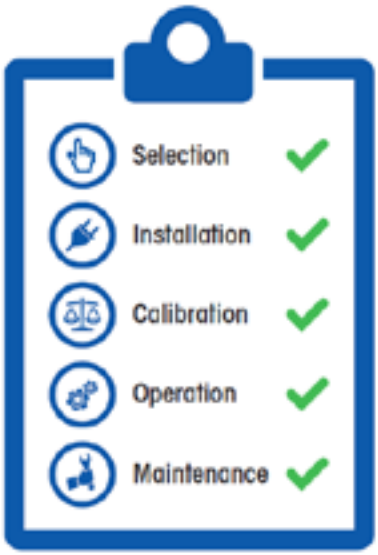
White Paper

Regulatory Compliance

Weighing in Pharma Manufacturing

Weighing applications in pharma manufacturing can strongly influence final product quality. However, broad regulations, such as GMP, usually leave much to interpretation. This white paper explains which regulations are relevant and how to ensure compliance along the entire weighing product lifecycle.

The pharmaceutical industry is one of the most regulated in the world. National and international standards and regulations, such as Good Manufacturing Practice (GMP), are becoming increasingly important, if not a prerequisite for conducting business. Companies are allocating significant resources to ensure regulations are implemented and processes are validated. According to a survey recently conducted by Pharma IQ[1], nearly 50 percent of the participating pharma professionals stated that they spend more than 40 percent of their working time dealing with regulatory issues. When asked how they would classify the level of governmental regulation, 67 percent of the respondents stated that the pharma industry is "regulated the correct amount" or "regulated too lightly."



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The Pharma IQ survey depicts the trend of increasingly stringent regulations in the pharmaceutical industry. However, regulations usually only provide broad guidance (e.g. measuring devices must be calibrated) and leave it to the manufacturer to define the criteria to ensure regulatory compliance (e.g. how often to calibrate). This intentional vagueness provides the necessary flexibility to the manufacturer to adapt quality control procedures to the specific process requirements, but it also contributes to uncertainty about which practices are sufficient. Thus, an in-depth understanding of the regulations, processes, technology and metrology is essential to ensure compliance.

Weighing applications in pharma production are usually only one part in a complex process. However, they can strongly influence the quality and integrity of the final product. For example, weighing is critical to achieving batch uniformity and consistency in dispensing or formulation processes. When planning to purchase new weighing solutions, companies usually define the requirements according to the relevant regulations and the company's processes in a User Requirement Specification (URS) document. Once the weighing solution has been selected and installed, equipment qualification and, if required, process validation must be conducted to prove that the installed solution fulfills the requirements as specified in the URS and that it is compliant with regulations and process specifications.

But what are the relevant regulations with regard to weighing applications? How should weighing systems be selected, installed and validated? How should maintenance and service processes be established? The aim of this white paper is to provide an overview of the regulatory landscape related to weighing processes in pharmaceutical production and explain the challenges those regulations pose to manufacturers. Furthermore, the white paper shows how manufacturers can utilize the weighing standard GWP® to ensure regulatory compliance throughout the entire weighing product lifecycle.

1 Regulatory Overview

In pharmaceutical manufacturing, a range of regulations and industrial standards, both national and international, provide guidance to help ensure product safety and efficacy.

Good Manufacturing Practice (GMP)

Good Manufacturing Practice (GMP) can be considered the most important regulation, defining the rules for safe and effective manufacturing of pharmaceutical products. GMP regulations are not prescriptive instructions but consist of guidelines based on general principles that must be observed by the manufacturer. These principles include, for example, the validation of processes, recordkeeping, operator training or prevention of cross-contamination. However, they usually refer to a Pharmacopoeia for specific standards and methods. It is up to the manufacturer to design the production processes and quality programs in accordance with GMP principles.

[1] Pharma Regulations Landscape 2020, Pharma IQ, 2014

Most countries have legislated that pharmaceutical manufacturers must follow GMP procedures and have developed their own version of GMP. However, two main bodies drive the development of GMP with a strong global influence. These are the U.S. Food and Drug Administration (FDA) and the European Medicines Agency (EMA).

The FDA historically has had a leading role in establishing procedures and legislation for the pharmaceutical, food and cosmetics industries. It governs the Code of Federal Regulations Title 21 (21 CFR). Relevant for drug manufacturing is specifically the 21 CFR Parts 210 and 211, also called "current Good Manufacturing Practice" (cGMP)[2]. FDA governance has significant international influence because manufacturers outside the USA have to adhere to FDA regulations if they want to export to the country. This is especially relevant because the USA is the largest market for pharmaceutical products, both in production and consumption.

Weighing in the dispensing room

Within the European Union, the EMA provides harmonized GMP guidelines (EudraLex Volume 4[3]) for 28 European member states and governs a centralized authorization procedure for pharmaceutical products. Many regulatory authorities from countries around the world have adopted the International GMP[4] developed by the World Health Organization (WHO).

Due to the fast-growing globalization of the pharmaceutical industries and markets, regulatory authorities are striving to harmonize regulations and facilitate faster and more efficient drug development and production processes. For example, the ICH (International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use) has developed harmonized guidelines for the manufacturing and testing of Active Pharmaceutical Ingredients (API)[5]. These guidelines have been adopted by the member countries USA, Europe and Japan, as well as several other countries. They are gradually becoming globally accepted as the de facto standard for API production. Similarly, the Pharmaceutical Inspection Cooperation Scheme (PIC/S) aims to harmonize GMP regulations and quality systems of inspectorates in the field of medicinal products[6]. PIC/S members are regulatory authorities from many countries as well as international organizations such as WHO and UNICEF.

2 U.S. Food and Drug Administration, Code of Federal Regulations (CFR), Title 21
3 European Commission, Eudralex, Volume 4: EU Guidelines to Good Manufacturing Practice
4 WHO, Annex 3, Good Manufacturing Practices for Pharmaceutical Products: Main Principles
5 ICH, Good Manufacturing Practice Guide for Active Pharmaceutical Ingredients (API) Q7
6 PIC/S, Guide to Good Manufacturing Practice for Medicinal Products (Part 1) / API (Part 2)

Consequences for non-compliance with GMP regulations can be harsh. The US FDA, for example, enforces deviations and violations as follows[7]:

- Following an inspection, the FDA documents and communicates concerns in a Form FDA 483, which is a list of inspectional observations. However, Form 483 is not a final determination regarding compliance. The company is expected to submit a response within 15 days.
- If the response is not satisfactory, FDA issues a warning letter, which is an official document from the agency to the plant, listing major GMP violations. Typically, the plant has three weeks to take adequate measures and correct the problems.
- If adequate measures are not taken and implemented sufficiently, the agency may fine the company, shut down the operation and ban or recall all corresponding batches from their market.
- In very severe cases, the agency may ban or recall all products from the corresponding company, shut down operations and criminally prosecute responsible people.

Pharmacopoeia

A central document for the pharmaceutical industry is the Pharmacopoeia (or Pharmacopeia), which is a collection of published standards that describes requirements for testing of chemical and biological drug substances and dosage forms as well as methods of analysis for medicines. These standards are defined to ensure pharmaceutical products are of the appropriate identity, as well as strength, quality, purity and consistency. The first Pharmacopoeia was published by the United States Pharmacopeial Convention (USP). Today, many national and some international Pharmacopoeias exist, such as the International Pharmacopoeia of the World Health Organization (WHO)[8] or the European Pharmacopoeia. However, the U.S. Pharmacopoeia is considered as a de facto standard and its standards and methods are regularly adopted by other Pharmacopoeias. In most countries, the respective national Pharmacopoeia is a legally binding document. In the USA, the U.S. Pharmacopoeia and the National Formulary are designated by the U.S. Federal Food, Drug, and Cosmetics Act as official compendia (USP-NF)[9] for drugs marketed in the United States.

International Organization of Standardization (ISO)

The International Organization of Standardization (ISO) is a international organization with the purpose of setting industrial and commercial standards. However, these standards are legally not binding. The representatives of the ISO organization come from recognized national standards authorities, each one representing one country. With regard to weighing quality in pharmaceutical manufacturing, one of the most important standards published by the organization is ISO 9001:2008[10]. It was last updated in 2008.

The standard sets the criteria for a quality management system and is based on a number of quality management principles. Third-party certification bodies can certify a company to ISO 9001:2008. Today, the standard is implemented by more than one million companies and organizations in over 170 countries. One reason for the global adoption of the standard is that major purchasers increasingly require their suppliers to hold ISO 9001 certification.

7 FDA, Guidance for Industry, Formal Dispute Resolution: Scientific and Technical Issues Related to Pharmaceutical CGMP, 2006
8 WHO, The International Pharmacopoeia (Ph.Int.)
9 U.S. Pharmacopoeia, The United States Pharmacopeia and The National Formulary (USP–NF)
10 ISO 9001:2008 Quality Management System, TCISO/TC 176/SC 2

2 Weighing-related Regulations

A number of regulations and standards, including GMP, have been established to ensure accurate and consistent measurements. Some, such as the USP-NF, have defined specific standards while others set general principles. In this chapter, we examine the standards and principles relevant for weighing processes and we provide guidance on how to ensure regulatory compliance.

Although there are differences in the wording of the various GMPs, the underlying principles are similar. Therefore, we focus on the documents provided by the FDA (21 CFR), the EU (EudraLex) and the ICH (Quality Guidelines such as Q7: GMP for APIs). In addition, we examine how USP and ISO standards and regulations influence selection, installation, operation and maintenance of weighing instruments.
The regulations that are relevant for weighing instruments and weighing processes can be summarized as follows:

- Weighing equipment should be designed for its intended use, should prevent contamination of the drug product and facilitate easy cleaning.
- The manufacturer needs to select the right equipment with suitable weighing ranges and accuracy to meet the defined process tolerance.
- Weighing equipment should be calibrated according to written procedures and established schedules.
- Weighing systems need to be qualified and weighing processes must be validated to document conformance with defined specifications.
- Advanced weighing systems based on computer hardware and software need to comply with specific regulations for computerized systems.

In the following sections we examine the relevant regulations in each of those five topics.

Equipment Design and Construction

> *Equipment … should be of appropriate design … for its intended use, cleaning, sanitation … and maintenance.* ICH Q7A GMP Guidance for API, Sec. 5.1

> *Equipment used in the manufacture … of a drug product shall be of appropriate design … to facilitate operations for its intended use and for its cleaning and maintenance.*
> FDA 21 CFR Part 211, Sec. 211.63

> *Manufacturing equipment should be designed … to suit its intended purpose.*
> *Manufacturing equipment should be designed so that it can be easily and thoroughly cleaned.*
> Eudralex Volume 4, Sec. 3.34 and 3.36

In terms of equipment design, all GMP guidelines state that equipment should be designed to suit its intended use. Another aspect that is specifically mentioned is the ability to clean the equipment easily and thoroughly. Because weighing instruments and weighing applications are present in almost every stage of the manufacturing workflow, the intended use for the equipment varies a great deal. It makes a big difference for requirements if we look at a floor scale in a warehouse used to weigh pallets of packaging material, a precision bench scale in a

dispensing clean room or a drum-filling application in production. Depending on the intended use and the environment of the process, critical aspects of equipment design could include the following:

- Robustness of the construction and the ability to absorb shocks and vibrations
- Durability of the construction material to resist harsh production and cleaning processes
- Easy cleanability (e.g hygienic design of construction, water and dust ingress protection, liftable floor scale to clean below) to prevent cross-contamination

One key requirement for equipment design that is specifically mentioned in the guidelines is to prevent contamination.

Hygienically designed weighing platform prevents accumulation of material and facilitates easy and thorough cleaning.

> *The parts of the production equipment that come into contact with the product must not be reactive, additive or absorptive to such an extent that it will affect the quality of the product … .*
> Eudralex Volume 4, Sec. 3.39

> *Equipment shall be constructed so that surfaces that contact components, in-process materials, or drug products shall not be reactive, additive, or absorptive so as to alter the safety, identity, strength, quality, or purity of the drug product …* FDA 21 CFR Part 211, Sec. 211.65

In short, this means that the material of which the scale is constructed must not interfere with the properties of the processing materials. Stainless steel is the de-facto standard for scales in pharmaceutical environments. Stainless steel of grades AISI 304 and 316 are highly resistant to corrosion and do not emit particles that could lead to product contamination. For additional hygienic performance when the scale comes into contact with material, a polished surface with low roughness of Ra< 0.8µm prevents accumulation of contaminants and microorganisms.

Equipment Selection

> *Equipment used in the manufacture … of a drug product shall be of appropriate design … to facilitate operations for its intended use …* FDA 21 CFR Part 211, Sec. 211.63

> *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 organization shall determine the monitoring and measurements to be undertaken and the monitoring and measuring devices needed to provide evidence of conformity of product to determined requirements.* ISO9001:2008 Sec. 7.6

> *… when substances must be "accurately weighed", the weighing should be performed using a calibrated balance that meets the requirements defined for repeatability and accuracy … . For balances used for other applications, the balance repeatability and accuracy should be commensurate with the requirements for its use.* USP, General Chapter 41

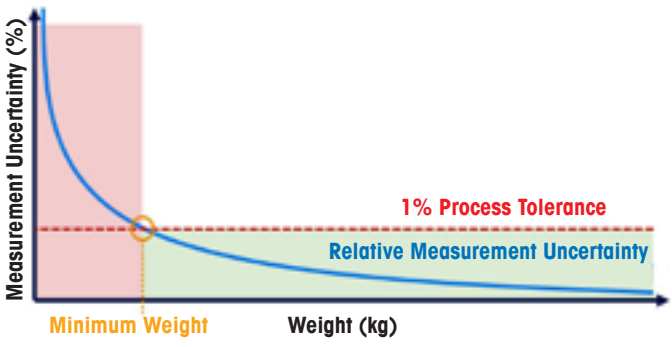
When it comes to the selection of weighing equipment for pharmaceutical manufacturing processes, the regulations remain rather vague or don't refer to measuring equipment specifically. The FDA, for example, only mentions manufacturing equipment in general and requires that it should be of "appropriate design … to facilitate operations for its intended use."

Both ICH and EU-GMP are more specific on weighing-equipment selection criteria. While the ICH states that weighing devices should be of "suitable accuracy for the intended use," the EU-GMP asks for "appropriate range and precision" of balances and measuring equipment. ISO 9001 specifies that the organization must select the measuring equipment so that measurements are carried out in a manner consistent with the monitoring and measurement requirements.

While USP General Chapter 41 generally refers to analytical balances used for quality control of drugs ("…balances used to weigh analytes for quantitative measures…"), some Pharmaceutical companies also voluntarily apply the requirements of this chapter to other applications. The rationale behind this approach is the lack of process specific tolerance requirements so that the stringent requirements of USP General Chapter 41 are taken instead.

As mentioned before, GMP regulations provide general principles and guidelines that have to be interpreted according to the specific manufacturing processes. In other words: The measuring equipment must be accurate and precise enough to ensure that measurements meet the defined process tolerance. However, 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.

It is important to understand that relative Measurement Uncertainty increases significantly with decreasing measurement weight. At some point, the relative uncertainty is so significant that—depending on the defined tolerance—the reported weight value can no longer be trusted. This minimum weight at which the Measurement Uncertainty does not exceed the defined weighing tolerance must be determined. Weighing above minimum weight will ensure that measurement uncertainty is always smaller than the accuracy required: The result is accurate.



When weighing above the minimum weight, measurement uncertainty is always smaller than the accuracy required: The result is accurate.

To ensure accurate and repeatable measurements, the following factors need to be considered prior to the selection of a scale:

- Largest weight to be weighed (including tare and possible pre-load) -> specifies the capacity of the scale
- Smallest (net) weight to be weighed -> required to specify the minimum weight of the scale
- Weighing accuracy required -> sets the upper limit to the allowable measurement uncertainty of the scale
- Environmental conditions and weighing application -> specify other scale properties

Weighing results are affected by the environment, by the user or simply by random processes. To guarantee safe and reproducible results, potential deviations should be compensated by applying a safety factor. The safety factor determines the margin between accurate measurement results and out-of-tolerance results.

In Chapter 4 we explain how the global weighing standard GWP® can be utilized to ensure secure selection of weighing equipment.

Equipment Calibration

> *Control, weighing … equipment critical for ensuring the quality of intermediates or APIs should be calibrated according to written procedures and an established schedule. Equipment calibrations should be performed using standards traceable to certified standards … Records of these calibrations should be maintained.* ICH Q7A GMP Guidance for API, Sec. 5.1

> *Measuring, weighing, recording and control equipment should be calibrated and checked at defined intervals by appropriate methods. Adequate records of such tests should be maintained.*
> Eudralex Volume 4, Sec. 3.41

> *[Equipment] shall be routinely calibrated, inspected, or checked according to a written program designed to assure proper performance. Written records of those calibration checks and inspections shall be maintained.* FDA 21 CFR Part 211, Sec. 211.68

> *Where necessary to ensure valid results, measuring equipment shall … be calibrated or verified at specified intervals, or prior to use, against measurement standards traceable to international or national measurement standards … Records of the results of calibration and verification shall be maintained.* ISO 90001:2008 Sec. 7.6

The performance of a weighing instrument will change over time due to wear and tear or accidents. To ensure the instrument continues fulfilling the requirements for process tolerances, a monitoring strategy is needed. GMP regulations and ISO specifications are mostly in agreement about the requirements for calibration and routine testing of measuring equipment and refer to four key elements:

- The equipment shall be routinely calibrated and checked at specified intervals
- Calibration shall be conducted according to a written procedure
- Calibrations shall be performed against traceable and certified standards
- Records of the calibrations 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. The main challenge for the user is to define test and calibration intervals that ensure consistent measurement accuracy while avoiding unnecessary costly activities. This requires a thorough analysis of the risks inherent to the weighing process, the weighing system performance and the applicable regulations.

Calibration of the weighing equipment must be conducted according to globally recognized standards, such as EURAMET (European Association of National Metrology Institutes)[11] and SIM (Inter-American Metrology System)[12] guidelines, and need to account for metrology as well as equipment construction. Testing itself should be conducted in-situ (at the location of operation) by authorized personnel and should include determination of measurement uncertainty and minimum weight under normal conditions of use. The aim is to assess the complete performance of the instrument by testing all relevant weighing parameters. Testing itself should to be done with certified, traceable calibration weights. In the pharmaceutical industry, it is important to carry out an as-found calibration (before the instrument is serviced/adjusted) as well as an as-left calibration (after the instrument has been serviced/adjusted). This ensures the necessary traceability of the measurement results of the weighing carried out before the service intervention.

Calibration weights must be certified and traceable

In addition to regular calibration intervals and depending on the risk evaluation, periodic routine tests should be established. These routine tests are conducted in-situ by the user and assess only those weighing parameters that have the largest influence on the performance of the instrument. Here the aim is to confirm the suitability of the instrument for the application.

Technically advanced scales may include built-in weights for adjusting the sensitivity of the device at defined intervals. While this functionality significantly reduces the workload for the operator and ensures routine tests are conducted reliably, it cannot completely replace regular manual testing procedures. According to FDA guidance, "for a scale with a built-in auto-calibrator … external performance checks (should) be performed on a periodic basis, but less frequently as compared to a scale without this feature. The frequency of performance checks depends on the frequency of use of the scale and the criticality and tolerance of the process or analytical step."

In Chapter 4 we examine how the global weighing standard GWP® can help defining suitable calibration and routine testing strategies in compliance with regulations.

[11] EURAMET, "Guidelines on the Calibration of Non-Automatic Weighing Systems," EURAMET cg-18, Version 3.0, 2011.
[12] SIM, "Guidelines on the calibration of non-automatic weighing systems," Sistema Interamericano de Metrología, 2008.

Legal Metrology

For commercial transactions in which product is sold by weight or weight is the basis for a tariff, it is a legal obligation that weighing equipment is approved, verified and marked as legal for trade. This means that the equipment has successfully passed a stringent set of tests to ensure it is sufficiently accurate enough to obtain this type of approval.

According to OIML (International Organization of Legal Metrology), legal metrology "... concerns regulatory requirements of measurements and measuring instruments for the protection of health, public safety, the environment, enabling taxation, protection of consumers and fair trade." The two most important legal metrology publications globally are OIML (R76-1) and US NIST (Handbook 44). They describe very clear rules that should finally lead to sufficiently accurate measurements for commercial transactions.

International Organization of Legal Metrology

However, it is impossible to cover every possible application and individual quality requirements vary greatly. In particular, weighing small amounts accurately requires stricter guidance. Furthermore, it is important to monitor the performance of a weighing instrument continuously and the yearly or bi-annually accredited verification of the instrument requested under local national law may not be sufficient to detect a possible drift or deterioration of the instrument's performance over time.

National Conference on Weights and Measures

Therefore, before selecting weighing equipment, the process requirements should be determined. If legal-for-trade requirements must be fulfilled, only an instrument that has been approved for such a usage can be selected. However, it is also imperative to consider the quality requirements and ensure that the instrument can fulfill those requirements (e.g. process tolerance and measuring range). A risk analysis is essential to assess the criticality of the weighing process to determine the routine testing required and its frequency.

Process Validation and Equipment Qualification

> *There shall be written procedures for production and process control designed to assure that the drug products have the identity, strength, quality, and purity they purport or are represented to possess.* FDA 21 CFR Part 211, Sec. 211.100

> *It is a requirement of GMP that manufacturers identify what validation work is needed to prove control of the critical aspects of their particular operations. Significant changes to the facilities, the equipment and the processes, which may affect the quality of the product, should be validated.*
> Annex 15 to Eudralex GMP

Those guidelines state that the manufacturer must design and control the manufacturing process to conform to cGMP and it must be able to prove that the finished product meets pre-determined requirements. This includes

training of people, qualification of equipment and validation of processes. Simply testing a sample of the final product does not provide appropriate evidence that every product within a batch fulfills the defined specifications.

> *Before initiating process validation activities, appropriate qualification of critical equipment and ancillary systems should be completed.* ICH Q7A C. Qualification, Sec. 12.3

All equipment intended to be used in manufacturing must be qualified by executing a qualification procedure. The qualification process includes four activities that can be carried out individually or combined and is often described as Equipment Qualification (EQ). The four activities are listed below as defined by ICH guidance and amended with explanations what this means for setting up a weighing system[13]:

Design Qualification (DQ) - *Documented verification that the proposed design of the equipment or systems is suitable for the intended purpose.*
The Pharmaceutical company needs to define what the weighing system is supposed to do. This is usually done by specifying the requirements in the User Requirements Specification (URS). Key aspects include: Required weighing capacity, process tolerances and environmental influences. In addition, a test plan needs to be defined to challenge the equipment. The equipment is then either designed by the supplier or purchased according to the URS.

Installation Qualification (IQ) - *Documented verification that the equipment or systems, as installed or modified, comply with the approved design, the manufacturer's recommendations and/or user requirements.*
Installation Qualification verifies that the weighing instrument is received as designed and specified, that it is properly installed in the selected environment and that this environment is suitable for the operation of the instrument. In addition, product documentation and operating instructions need to be tested for conformity.

Operational Qualification (OQ) - *Documented verification that the equipment or systems, as installed or modified, perform as intended throughout the anticipated operating ranges.*
In this step of the qualification process, the correct function of the equipment is tested. A key element is the calibration of the weighing instrument, which is discussed in detail in Chapter 3.3. This includes estimation of measurement uncertainty and determination of minimum weight. In addition, operating and service personnel are trained on using and maintaining the equipment correctly.

Performance Qualification (PQ) - *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 to ensure and document that the equipment is performing as required. The frequency of test and calibration intervals needs to be based on a risk assessment of the actual application.

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-validation is required.

[13] ICH, Good Manufacturing Practice Guide for Active Pharmaceutical Ingredients (API) Q7

Computerized Systems

Computerized systems and their validation requirements are specifically recognized in GMP documents.

> *GMP-related computerized systems should be validated. The depth and scope of validation depends on the diversity, complexity, and criticality of the computerized application.*
> ICH Q7A GMP Guidance for API, Sec. 5.4

> *Automatic, mechanical, or electronic equipment or other types of equipment, including computers, or related systems that will perform a function satisfactorily, may be used in the manufacture, processing, packing, and holding of a drug product. If such equipment is so used, it shall be routinely calibrated, inspected, or checked according to a written program designed to assure proper performance. Written records of those calibration checks and inspections shall be maintained.*
> FDA, 21 CFR Part 211, 211.68

Sophisticated weighing systems are increasingly based on computer hardware and can feature complex software functionality. An in-process quality control system, such as FreeWeigh.Net®, for example, provides extensive functionality. It captures, evaluates and manages process data and can be integrated into the company's network infrastructure. It must comply with specific regulations regarding validation of computerized systems and handling of electronic records and signatures.

The IND890 Weighing PC System can run sophisticated and customized software applications.

FDA 21 CFR Part 211.68 and ICH guidance Q7A section 5.4 provide guidance on how to validate computer systems. In addition to this general guidance some specific requirements regarding access to and maintenance of data are specified:

- Access and changes to data need to be controlled and documented.
- An additional check (by the system or a second operator) is required where critical data are being entered manually.
- A back-up system is required to prevent the permanent loss of data and data protection means should be established.

Furthermore, electronic records and signatures are specifically regulated in the FDA 21 CFR Part 11 to ensure the authenticity, integrity, and, when appropriate, the confidentiality of data.

3 Ensuring Regulatory Compliance

As shown in the previous chapters, regulations usually consist of general principles and vague guidance. The purpose of this approach is to let the manufacturer define the best method of ensuring consistent process quality. After all, the manufacturer should know its processes best. However, the manufacturer must be able to prove to the inspecting agency that it has:

- A thorough understanding of its processes and
- Implemented the right measures to fulfill relevant quality regulations.

When it comes to weighing systems, in-depth metrological know-how is required to ensure accurate measurements over time. In order to install and maintain a compliant weighing process, the entire weighing equipment life-cycle must be considered, including equipment evaluation and selection, installation, calibration and routine operation.

The global weighing standard GWP® (Good Weighing Practice™) is a scientific methodology for the secure selection, calibration and operation of weighing equipment. It can be applied to new or existing weighing equipment from any manufacturer. Most importantly, GWP® provides the documented evidence for reproducible weighing results in harmony with all current quality standards:

- Metrological Guidelines, such as OIML R76-1 and HB44, define the minimum requirements for an approved weighing device. However, because their purpose is mainly to provide a legal framework for commercial transactions, they lack the guidance required for specific process requirements.
- Quality Standards, such as GMP, USP, ISO, and others, require continuous equipment monitoring. However, due to their mostly generic scope, those guidelines do not give any specific information on their implementation.

GWP® documents that the weighing equipment fulfills the measurement accuracy requirements on the basis of on-site calibration and measurement uncertainty determination. Furthermore, GWP® helps to determine the specific methods and frequency of regular calibration and performance verification required by the quality standards (ISO, GMP, GLP, etc.).

A GWP® certification provides an audit trail, proving that the weighing system complies with regulatory requirements and quality standards. The weighing standard helps to build exact metrological standards while ensuring that the company's resources are invested only in appropriate activities.

METTLER TOLEDO offers two unique service products based on GWP®:

GWP® Recommendation
This free service integrates metrological science with your specific requirements in a simple tool. It provides documented evidence that the selected instrument meets metrological, environmental and regulatory requirements.

GWP® Verification
This service provides a complete set of necessary documentation to pass any external or internal audit. It qualifies the measurement range of your weighing equipment by documenting measurement uncertainty and minimum weight and provides SOPs, test intervals and test limits for lifetime performance verification. Furthermore, GWP® Verification reveals tests that are redundant, too strict or even erroneous. By benchmarking your testing procedures with a risk-based algorithm, it clearly pinpoints where testing can be optimized and where costs can be saved without compromising compliance.

4 Summary

In in the pharmaceutical industry, regulatory compliance is essential to maintaining manufacturers' license to operate. Regulatory publications, such as GMP, provide general principles rather than specific instructions. They are vague when it comes to guidance on how accurate weighing results are defined and verified. As a result, selecting the right weighing instrument and implementing suitable testing routines according to the specific process requirements can become a challenge. Implementing GWP®, the science-based global standard for efficient lifecycle management of weighing systems, reduces measurement errors and ensures reproducibly accurate weighing results. GWP® provides documented proof that weighing system complies with regulatory requirements and quality standards.

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