

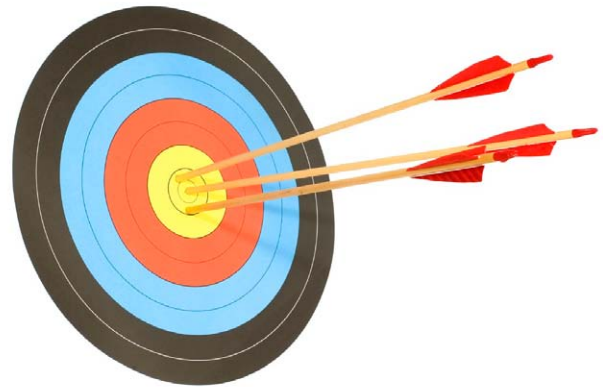
QbD and Weighing

Ensuring Accurate Measurements

Weighing is a critical step in most pharmaceutical manufacturing processes and significantly impacts final product quality. The selection of the right weighing equipment depends on many factors and needs to be considered in any manufacturing approach based on the Quality by Design concept.

Incorrectly measured active ingredients included in a pharmaceutical formulation can lead to an out-of-specification batch that will need to be reworked or disposed of, adding extra labor and costs. It may even harm patients if not detected.

This white paper explains how you can proactively build sound weighing processes, based on Quality by Design, to ensure consistent quality of your products, improve productivity and reduce costs



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1 Introduction

Quality by Design (QbD) is increasingly implemented in pharmaceutical manufacturing, driven by the need to improve final product quality and manufacturing process efficiency. QbD is strongly supported by regulatory authorities, such as the U.S. Food and Drug Administration (FDA) because it focuses the manufacturing process on consumer safety—from the beginning.

Build quality into the process

The underlying concept of QbD is that quality should be built into each process step—not only tested at the end. With this scientific, risk-based approach, potential process errors are identified early and proactive steps are taken to ensure safety and efficacy of medications. A key aspect of the QbD framework is the risk assessment of process parameters and material attributes that influence finished product quality.

While discussions on QbD implementation in pharmaceutical manufacturing focus to a large extent on Process Analytical Technologies (PAT), weighing processes should be considered in comprehensive QbD frameworks as well due to their critical influence on product quality.

If the wrong scale for a particular application is used, or if the right one is not maintained correctly, the measurement and resulting quality will be compromised. Therefore, selecting the correct measurement tool and calibration is a prerequisite to produce sound products and comply with regulations.

Process tolerances define selection criteria

It is also important to note that the benchmark depends on each product's tolerance and a risk analysis defined in the manufacturing process. The narrower the process tolerance, the higher the requirements for a qualified weighing instrument, which will drive the selection of the scale. Furthermore, a calibration program and a selection of test standards are required to ensure compliance to process tolerances over time.

The aim of this white paper is to help understand the potential influences of weighing on product quality and its relevance for QbD concepts. However, this document does not provide an introduction to Quality by Design and is not intended as a guide on how to integrate QbD in pharmaceutical manufacturing because there are many other factors to consider.



The Quality by Design Concept

2 GWP® - A Risk-Based Approach to Weighing



The quality of weighing strongly influences the quality of the final product. Ensuring consistently accurate results within a QbD-based process requires an understanding of the parameters influencing the accuracy of weighing processes.

METTLER TOLEDO has developed the global standard Good Weighing Practice™ (GWP®) as a unique approach that provides a scientific methodology to selecting and testing weighing instruments within an integrated qualification approach. Based primarily on the user's weighing requirements and prevailing weighing risks, the methodology provides a state-of-the-art strategy to reduce measurement errors and to ensure reliable weighing results.

Manage all phases of the life-cycle

The understanding of weighing process requirements and important scale properties, such 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.

GWP® provides the necessary information to make decisions about your weighing system. By testing the scale in place, weighing experts can certify the weighing process, meet final product quality requirements and ensure the scales are proven to be fit for their intended use. Verification can also identify weighing installations that may not be suited for the particular application and could affect quality.

The GWP® standard provides guidance for all phases of the life-cycle—from evaluation of the weighing process and selection of the equipment to installation and calibration and finally routine operation. Risk- and life-cycle management form an integrated part of the overall strategy of Good Weighing Practice™ to bridge the gap between regulatory compliance, process quality and cost consciousness.

| Quality Attributes | Selected Solutions | Key Features |
|--|---------------------|---|
| Evaluating the appropriate equipment for the specific requirements | GWP® Recommendation | <ul style="list-style-type: none"> Equipment selection with the right accuracy for specific process and quality requirements Environmental and regulatory factors are taken into account before equipment selection |
| Ensuring reliable performance of the equipment in use | GWP® Verification | <ul style="list-style-type: none"> Proves that scales are accurate and meet process quality and regulatory requirements Provides complete set of necessary information to pass any audit Provides all information needed to calibrate and test the equipment efficiently |



3 Weighing Process Parameters

A dependable QbD-based weighing process requires a clear understanding and risk analysis of the parameters influencing measurement accuracy.

Readability (or display resolution) of a balance or scale is often mistaken for accuracy. In fact, readability is just one contributor to the measurement uncertainty, which is the scientific expression of an instrument's accuracy. Any measuring device, whether it is a ruler, a speedometer or a scale, is associated with some measurement uncertainty. Uncertainty means that no measurement is perfect; it is always distorted by random, environmental and unknown systematic errors.

Define measurement uncertainty

For example, suppose you have a scale that is accurate to plus or minus 1 gram. At 10,000 grams (10 kilograms), this uncertainty represents one hundredth of one percent (0.01%) of the weight. In many situations, that uncertainty is small enough that it won't affect quality. Now suppose you are weighing a 10 gram sample on this scale with an uncertainty ± 1 gram. Now the uncertainty represents a full 10% of the reported weight. Your actual sample may be 10% larger or 10% smaller than what this scale is reporting just due to the uncertainty!

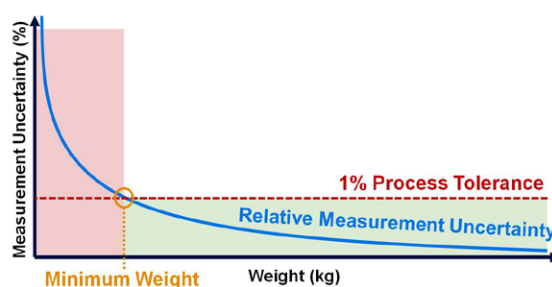
The measurement uncertainty of a weighing system is a combination of many factors. The readability, sensitivity, repeatability, non-linearity and eccentricity of the scale are all factors affecting measurement uncertainty and are associated with the scale design. The scale manufacturer can calculate the uncertainty of the weighing system associated with these factors.

However, the environment in which the scale is used also impacts the uncertainty of the weighing system. The environment is unique to every scale installation and cannot be calculated at the time the scale is manufactured. Significant impacts from the environment on weighing uncertainty can be attributed to wind, dirt or dust; temperature fluctuations; vibrations; and operator errors among other factors. The only way to calculate the measurement uncertainty associated with the environment is to test the scale installed in the environment using the appropriate tools and methods.

Specify minimum weight



As with any measurement device, uncertainty directly affects the accuracy of the reported value in a weighing system. The error is less significant when you are weighing something large relative to the capacity of the scale. However, as you attempt to weigh something small on the scale, the relative uncertainty becomes more significant. At some point, the relative uncertainty is so significant that you lose your confidence in the reported weight value.

This is usually expressed as "being below the minimum weight threshold" and is typical in situations where the scale is too large for the measurand. Minimum weight is usually determined and specified in order to be compliant with the necessary weighing tolerances. To ensure weightings at or above the determined minimum weight, either the process or the measuring device should issue a warning in those instances where the weight measurement is too small to be accurately weighted. Normally, this can be signaled in the weighing indicator via an icon or a weight value which changes color to indicate that the measurement will not yield the desired results.



Process tolerance defines minimum weight

The indication of the measurement uncertainty is a part of quality systems, such as ISO, GMP or pharmacopoeia such as USP. The accuracy of measurements can be checked during an inspection and needs to be documented.

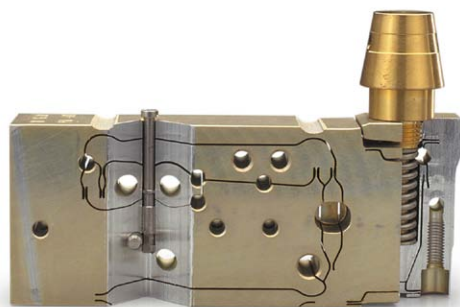
| Quality Attributes | Selected Solutions | Key Features |
|--|----------------------------|--|
| Understanding of process parameters influencing measurement accuracy | GWP® Verification |  <ul style="list-style-type: none"> • Proves that scales are accurate and meet process quality and regulatory requirements • Provides complete set of necessary information to pass any audit • Provides all information needed to calibrate and test the equipment efficiently |
| Identified minimum weight at defined process tolerances | Minimum Weight Certificate |  <ul style="list-style-type: none"> • Provides verified minimum weight of a scale in its working location • Ensures accurate weighing over the whole range |

4 Weighing Instrument Attributes

Weighing processes with narrow process tolerances require precise, rugged and reliable equipment that deliver accurate results.

Ensure precision and reliability of the weighing cell

Depending on the required weighing range and environmental conditions, several weighing-cell technologies may be suitable for your measurement process. However, when accurate weighing is a critical quality criterion, the precision of the scale plays a decisive role. Commonly used strain-gauge scales can deliver measurements expressed as 1 in 3,000 up to 1 in 10,000; high-precision electromagnetic force compensation weighing technologies deliver higher performance of up to and including 1 in 300,000 verified intervals "e". It is also important to understand that weighing readability or resolution "d" does not equate to accurate measurements. This is why METTLER TOLEDO provides documentation of actual performance, backed by our own testing as well as by the results of notified bodies operating under OIML or NIST guidelines, such as METAS, NMI, PTB and NTEP.



MonoBloc® load-cell technology is designed for high-precision weighing

While the weighing technology is certainly the most important element regarding weighing precision, the manufacturing technology of the weighing cell itself is also relevant. For example, MonoBloc® technology, developed by METTLER TOLEDO, is spark-eroded from a single aluminum alloy workpiece. This construction prevents stresses and torsion forces acting on the mechanical parts to ensure highest measurement precision as opposed to other manufacturing methods, which are employed in other weighing instruments.

Prevent environmental influences and cross-contamination

Another important quality aspect in selecting the right weighing equipment is the possible impact that the environment plays on your measurement. This includes influences, such as temperature changes, handling of aggressive substances, cleaning requirements and ingress of dust and water. Premium weighing modules and platforms are protected against water, dust or aggressive substances and compensate for influences, such as temperature and humidity. Any processing equipment that may come into contact with materials, especially active ingredients, poses a risk for contaminating products and exposing operators. To prevent cross-contamination, weighing equipment, such as floor scales, indicators, bench and portable scales, must be designed according to sound sanitary design principles and be capable of delivering continuously good results despite aggressive cleaning.

| Quality Attributes | Selected Solutions | Key Features |
|---------------------------------------|---|---|
| Accurate and reliable weighing result | K-line scales with MonoBloc® technology  | <ul style="list-style-type: none"> Exact weighing within smallest tolerances with an approved resolution up to 30.000e Built-in calibration weight for on-site adjustment of the measuring cell Dust and water protection to IP66 and IP67 |
| Prevention of cross-contamination | PUA579(x) floor scales  | <ul style="list-style-type: none"> Easy to clean, GMP compliant design Dust and water protection to IP65 and IP68 Lifting device allows quick access to the bottom of the platform and to the floor for thorough cleaning |

5 Usability and User Guidance

Sophisticated weighing systems help prevent operating errors by safely guiding users through the formulation process.

Operating errors are a main reason for out-of-specification batches and product recalls due to quality issues. Obviously, the risk of human mistakes in a manufacturing process can be significantly reduced by automating the entire process. In line with QbD principles, such an approach would provide a fully monitored and controlled process, ensuring consistent product quality. However, in pharmaceutical manufacturing, relevant process steps, such as the weighing of formulation components, involve manual tasks that cannot easily be automated.

Guide operators to ensure a consistent process

The challenge in ensuring process safety and product quality is to eliminate the risk of operating errors during manual weighing processes as far as possible. Both the usability of the weighing equipment, especially with regard to terminals and software solutions, as well as user guidance contribute to secure handling of the weighing process by operating personnel.

Sophisticated weighing solutions can easily guide the operator without errors through the weighing process, whether in simple filling applications or complex formulations. In formulation, for example, the application asks the operator to add each component of the recipe one after the other with the specified weight. The cor-

rect raw material is verified via barcode scanning of the lot number attached to the container.

Improve ease of use to prevent operating errors



During weighing, the target weight is displayed graphically and numerically and the required tolerances are clearly displayed as limits. Weighing results that exceed or fall below these limits are immediately shown to the operator in colors, helping prevent incorrect weighing. The system can even be set up to only allow the next process step and log the component weight if the actual weight is within defined tolerances. A number of advanced features can help improve usability of the weighing equipment for the operator, including:

- A large and clear display improves the readability of the weighing result, numerically or graphically.
- Self-explanatory and visually appealing icons help the operator make the right selections and avoid errors.
- An integrated user-management system only displays the information to the operator needed to perform the required tasks.
- Country- and language-specific screen layouts further help improve usability.

- Depending on the application and materials used, a touch screen or keys optimized for usage with gloves help prevent operating mistakes.

Finally, it is possible to automatically document all batch-relevant information to prevent possible errors

during manual or paper-based documentation. All process steps can be filed in detail in the database and electronic signatures can be given if required to comply with regulations such as FDA's Good Manufacturing Practice (GMP) regulation CFR 21 Part 11.

| Quality Attributes | Selected Solutions | Key Features |
|--|---|---|
| Easy usability prevents operating errors | IND890 PC weighing terminal  | <ul style="list-style-type: none"> • Large, clear display with excellent readability • Self-explanatory icons improve usability • Display of user and task specific functions only • Key information of up to 4 scales simultaneously • Touch screen enables direct user input |
| Comprehensive process quality monitoring and control | FormWeigh.Net  | <ul style="list-style-type: none"> • Material identification prevents material mismatch • Transfer of weight values within tolerances only • Automatic calculation of active ingredients and ingredient overweight correction options |

6 Calibration, Qualification and Maintenance

Calibration and qualification of weighing equipment are a prerequisite to ensure consistent process quality – as is ongoing equipment maintenance.

Getting the design and operational specifications right and selecting the proper equipment for the specified process are essential steps to achieve quality results. But quality also depends on precise installation, setup, calibration and maintenance of the weighing equipment.

Implement regular calibration intervals

According to FDA's GMP regulation 21 CFR Part 211, "automatic, mechanical or electronic equipment ... shall be routinely calibrated, inspected or checked according to a written program designed to assure proper performance. Written records of those inspections shall be maintained." In essence, this means that evidence that the weighing instrument works correctly needs to be provided and it needs to be demonstrated that the manufacturer understands what is measured. High risk and a narrow process tolerance may call for frequent instrument accuracy verification. Even under a more frequent testing schedule, regulators determine an instrument's uncertainty principle based on an assumption that proper installation and calibration actions have been performed.

Calibration of the weighing equipment must be conducted according to globally recognized standards, such as OIML and EA 10/18, and need to account for metrology as well as equipment construction. During calibration, eccentricity, linearity and repeatability of the device needs to be tested in order to evaluate if the device performs within the range of allowable errors for all final tests. These results must be documented and maintained.

Ensure correct equipment qualification

Documented equipment qualification ensures compliance with quality assessment systems, such as GMP and ISO. All equipment intended to be used in manufacturing must be qualified by executing a qualification procedure. This includes confirmation that the equipment is set up correctly and filter settings are configured. Furthermore, it needs to be documented that the right methods and tools were used for calibration and users are familiar with the correct use and maintenance of the equipment. Equipment that is repurposed or moved also needs to be re-qualified to ensure weighing results fulfill required quality targets.



Regular calibration and maintenance of the weighing instrument ensure consistent measurements

Finally, validation methods and protocols are required to ensure process reproducibility and safe data management when it comes to software, such as formulation or batching applications.

Competent suppliers of weighing equipment not only help specify the right equipment for the intended purpose, but also have knowledgeable service professionals to confirm satisfactory installation of new weighing systems and conduct initial commissioning, set up and testing.

Define adequate maintenance plan

If scales fail or deliver inaccurate measurements, the impact on final product quality and thus patient health, can be significant. Regular maintenance of the




weighing equipment is required to realize and sustain accurate, dependable, legal and accountable weighing results.

Depending on the installed weighing equipment, a range of maintenance tasks need to be performed, including:

- Cleaning of the scale, terminal and peripherals
- Inspection for proper environmental sealing (IP – Ingress Protection)
- Adjustment of critical scale components when required
- Examination of cabling and wiring
- Testing of terminal human interface and electronics
- Review of terminal predictive diagnostics and logs
- Confirmation of proper operation of applications and interfaces
- Testing and certification of accuracy using reference weights
- Determination and certification of minimum weight

Preventive maintenance solutions are able to monitor the condition of the weighing system and alert designated individuals of potential failures or maintenance requirements via email, SMS or via the operator interface. Built-in diagnostics monitor each individual load cell and control and log various operation parameters, such as zero and span, alarms, errors, scale impacts and overloads, etc., for quick diagnostics and immediate action.

These solutions not only ensure reliable accurate weighing results, but also comply with GMP procedures and tracking and tracing requirements.

| Quality Attributes | Selected Solutions | Key Features |
|--|---|---|
| Ensuring equipment is qualified for the intended process | IPac Qualification Service  | <ul style="list-style-type: none"> • Achieve and maintain the qualified state • Reduce the risk of audit challenges • Ensure proper results using OEM protocols functions only |
| Maintaining equipment performance with correct calibration | MiraCal™ Calibration Service  | <ul style="list-style-type: none"> • Long-term consistency of calibration procedures • Preserve calibration history • Reduce of weighing risk |
| Predicting and preventing malfunctioning equipment | IND780 Weighing Terminal with TraxEMT™  | <ul style="list-style-type: none"> • Predictive alerts and automatic email notification when service is required • Maintenance/error logging tracks terminal and user performance |

7 Summary

Quality by Design is a risk-based approach to integrating quality into the manufacturing process. Based on the defined target product quality, the entire manufacturing process is analyzed to identify material and process attributes that may influence product quality. These critical quality attributes must be managed to ensure consistent product quality over time.

Weighing has a critical impact on product quality. The weighing instrument not only needs to deliver accurate weighing results, it also must ensure consistent measurements over time in often challenging production environments. Furthermore, possible operating errors during the weighing process need to be identified and eliminated.

Additional References

METTLER TOLEDO white papers

- QbD and Weighing – Building Consistent Processes
- QbD and Weighing – Integrating Weighing Process Data

METTLER TOLEDO webinar

- QbD and Weighing - Ensure Consistent Weighing Quality in Pharmaceutical Manufacturing

Good Weighing Practice™ from METTLER TOLEDO provides a standardized scientific methodology for secure selection, calibration and operation of weighing equipment. On the basis of this evaluation, select from a broad range of scales, indicators and weighing applications to match specific process requirements and ensure the highest accuracy and reliability standards. Rely on a competent service offering and the largest field force in the industry to help maintain this integrated quality.

Learn more about how weighing solutions support Quality by Design principles:

► www.mt.com/ind-qbd

QbD guidance documents

- ICH Q8(R2): Pharmaceutical Development
- ICH Q9: Quality Risk Management
- ICH Q10: Pharmaceutical Quality System
- ICH Q11: Development and Manufacture of Drug Substances
- FDA: Pharmaceutical cGMPs for the 21st Century – A Risk-Based Approach
- FDA: Quality Systems Approach to Pharmaceutical CGMP Regulations

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