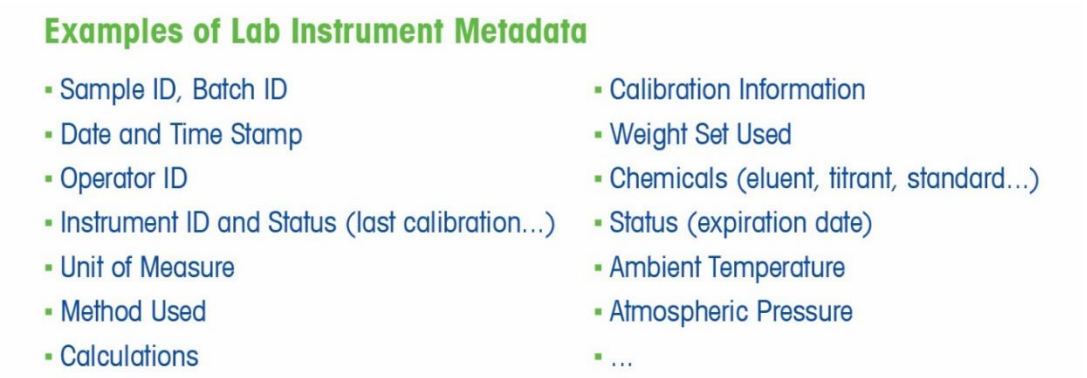

Figure 3: *Examples of metadata available from laboratory instrumentation*

Automated data transfer and standardization of weighing workflows

Many labs have discovered that transferring metadata from bench top analytical instruments is much more complex than only the transfer of a few parameters, such as sample weight and unit of measure. Leveraging the potential of appropriate software technology, such as LabX, enables users to transfer weighing results with all the associated metadata directly to their LIMS systems - thereby ensuring the data is complete and traceable.

Additionally, the weighing workflow can be automated and standardized to the specifications of the unit or lab (*Figure 4*). This guarantees and proves that the same weighing process is used for each sample, regardless of who performs the steps – ensuring consistency in every analysis. For example, the administrator can elect to have the balances locked down every morning until an analyst logs in and performs an adjustment of the balance by means of the built-in weights. Only once that has been completed can the balance user proceed to a guided weighing process on the terminal of the balance.

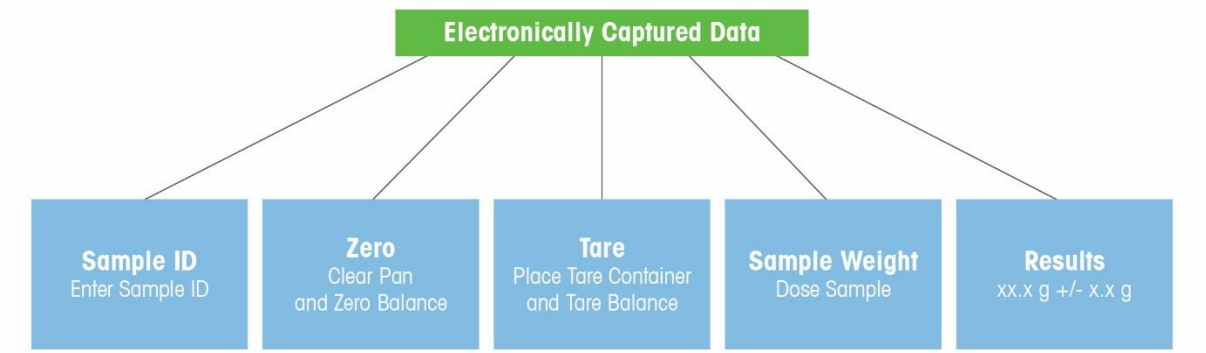

Figure 4: *Example of a standardized weighing method*

Another example of a benefit the software provides is the ability to capture not only the net weight of the substance, but the weight of the tare vessel used in each weighing event. This allows the

analyst to provide documentation during trial, confirming the tare vessel weight was not included in the net weight of the substance in question.

Conclusion

To increase accuracy of qNMR analysis, it is crucial to minimize weighing and sample preparation uncertainty. Error elimination, process simplification and data traceability are the keys to succeed in qNMR application which can be supported by the following.

- Establish a harmonized approach to the calibration of balances
- Ensure all weighing is performed in the safe weighing range, well above the minimum weight
- Automate data capture and transfer of weighing data to ensure traceable data and to reduce operator errror

References

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Figure captions

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Figure 2: *Simple example of metadata in an everyday situation*

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Figure 4: *Example of a standardized weighing method*

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