Quality by Design

QbD and Weighing

Building Consistent Processes

Weighing processes can contribute significantly to consistent final product quality in pharmaceutical manufacturing. Whether in formulation or filling, it is critical that the weighing solution is carefully selected to match the process requirements.

Weighing processes are important elements in many pharmaceutical manufacturing processes, such as batching, formulating or filling. Depending on the application, different aspects of weighing can play an important role in maintaining an accurate and reliable process and ensuring consistent product quality.

This white paper takes a look at the impact of these weighing processes on final product quality and explains what needs to be considered in a Quality by Design (QbD) based manufacturing process.

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METTLER TOLEDO

1 Introduction

Quality by Design (QbD) is increasingly implemented in pharmaceutical manufacturing, driven by the need to improve the final product quality and manufacturing process efficiency.

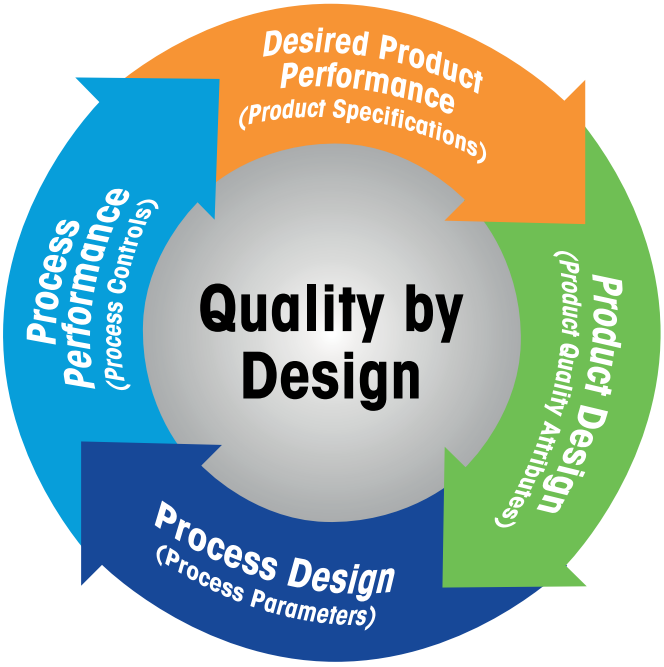
Build quality into the process

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. Weighing processes, such as batching, formulating and filling, critically influence product quality and should be considered in a comprehensive QbD concept. Inaccurate weighments can negatively impact the consistency of the blend of ingredients or the correct potency of the final product.

Optimize weighing processes to drive quality

Other applications, such as in-process control, check-weighing and contamination detection, help monitor and control the manufacturing process in real-time to ensure consistent product quality. Finally, the ability to track and trace the entire process from raw material to final product enables fast reaction and correction of relevant process parameters in case of quality deviations.

The aim of this white paper is to help understand the potential influence of weighing processes 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.



The Quality by Design Concept

2 Batching

An accurate, reliable weighing system that precisely measures and transfers ingredients is an essential part of the batching process.

Batch manufacturing is the dominant process in current pharmaceutical manufacturing. Whether automated, manual or a blend of both, the batching process requires an accurate and reliable weighing system to precisely measure and transfer ingredients. Furthermore, comprehensive monitoring and control of the process is essential in order to ensure high quality and batch-to-batch consistency.

Precision instruments ensure accurate weighments

Whether in a stand-alone or fully integrated batch control system, the precision required to achieve consistently high-quality products can be achieved with high-resolution weighing platforms.

The overall solution must manage the various types of material transfer onto the weigh platform and weigh each ingredient. A weighing terminal that can manage both activities lends itself to batching applications. It can help a control engineer simplify processes, because ingredient weighing and material transfer are essentially two parts of a single action.

In stand-alone systems, automated transfer and batch control can be managed with a weighing terminal with built-in S88 batch control guidelines. This provides a consistent application of the control system and helps eliminate operating errors due to inconsistent operation standards and user interfaces.

Advanced controllers enable exact material transfer

These batch controllers work as terminals for single or multi-scale or flow meter applications. High-speed filling, fast update rates and multiple-speed capabilities ensure that target weights are achieved quickly and accurately with extremely precise cut-offs. Automatic systems optimize the material-transfer process, ensuring that delivered quantities are within tolerance, even in environments where mixing occurs or there is excessive mechanical vibration.

Ensuring comprehensive monitoring and control of the batching process helps achieve a consistent product quality and fulfills an important aspect of the batch-release procedure.

Quality Attributes	Selected Solutions	Key Features
Accurate and reliable measurement results	K-Line precision-weighing platforms 	• Exact weighing within small 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
Precise and consistent creation of batches, measurement and transfer of ingredients	IND780batch weighing terminal with Q.i. material transfer software 	• Automatic control with hand-add flexibility • Predictive, adaptive control algorithms for optimal accuracy and throughput • Digital filtering of disturbing vibrations and noise

3 Formulation and Recipe Weighing

Sophisticated weighing systems safely guide users through the formulation process and help prevent operating errors.

Manual formulation remains very important—even on highly automated cutting-edge production lines. To ensure consistent product quality and process stability, several aspects must be realized. As a prerequisite, the weighing system must provide the required precision and accuracy to guarantee a correct measurement of ingredients. The use of correct formulation and weighing procedures helps prevent operating errors—whether in a stand-alone single-weighing station or an ERP integrated multi-user system.

Improved usability and secure guidance of operators help prevent measurement errors

Ensure safe and secure operator guidance

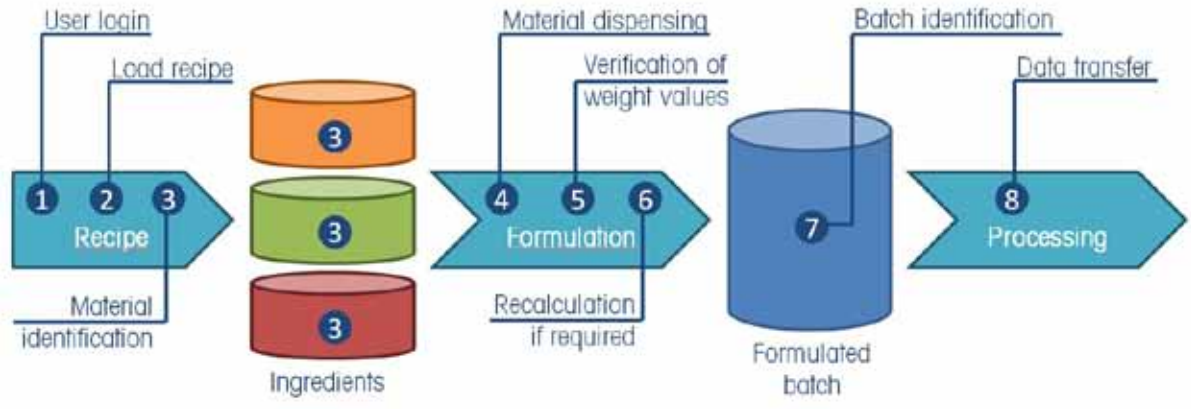
Simple and consistent prompts via the user interface ensure secure user guidance and reliable weighing. Screens must be designed for optimum readability for fast information recognition and analysis. Clearly visible instructions and color-coded weigh process results can help ensure a reliable and efficient process that increases accurate throughput.

Functions, such as batch identification, transfer of weight values within tolerances only, ingredient overweight correction options and automatic calculation of active ingredients, help maintain reliable product quality and avoid incorrect mixtures and waste of expensive ingredients.

Monitor and control the formulation process

Operator security plays a role here, too. Only trained and authorized users should be able to manage materials according to defined user rights. Additionally, the formulation system can reduce the risk of human error by checking the scanned material ID against the recipe and rejecting it in case of a mismatch. Hazardous material precautions can also be indicated clearly if necessary.

A formulation solution with easily integrated, standardized weigh stations, label printers and barcode scanners helps prevent material mix-ups and wrong material quantities. The solution helps ensure consistent product quality while also increasing production efficiency by reducing the number of out-of-specification batches that would need to be reworked or disposed.



Typical formulation workflow with quality-critical process steps

Quality Attributes	Selected Solutions	Key Features
Easy usability prevents operating errors	IND890 PC weighing terminal 	• 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 	• Material identification prevents material mismatchto the interior of the scale for thorough cleaning • Transfer of weight values within tolerances only • Automatic calculation of active ingredients and ingredient overweight correction options

4 Filling

Weighing is an ideal measurement for filling applications, ensuring consistent accuracy at high process speed.

Exact filling of raw materials or components is crucial for the effectiveness of pharmaceutical preparations. Both underfilling and overfilling are a health risk for consumers; underfilling can render a treatment ineffective while overfilling can endanger the patients' health. Therefore, process tolerances used for pharmaceutical production must be strictly adhered to.

Filling applications prevent over- or under-filling

Weight is an ideal measurement for filling applications, especially for liquid products, as it is determined completely independent from density, temperature and effects such as formulation of bubbles. However, the chance for errors in manual operation is considerable. These risks can be reduced by using sophisticated weighing solutions to automate relevant parts of the filling process and store important process data. The combination of high-resolution weighing equipment and statistical process and quality control software facilitates a highly accurate and reliable filling process.

Advanced functionality improves the filling process

High resolution and fast update rates of weight data allow for precise cut-offs required in filling processes to ensure accurate weighments. Further functionality, such as multi-speed filling, programmable spill values and jog functions, provide increased accuracy. In addition, a capable filling solution can perform rescaling based on the percentage of the programmed target, percentage of the available amount of material in a formula or a desired total formula weight. Finally, vibration effects from the manufacturing process can be suppressed effectively by a digital filtering system. This increased control and flexibility of the filling process can contribute significantly to the overall product quality.

Quality Attributes	Selected Solutions	Key Features
Precise, repeatable measurement data at high update rates	IND560 weighing terminal TraxDSP digital filtering 	• Utrafast A/D conversion and I/O bus update rate ensure precise measurement control • Tunable digital filtering suppresses environmental effects on weighing accuracy • Graphical display indicates current weight in relation to target value, reducing operating errors
Prevention of operator errors and improved filling accuracy	FillPlus Software 	• Programmable spill values and jog functions • Storage of up to 25 custom material formulas simplifying change-over and reducing programming errors • Automatic formula rescaling based on a percentage of target weight, or amount of material available

5 In-Process Control

In-process control solutions help to systematically record and eliminate product defects and ensure quality control in compliance with regulations.

The exact mixture and concentration of Active Pharmaceutical Ingredient (API) and excipients is crucial. Both underfilling and overfilling are a risk to consumer health and must be strictly avoided. As such, uniformity of dosage is the leading target of pharma production. Tolerance systems used for pharmaceutical products must follow strict rules for overfill and underfill.

Improve quality with systematic data analysis

Two important steps are performed in pharmaceutical production, which require thorough quality control to ensure consumer health and safety. One is in-process tablet testing after pressing or encapsulation and the other is packaging control of the complete product. The use of a capable statistical process and quality control tool allows the systematic acquisition of quality data, their analysis, documentation and monitoring based on predefined tolerance values.

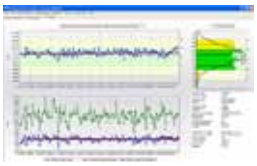
Such an in-process control system should help to enforce predefined quality standards, which already exists in many cases. Therefore, it is important that the system is flexible enough to adapt to the specific procedures and to allow implementation into an existing environment.

In-process control systems help record and analyze process data to ensure consistent quality

Ensure adaptability of the in-process control system

The system should also be open to connect a wide range of measuring equipment and sensors directly or through the local area network. Solutions for in-process control range from embedded compact products up to networked systems with distributed test sites and a centralized database.

In addition to controlling the individual tablet and its correct amount of active ingredient, an in-process control solution can check completeness of individual blisters or the entire consumer package including box, blisters and leaflet.

Quality Attributes	Selected Solutions	Key Features
In-process control of quality attributes	FreeWeigh.Net 	• Real-time monitoring and control of predefined tolerance values • Systematic capturing, analysis and documentation of quality data • Quality control of single units (tablets) • Filling control of individual blisters or completeness checks of entire consumer packages

6 Checkweighing

Checkweighers are important quality-control tools, ensuring completeness and integrity of ingredients and products as well as packaging.

The pharmaceutical industry has very unique and demanding requirements in its choice of manufacturing equipment. This is especially true in the field of checkweigher software requirements and safe product handling where high volumes of lightweight and difficult-to-handle products need to be weighed at very high production speeds with extremely tight tolerances. Checkweighers are used as part of overall quality control programs, providing safety to both manufacturer and consumer. They ensure that products fully comply with industry standards and government regulations and contain the correct quantity of ingredients or parts.

This includes:

- Weight-based counting of contents in bottles and packaged parts,
- Checking volume or density of a mixture and
- Checking for missing leaflets or instructions, blister packs of products or single tablets and capsules.

As checkweighers weigh 100 percent of the items on a production line, they provide a complete overview of production data, such as production counts, batch tracking, total weights, good weights and rejected weights.

Although checkweighers can represent a significant capital investment, not only do they provide quality-control functionality, but they also help improve performance through waste reduction, tighter tolerances and more consistent end products. The information that a quality team would previously have collected manually can be collected in a fraction of the time by a checkweigher.

Integration of other devices such as cameras, scanners, metal detectors and x-ray devices add up to a high performance inspection solution.

Combine accurate weighing, marking and vision verification control in one compact system

Quality Attributes	Selected Solutions	Key Features
Completeness of content or packaging	XS2 Pharma 	• "Weights and Measures" design-approved • Completeness check (leaflet, blister) and up to 200 product memories • Validation support with PQ, OQ, IQ, DQ material • Access protection by password material

7 Contamination Detection

Metal detectors and X-ray systems help to identify contaminants in-line and at the end of the process to ensure consistent quality of the final product.

For many years X-ray inspection and metal detection systems have been popular because of their ability to detect and reject a wide range of metallic contaminants from within the production process. X-ray machines are also now gaining popularity by adding mass measurement, identification of missing/broken parts and fill level while also offering exceptional glass, stone, high-density plastic and rubber compound detection.

The main sources of contamination come from raw materials used in the production of pharmaceuticals as well as from the manufacturing process itself. Eliminating contaminants as early as possible in the production process is vital. For example, mechanical processing can break contaminants down into smaller, less detectable pieces that are more widely spread. Although modern manufacturing techniques constantly strive to eliminate contaminants, there is an inherent risk of contamination during the production process for example, when product is transferred from one process to the next or new installations or maintenance routines are performed.

On its own, a contamination detection system cannot guarantee a product is free from foreign bodies. A well-designed contamination detection program focuses on good manufacturing practices, correct equipment selection, proper installation and consideration of equipment in a broader contamination detection program.

The goal should be to prevent contaminants in the first place and not to simply catch them before they leave the factory. As part of a continuous improvement program, a contaminant detection system will lead to overall quality improvement.

Quality Attributes	Selected Solutions	Key Features
Detection of metal contaminants	Safeline Tablex-PRO ablet metal detector 	• Supports compliance needs to 21 CFR Part 11, Part 210 and Part 211. • Detects ferrous, non-ferrous and non-magnetic stainless steel sieve wire, sliver and swarf metals to 0.3mm and less. • Comprehensive support documentation and Equipment Qualification EQ Pac-PRO
Detection of metal and non-metal contaminants and identification of missing or broken parts	Safeline X-ray inspection 	• Exceptional detection of contaminants such as metals, glass, stone, calcified bone, and more • Simultaneous performance of a range of in-line product integrity quality checks • Compliance with Hazard Analysis and Critical Control Points (HACCP), retailer requirements, national and international regulations

8 Tracking and Tracing

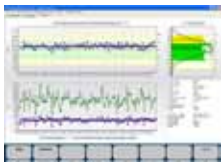
Weighing systems can capture and store relevant process data according to regulations to enable quick identification and correction of quality issues.

The ability to document the entire manufacturing process and trace back from the final product to its production batches and raw materials is an important aspect of the weighing applications discussed in this document. Whether in dispensing, formulation or filling, regulations require the documented information of when the product was made, what and how much material was used and which operator ran the particular batch.

- PC-based recipe weighing solutions provide seamless documentation of which recipe was weighed when, where, how and with which raw materials.
- Stand-alone scales function as identification points with barcode scanners and printers.
- Fully integrated solutions with scales, touchscreen terminals, scanners and printers capture relevant process data from goods-in to commissioning and shipment.
- Data integration into existing manufacturing execution systems or enterprise resource planning systems ensure traceability along the entire value chain.

Weighing solutions can be a key component in ensuring the required traceability is fulfilled and compliance with GMP regulations, such as the U.S. Food and Drug Administration's 21CFR Part 11, is ensured. This includes implementation of user-access control, electronic signatures, device version and serial number control as well as audit trail functionality.

Implement consistent tracking and tracing capabilities

Quality Attributes	Selected Solutions	Key Features
Consistently documented and traceable quality	FreeWeigh.net 	• Comprehensive monitoring of quality critical process steps • Consistent documentation of production process and capturing of quality data • Designed for 21 CFR Part 11 compliant production environments
Comprehensive capturing of process data	FormWeigh.Net 	• Easy identification of components, raw materials, devices and resources • Documentation of every process step • Implementation of audit trail functionality • Designed for 21 CFR Part 11 compliant production environments
Track-and-trace information inscription	XS2 MV 	• Global anti-counterfeiting solutions and brand protection • Fulfillment of legal requirements • Improved product safety • Validation support with PQ, OQ, IQ, DQ material

9 Summary

Weighing processes are an essential element in ensuring consistent product quality and meeting regulatory requirements. Depending on the application, different quality attributes need to be considered in a risk assessment approach. The availability of accurate and reliable measuring results is the basis for all weighing related applications. In batching and filling, the accurate and fast transfer of these results to controller and I/O devices is essential to ensure consistent product quality. In formulation, it is critical to prevent the use of wrong amounts of material or even wrong materials to guarantee accurate formulations. Checkweighing, x-ray, and metal detection systems as well as in-process control solutions help fulfill regulatory requirements and ensure consistent product quality. Finally, the solutions described herein provide comprehensive monitoring and control of the manufacturing process, enabling real-time corrections of manufacturing tolerance deviations and fulfilling required regulatory requirements.

A comprehensive Quality by Design framework for pharmaceutical manufacturing needs to consider the risks that an inadequate weighing process may pose, as well as the benefits that a well-designed solution can provide to ensure consistent product quality.

Learn more about how METTLER TOLEDO weighing solutions support Quality by Design framework at

▸ www.mt.com/ind-qbd

Additional References

METTLER TOLEDO white papers

- QbD and Weighing – Ensuring Accurate Measurements
- QbD and Weighing – Integrating Weighing Process Data

METTLER TOLEDO webinar

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

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

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