

Validation of Weighing Processes

Are You Up-to-Date?

Good Manufacturing Practice guidelines are continuously revised to consider technological changes and current practices in pharmaceutical manufacturing. Process validation is a key requirement of all regulations.

The weighing experts from METTLER TOLEDO help you design weighing processes, qualify weighing equipment and continuously monitor it to ensure reliable product quality and avoid unpleasant surprises during audits.

Process validation contributes significantly to ensuring drug quality, but it also places a heavy burden on pharmaceutical manufacturers. It requires significant effort and resources that result in additional costs. Pharmaceutical production, and the validation of such a process, is a complex task that needs to consider many aspects, including weighing. Weighing has a significant impact on quality, both in production and in the laboratory. Therefore, weighing equipment must be qualified and critical weighing processes need to be validated. This white paper explains how METTLER TOLEDO weighing compliance experts can help you get through the validation lifecycle efficiently.



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1 Validation Overview and Recent Regulatory Changes

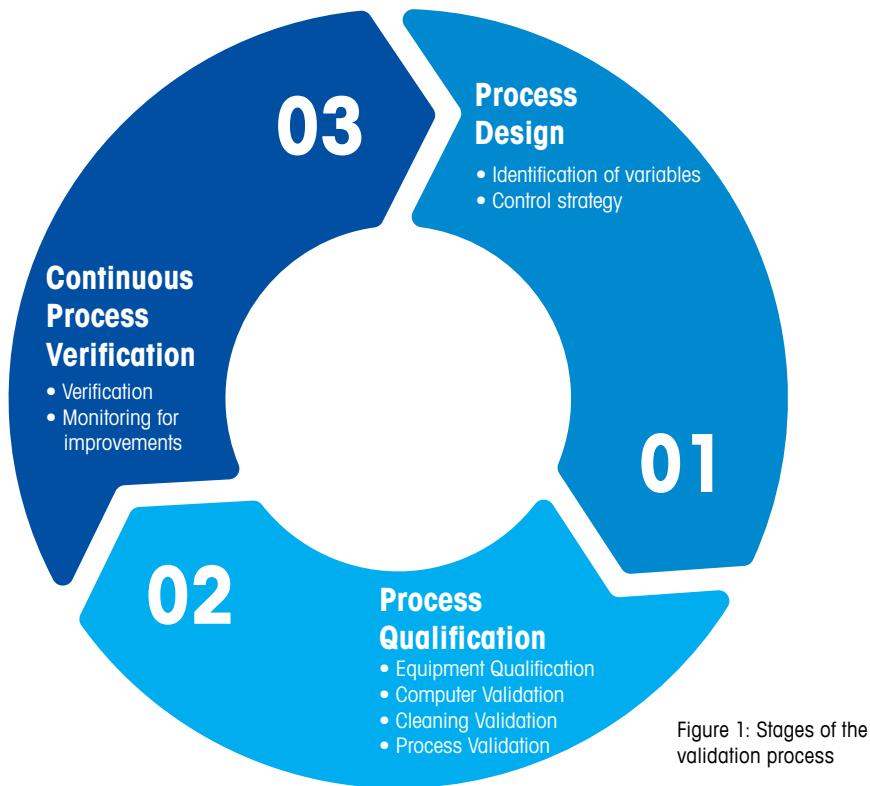
Charles Darwin famously said that "nothing in the history of life is as constant as change." That also is true for Good Manufacturing Practice (GMP) Guidelines. In 2015, the European Commission published a revision of Annex 15^[1], focusing on Qualification and Validation. The World Health Organization (WHO) also published Appendix 7 on "Non-sterile process validation."^[2] The U.S. Food and Drug Administration (FDA) published updated guidance on process validation in 2011^[3]. The revisions include consideration of technological changes and current best practices in GMP.

Process validation is a legally enforceable requirement in the U.S. and the European Union, as well as many other countries where drugs are produced. It is defined as a series of activities that establish scientific evidence that a process is capable of consistently delivering high-quality product.

All of the guidelines describe the validation process in three main stages over the lifecycle of the product and processes.

- Stage 1 is the **Process Design** of commercial manufacturing processes, which include the identification of critical process attributes and parameters.
- In Stage 2, the **Process Qualification** stage, the design is evaluated to confirm reproducibility and consistent quality.
- Stage 3 includes **Continuous Process Verification**, carried out during routine production to gain assurance that the process remains under control.

Understanding and controlling the sources and impact of variations on product attributes is the goal of the validation process. The revised guidelines place considerable emphasis on this task.



2 Weighing Processes in Pharmaceutical Manufacturing

Weighing occurs at various stages of the pharmaceutical manufacturing process. Nowadays, scales are built into complex machinery, such as filling machines or reactors. They also can be connected to human machine interfaces (HMIs) or computers running software that guides operators through production processes. Initially, scales are used in material receiving to verify incoming or outgoing components and reconcile inventory. Next, scales and balances are found in dispensing areas to weigh components according to predefined formulations. Then, scales are used when checking for completeness or monitoring production yield. Finally, weight-based quality control confirms the weight of tablets using the principle of mass uniformity or vial fill level is qualified using statistical quality control (SQC) software. In quality control labs, balances belong to the most widely used equipment for standard preparation, assays and impurity profiles.

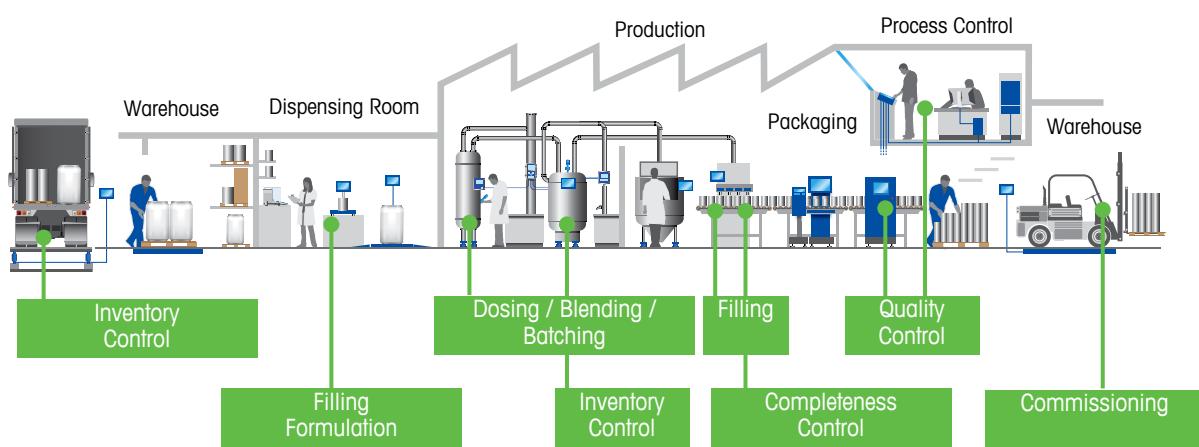


Figure 2: Weighing processes in pharmaceutical manufacturing

Weighing processes are critical to high-quality products and the performance of the scale is a critical process parameter (CPP). Good Weighing Practice™ (GWP®) provides outstanding support in weighing process validation and equipment qualification.

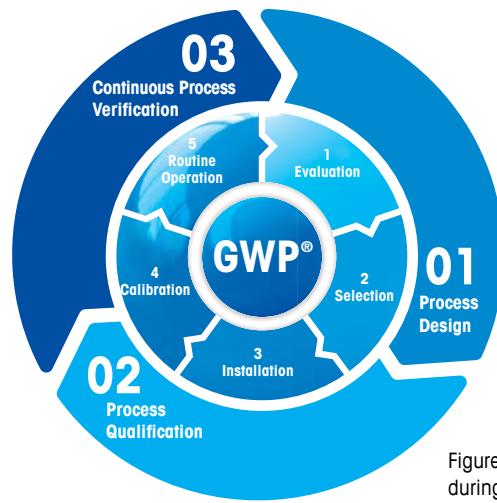


Figure 3: Good Weighing Practice™ during the validation process

The following chapters focus on the three stages of the validation process and describe important weighing considerations to ensure adherence to quality goals.

3 Process Design

The goal of this stage is to design a process suitable for routine commercial manufacturing. A combination of Design-of-Experiment (DoE) studies and risk analysis tools help establish ranges for incoming component quality, in-process parameters and in-process material qualities. Process controls consisting of material analysis and equipment monitoring at important processing points address variability to assure product quality.

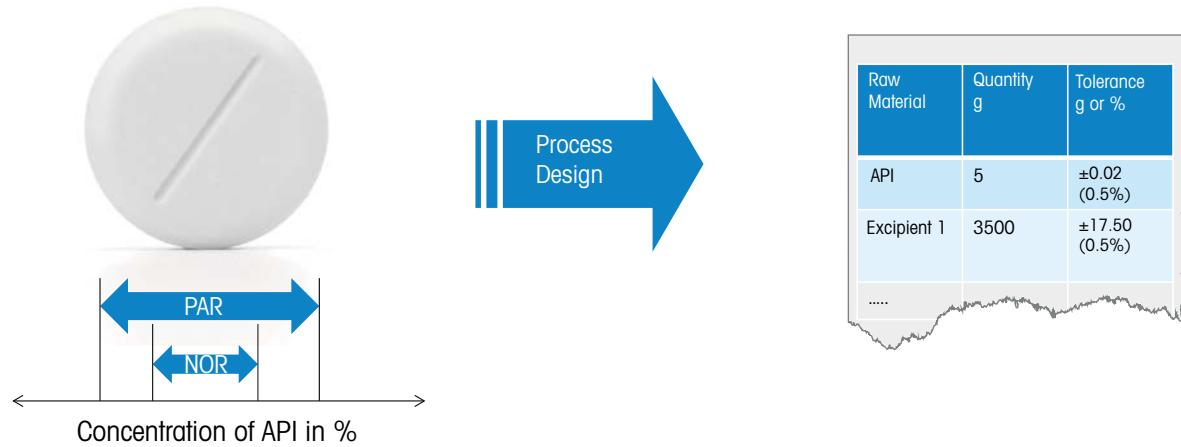
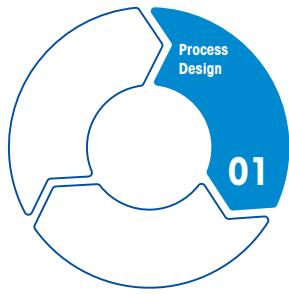


Figure 4: Process design, from product target profile—defined by proven acceptable ranges (PAR) and normal operating ranges (NOR)—to the production process.

Weighing-Process Design

When designing a weighing process for production, it is important to note that GMP gives general guidance, but defining tolerances remains the responsibility of the manufacturer^[4]. Therefore, criticality should be examined for each weighing step considering the impact of out-of-tolerance measurements on critical quality attributes and what extent of variability of the weighing result is still tolerable.

Such a risk assessment not only should consider the impact of inaccurate weighments on consumers, but also on business and how easy inaccurate measurements are detected. The results will directly influence your weighing tolerance, the safety factor to apply and, at a later stage, testing and calibration intervals.

Weighing Tolerance and Safety Factor

When one considers the experience gained during the design phase, as shown in Figure 4, the **weighing tolerance** can be calculated with the following formula:

$$\text{Weighing Tolerance (\%)} = \frac{\text{Allowable variance [g]}}{\text{Net weight [g]}} \cdot 100$$

GMP Guideline on Weighing Equipment

- "Weighing and measuring devices should be of suitable accuracy for the intended use." (ICH Q7A GMP, Sec. 8.1)
- "Balances and measuring equipment of an appropriate range and precision should be available for production and control operations." (Eudralex Volume 4, Sec. 3.40)

The **safety factor** helps to compensate for environmental influences, user error or other random influences on the weighing result, such as temperature variation, vibrations, draft, electrostatics and others. Figure 5 gives some examples on how to choose the safety factor^[5].

Condition	Safety Factor
Perfect at the time of installation (any operational and environmental variations will lead to failure in the future)	1
Low influence factors (very stable environment)	2
Higher influence factors	3
Unstable environment, harsh conditions	>4

Figure 5: Safety factors

Safe Weighing Range

The safe weighing range of a specific instrument is the range in which the user fulfills both the weighing tolerance requirement and adheres to the required safety factor (Figure 6).

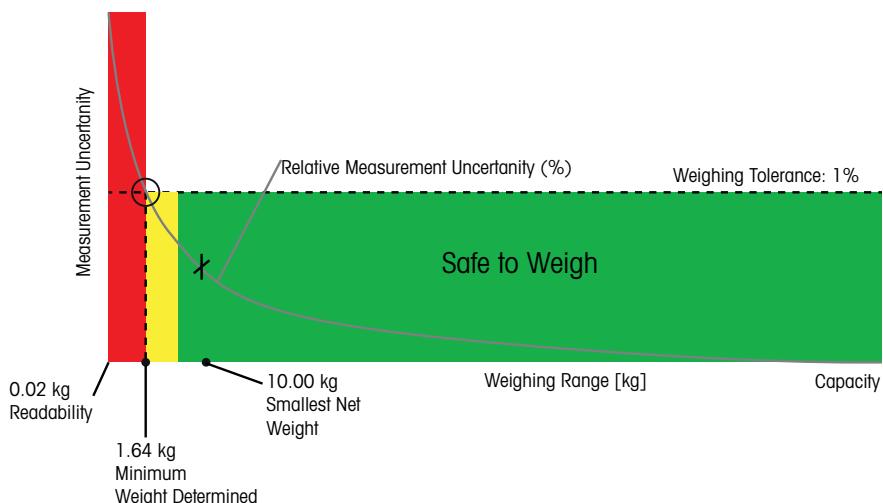


Figure 6: Safe weighing range

The lowest accuracy limit of the instrument, also called the minimum weight (MW), is the intersection point between the relative measurement uncertainty and the required relative weighing tolerance. Weighing quantities in the red area pictured above will result in non-compliance to accuracy requirements. Weighing quantities in the green area, which is the safe weighing range, ensures the tolerance requirements are met. Weighing quantities in the yellow area fulfills user accuracy requirements; however, the safety factor (SF), is not adhered to.

For example, in the dispensing area, typically one balance or scale is not enough to perform all necessary measurements because the component net weights vary between fractions of grams to hundreds of kilograms. Highly potent active pharmaceutical ingredients (APIs) not only are weighed in small amounts, but also have to be weighed with a high degree of accuracy. That means tighter tolerances must be used that require the use of a suitable weighing instrument to ensure the defined measurement uncertainty. The safe weighing range guarantees that every component is weighed on a scale with the appropriate proven accuracy.

High-accuracy scales minimize weighing result variability, leading to increasingly high quality. Scales based on the electro-magnetic force compensation principle, such as the METTLER TOLEDO PBK9/PFK9 line, result in a particularly broad safe weighing range. They make it possible to weigh small amounts within tight tolerances (for example, 50 grams +/-1% on a 600 x 0.001 kilogram scale). A typical lower accuracy analog scale would require that the minimum weight for the same tolerance be at least 10 times higher.

The selection of the "correct" weighing device is critical, but it can also be made simple by using a GWP® Recommendation, which takes into consideration your accuracy requirements.

Support during Process Design

Good Weighing Practice™ (GWP) is based on scientific methodology to help you select the scale that meets your accuracy needs^[6]. The resulting documentation provides evidence that you have selected the device that meets your exact process requirements.

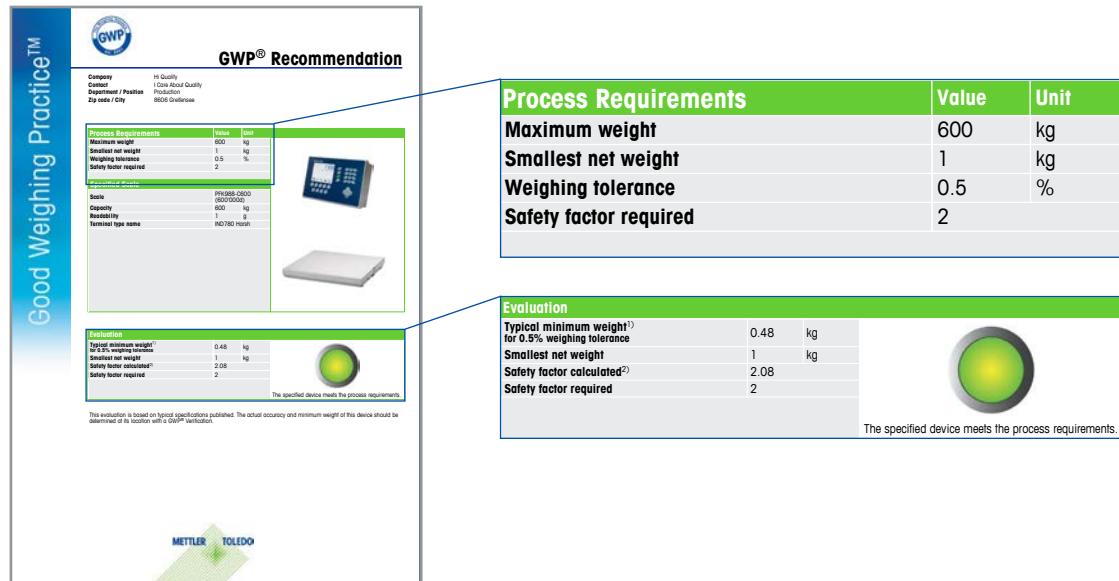


Figure 7: Example of a GWP® Recommendation

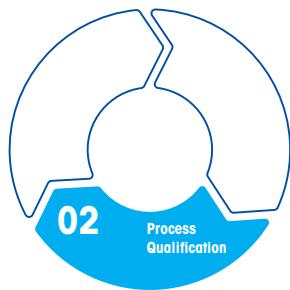
When designing a GMP-compliant weighing station, you may also need to consider the following non-metrological parameters:

- Designing the workspace to allow for efficient work flow
- GMP-compliant management of weighing data (considering documentation guidelines, data safety and 4-eye principle, connectivity to ERP and MES systems)
- Safety considerations and hazardous-area classification
- Efficient and thorough cleaning
- Maintenance, calibration and routine testing

A METTLER TOLEDO specialist can help you define the User Requirement Specifications (URS) for your weighing process meeting all the above mentioned considerations.

4 Efficient Process Qualification for Weighing Processes

Process qualification includes equipment qualification, software validation, cleaning validation and the process validation itself.



4.1. Equipment qualification

The qualification of important equipment – including weighing devices – used during drug manufacturing is a prerequisite for each process validation.

The first step is the **Design Qualification**. The purpose of design qualification is to obtain documented verification that the proposed design of the equipment or system is suitable for the intended purpose. To assist in this process, METTLER TOLEDO provides a GWP® Recommendation for each weighing device.

Installation Qualification is the documented verification that the equipment or system complies with the approved design, the manufacturer's recommendations and/or user requirements. It verifies that the weighing instrument is received as designed and specified; that it is properly installed in the selected environment; and that the environment is suitable for the operation of the instrument.

Operational Qualification is the documented verification that the equipment or system performs as intended throughout the anticipated operating ranges. In this step of the qualification process, the function of the equipment is tested. A key element is the calibration of the weighing instrument. That includes determination of measurement uncertainty and the safe weighing range (see Figure 7).

Performance Qualification is the documented verification that the equipment and ancillary systems, when connected together, can perform effectively and reproducibly based on the approved process method and specifications. Performance qualification provides assurance that the weighing system delivers consistently accurate measurements. A defined schedule for routine testing and calibrations is essential. The frequency of test and calibration intervals needs to be based on a risk assessment of the actual application.

Equipment Qualification Process			
DQ	IQ	OQ	PQ
Design Qualification	Installation Qualification	Operational Qualification	Performance Qualification
User Responsibility			
<ul style="list-style-type: none"> • Describe intended use of scale • Select scale • Select supplier 	<ul style="list-style-type: none"> • Compare equipment with PO • Check for damage • Completeness of documentation 	<ul style="list-style-type: none"> • Develop SOP for OQ • Set time intervals and acceptance criteria • Completeness of documentation 	<ul style="list-style-type: none"> • Select service provider • Define how to detect, record, and handle errors • Maintain log book
Support for Weighing Equipment			
<ul style="list-style-type: none"> • Documentation • Consultation • GWP® Recommendation 	<ul style="list-style-type: none"> • Technical Support • Manpower • Equipment Installation and Qualification 	<ul style="list-style-type: none"> • Initial Calibration • Documentation • GWP® Verification 	<ul style="list-style-type: none"> • Preventive Maintenance • Regular Calibrations • GWP® Re-Verification

Figure 8: Weighing equipment qualification process

Once the equipment qualification is successfully completed, the entire process can be validated. However, when critical components of the weighing system are replaced or modified, a re-qualification is required.

Revised Annex 15 states that qualification documents may be combined together (e.g. installation qualification and operational qualification). For complex equipment, such as filling machines or reactors using weigh modules, the preassembled factory acceptance test (FAT) can be an element in the equipment qualification process.

Support During Equipment Qualification

The **IPac installation package** for balances and scales covers the necessary steps of equipment qualification from IQ to OQ. A METTLER TOLEDO Service technician carries out all the steps according to standardized SOPs and describes the findings in a standardized format, making sure all the relevant parameters are tested. If required, user-specific formats can be used.

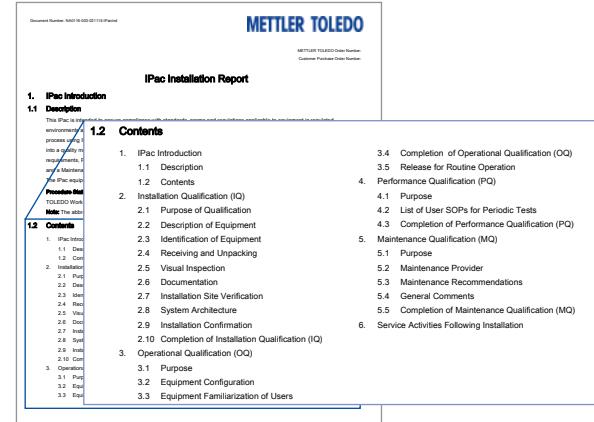


Figure 9: Scope of IPac installation report

A **GWP® Verification** considers the required accuracy of all installed weighing devices. Following calibration, the resulting Accuracy Calibration Certificate determines the measurement uncertainty of the scale in the installed environment. It also provides documentation that the scale performs according to your defined weighing tolerances. In a second step, according to a risk assessment, GWP® Verification provides information on performance verification, which forms basis for the standard operating procedures that define the frequency of routine calibration and routine tests, including the type of tests and required weights. METTLER TOLEDO provides sample SOPs describing procedures for each test as well and offers a service to help you adapt your SOPs accordingly.



Figure 10: GWP® Verification

4.2. Software Validation

Production data can be integrated into the weighing process and weight data is recorded and can be easily analyzed. Statistical process control software, such as Freeweigh.Net®, or FormWeigh.Net® formulation and dispensing software, manages materials efficiently and analyzes weighing data to continuously monitor critical process parameters. They offer thorough user guidance and automation of certain tasks to avoid errors. Both systems comply with specific regulations regarding validation of computerized systems and provide the necessary controls for handling of electronic records and signatures. Validation verifies whether the functions of the system comply with its specifications and proves that the functionality covers all aspects of its intended use.

All current GMP guidelines require that computer-assisted systems used in pharmaceutical production are validated at the level appropriate for their use and applications^[7]. The steps required for the validation of a computer-assisted system can vary depending on the scope and complexity of it. The GAMP Guide, now in its 5th edition published by ISPE in 2008, gives practical advice on how to satisfy regulatory requirements^[8].

In principle, software validation can be divided into five basic steps as described in Figure 11.

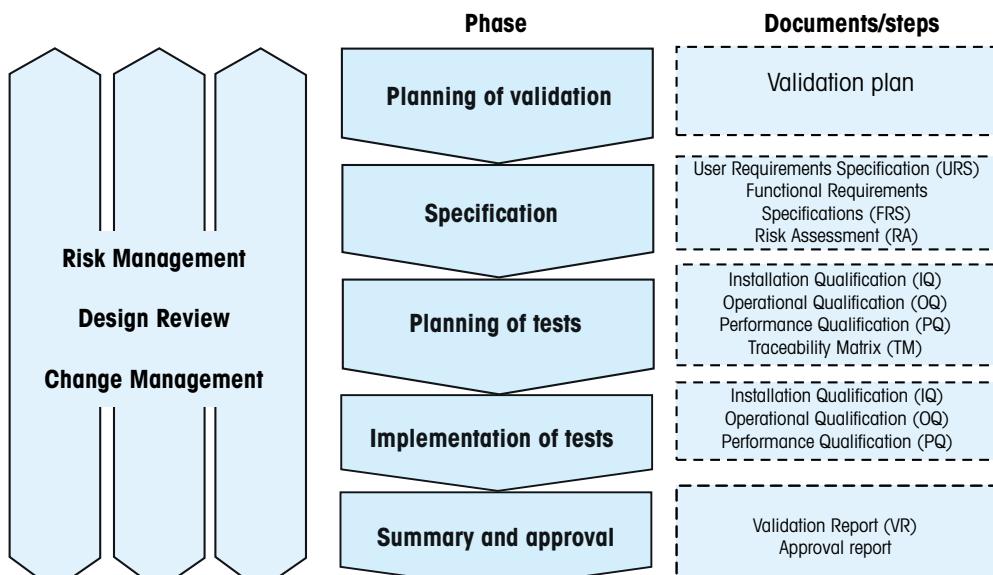


Figure 11: Phases of computer system validation

Revalidation of the system is required when critical components of a system are modified or replaced.

With the **Computer Software Validation Pac** (CSVpac), METTLER TOLEDO offers a comprehensive set of validation manuals and product documentation for FormWeigh.Net or FreeWeigh.Net following the GAMP guide to speed up the entire implementation and validation process. The validation manuals are pre-configured for a general system and contain all necessary information for a supplier audit and the procedures for IQ and OQ. As each system is tailored to specific processes and setups, users can create the manuals with the support of METTLER TOLEDO. In addition on-site service by a dedicated software validation specialist for all the process steps is available.

4.3. Cleaning validation

Another important step is the cleaning validation. It should be performed for all equipment that is in contact with the product and should confirm the effectiveness of cleaning procedures to prevent possible contamination and cross-contamination.

METTLER TOLEDO scales designed for use in pharmaceutical environments have been evaluated by an independent testing institute with consideration for GMP guidelines and current practices in cleaning validation. The certificate describes the risk assessment and a typical cleaning methodology^[9]. When looking at scales, this is especially relevant for platforms and the load plates. The cleaning ability is confirmed by the cleaning validation.

A general statement for non-critical products can be made with the criteria "visually clean." According to the literature, it means that backlogs of 375 µg per 100 cm² are not visible. However, in the new Annex 15, visually-clean criteria are not enough. Further tests including a swap test, extraction with a suitable medium and determination of the residual amounts with a suitable detection method have to be carried out to confirm cleanliness.

Stainless steel and electro-polished surfaces ensure that chemicals and bacteria are removed from the surface of the load plate more easily. They also help to avoid damage of surfaces by corrosion when working with aggressive chemicals or cleaning agents. Smooth welding seams and avoidance of sharp angles make the cleaning process safe and efficient and help avoid unpleasant surprises during the cleaning-method verification. An ingress protection level of IP65 or above ensures the load cell on the balance does not get damaged during the cleaning processes.

When developing your cleaning SOP, make sure to check that the scale is level and includes a routine testing and re-calibration of the device if it is moved.

5 Ensure Continuous Weighing Performance Verification

Manufacturers should monitor product quality to ensure that control is maintained throughout the product lifecycle with the relevant process trends evaluated. That also applies to equipment. The revised guidelines state that equipment should be evaluated at an appropriate frequency to confirm that it still remains in a state of control. Also the possibility of small changes over time should be assessed.



But what is the appropriate type and frequency of tests to verify the performance of weighing equipment? Again, a risk-based approach must be used to define routine testing, calibration intervals, the types of tests to perform and which test weights to use. The risk assessment is based on the criticality of each process and the weighing accuracy is completed using a calculator within the METTLER TOLEDO GWP® Verification.

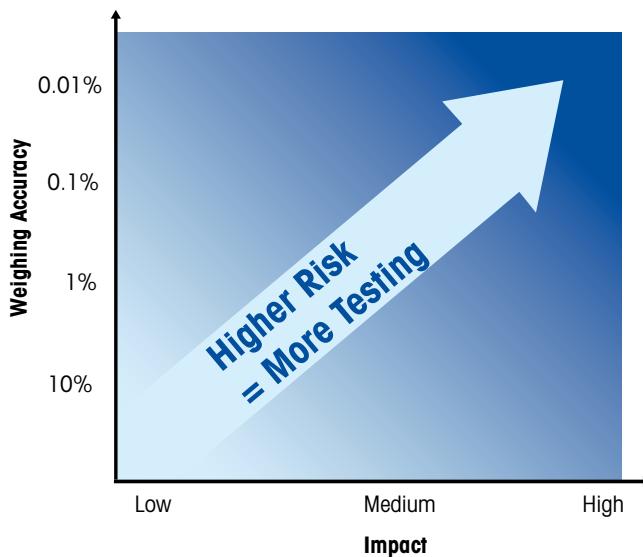


Figure 13: Risk assessment for defining testing intervals

GWP® Verification provides globally recognized assurance for optimal weighing performance with minimal testing efforts. All performance verification procedures are described in a single document devised for auditing purposes. This assessment is independent of the weighing equipment manufacturer, which means that it can be used for all weighing devices.

Risk Assessment

Weighing tolerance	0.5%
Business impact of inaccurate measurements	Medium
Consumer/environment impact of inaccurate measurements	Medium
Easy detectability of inaccurate measurements	No

Recommended performance verification

Tests			
Maintenance (by service)	Yearly		
Calibration (by service)	Yearly		
Minimum weight / GWP certificate (by service)	Yearly		
Linearity (by service)	Yearly		
Eccentricity (by user)	-		
Repeatability (by user)	Quarterly		
Sensitivity (by user)	Weekly		
Weights			
Weight 1 (Sensitivity and Eccentricity)	50kg	Class	M2 or better
Weight 2 (Repeatability)	5kg	Class	M2 or better
Weights recalibration interval ⁽²⁾	Every two years		
Test tolerances⁽³⁾			
Sensitivity			
Weight 1	Warning Limit	0.063 kg	
	Control Limit	0.125 kg	
Weight 2	Warning Limit	0.4 g	
	Control Limit	0.9 g	
Repeatability (minimum number of measurements: 6)			

Figure 14: Example of performance verification with GWP®.

6 Summary

Proper validation is the prerequisite for compliant production processes in pharma manufacturing. Thorough understanding of the processes and their critical process parameters is key to running a smooth and efficient validation. Because balances and scales are present throughout production and their performance is quality-critical, METTLER TOLEDO provides both GWP® Recommendation and GWP® Verification. METTLER TOLEDO can support you during the design, installation, testing and regular use of weighing equipment. Our scientific methodology and solid risk assessment according to Good Weighing Practice ensures stable product quality throughout the manufacturing process lifecycle. With the proper documentation, you can effectively satisfy GMP requirements in the validation process.

Stage 1 Process Design	Stage 2 Process Qualification	Stage 3 Continuous Process Verification
<p>Requirements:</p> <ul style="list-style-type: none">• Identifying critical weighing steps• Defining weighing tolerances• Defining URS• Describing the weighing process <p>Our support:</p> <ul style="list-style-type: none">• Specialist consultation• GWP® seminars• White papers, webinars, Application notes	<p>Requirements:</p> <ul style="list-style-type: none">• Equipment Qualification• Cleaning Validation• Computer Validation• Process Validation <p>Our support:</p> <ul style="list-style-type: none">• Documented installation procedures• Calibration certificates• GWP® Verification• SOP development• User training• Cleaning instructions and GMP certificates• Software validation	<p>Requirements:</p> <ul style="list-style-type: none">• Continuously verifying performance of equipment <p>Our support:</p> <ul style="list-style-type: none">• Maintenance contracts• Calibration services• GWP® Re-Verification• Test weights for routine testing

Figure 15: Our support to your validation of weighing processes

7 Additional Resources

- [1] EudraLex, Volume 4, Annex 15: Qualification and Validation;
- [2] World health organization (WHO), Annex 3, Guidelines on Good Manufacturing Practices: Validation, Appendix 7: non-sterile process validation
- [3] FDA, "Guidance for the Industry, Process Validation: General Principles and Practices, January 2011. CGMP Revision 1
- [4] White Paper: Regulatory Compliance – Weighing in Pharma Manufacturing
- [5] White Paper: GWP Verification – Safety Factor
- [6] K. Fritsch, "GWP® - The Science-Based Global Standard for Efficient Lifecycle Management of Weighing Instruments", J. Meas. Sci. 8, Vol. 3, p. 60 ff, September 2013
- [7] General Principles of Software Validation; Final Guidance for Industry and FDA Staff", US FDA
- [8] ISPE (2008). "GAMP5: Risk Based Approach to Computer Compliance". International Society for Pharmaceutical Engineers, Tampa, FL.
- [9] Certificate for suitability of weighing equipment in GMP environment; Steinbeis Transferzentrum Tübingen, 2015.

► www.mt.com/GWPVerification
► www.mt.com/IPac
► www.mt.com/Validation
► www.mt.com/Calibration