Quality management

The permanent assurance of quality

METTLER TOLEDO

Quality management

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1. Introduction

This brochure is concerned with the requirements of different quality management systems (QM systems) and uses practical examples to provide information on how to comply with them. The majority of the different QM systems have very similar requirements, but the nomenclature for similar processes can be different. This brochure explains the general requirements of QM systems using the example of *qualifying/validation* and the *control of inspection, measuring and test equipment.*

1.1. Why quality management?

Quality is understood here in the most general sense of the word to mean produced goods as well as services and research results. In all these areas the topic *"Permanent assurance of quality"* is arousing increasingly greater interest worldwide. The reason for this is illustrated by the following two examples:

– For the customer satisfaction of a production company, it is important always to assure consistently high quality of the company products. This requires the quality of the purchased components to be constantly high and the internal procedures of value added to be executed with corresponding care.
– In the past, misunderstandings arose and different interpretations were put on research results. Such confusions could hide dangers, not least for public heath.

The task of quality management is to ensure processes are transparent and traceable. Faulty processes can be identified and optimized resulting in an enormous gain in dependability for internal procedures.

Through meeting the requirements of a QM system, a company active on a worldwide basis has an appreciable advantage as far as trust is concerned as it is prepared to meet internationally recognized standards.

– The products have a high quality image, which increases the competitiveness.
– Complaints about quality can be traced to a source. This forms a basis for decision regarding whether the complaints are justified (liability questions).
– Proof of diligence as a supplier.
– Internal processes are controlled and can be optimized.

The measures which need to be implemented for successful quality management cost money. It is thus appropriate to restrict such activities to an economically reasonable level and to promote such measures which promise high utilizability.

1.2. Tasks of the company regarding the control of inspection, measuring and test equipment

If the procedures in a company are executed in conformance with the requirements of a QM system, in principle three relevant task blocks can be distinguished:

1. Proof of suitability for routine operation

– Qualification
– Validation
– System suitability test

2. Control of inspection, measuring and test equipment during routine operation
Quality management systems such as ISO 9001, GLP/GMP (Good Laboratory/Manufacturing Practice) and others set standards for the method of procedure and for measures of an active quality management.

3. Documentation
One of the most important requirements is complete documentation of all procedures and activities performed. It must be ensured that after the event all results are transparent, recoverable and hence traceable for an independent third party.

To ensure that a company meets the requirements, checks (audits) are performed either internally or by an independent external inspector (auditor).

Basic rules for documentation based on good laboratory practice:
1. What is not documented has formally also not been performed.
2. "5 W" rule: **W**ho has performed **W**hat, **W**hen, **W**here and **W**hy?
3. The documentation must be archived for 15 to 30 years.

```
----- Density Solid -----

Date:      03-Feb-2000
Time:      09:54

METTLER TOLEDO
Balance
Type:      AG204
SNR:       1113123456

ID:        ..............

Liquid:
H-2-O        0.9982 g/cm3
Temp.          20.0 °C

Weight in air:
            60.0020 g
Weight in liquid:
            49.9997 g
Volume of solid:
             1.625 cm3

Density:     5.988 g/cm3
           =============

Signature:

.........................
---------- END ----------
```

```
---- Density liquid ----

Date:      03-Feb-2000
Time:      10:37

METTLER TOLEDO
Balance
Type:      AG204
SNR:       1113123456

ID:        ..............

Temp. of liquid:
           ..............

Displaced liquid:
             10.0023 g

Density:      1.000 g/cm3
            ==============

Signature:

.........................
---------- END ----------
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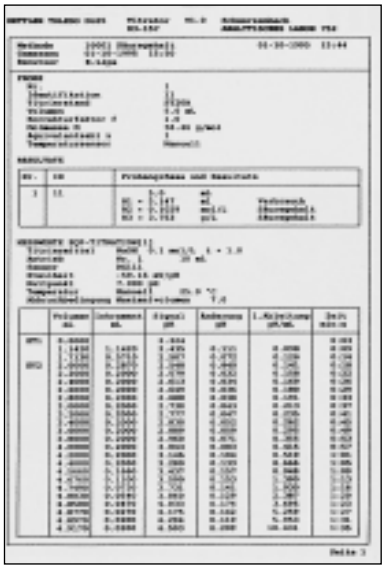


2. Quality management systems

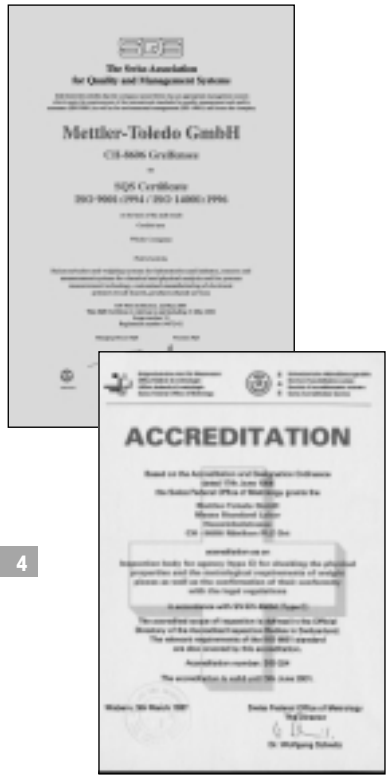
The following comments on the different QM systems are not complete, but attempt to highlight the most important differences and application areas.

All systems have one essential thing in common: They require that "measuring instruments of all types" are qualified before putting into operation and are checked and calibrated at regular intervals in routine operation. Discussion centers on not only systems of international validity, but also those with regionally limited (e.g. restricted to Europe) validity as it is highly probable that an internationally active company also exports to such countries.

In principle, QM systems can be divided into *universal* or *branch-specific* systems. *A company can voluntarily comply with a QM system or must satisfy the requirements of a legally established QM system.* You will find more detailed information in the appropriate specialist literature. See also the list of references at the end of this brochure.

2.1. Universal QM systems

Companies of all types can aim to comply with general QM systems for a freely selectable range of validity.



ISO 9000 ff

International standard which is developing more and more into an independent quality characteristic.

– Definition of the procedures
– Documentation in a quality management manual
– Integrated QM/QA unit, monitored by a quality representative (company management)
– Tests and control of the inspection, measuring and test equipment and instruments
– Internal audits
– Corrective measures
– Recertification every 3 years

ISO 17025

Recognition throughout the world for testing laboratories. Through the accreditation the testing laboratory attains the status of an independent institution.

– Ensures the quality of the test (requirements with regard to content), but not the assessment of the results
– Accreditation for a defined range of validity (scope) on a method basis. Other methods which are performed in the same laboratory are not accredited
– Validation
– Testing and control of the inspection, measuring and test equipment
– Recertification every 5 years

ISO 14001

Environmental management system of international validity encompassing all activities at the location.

– Conformance with the legal environmental regulations
– Documentation in an environmental management manual
– Continuous improvement

– Identification of environmentally relevant processes
– Formulate goals, publish an environmental policy
– Review at regular intervals (evaluation by person responsible in company management)
– Corrective measures
– Training of employees in environmentally relevant aspects
– Internal and external communication
– Internal audits
– Provisions and measures for emergencies
– Environmental declaration (only for EMAS, EU area)

2.2. Special QM systems

Various branches (e.g. chemistry, pharmaceuticals) stipulate conformance with the directions of QM systems and in some countries these requirements are anchored in the legislation. If products are exported to such a country, the supplier must prove that the corresponding criteria have been met.

GLP: "Good Laboratory Practice"

The basic principles of "Good Laboratory Practice" provide a formal framework for the performance of safety tests on chemical products and have a legal character in many countries. These basic principles of GLP apply particularly in laboratories in the chemical, pharmaceutical and plant protection industries. The formal aspect is study oriented and particularly suitable for long term test plans.

– GLP was originally introduced as a criterion for the approval of drugs and medicinal preparations and is also valid for environmentally relevant substances (all types of chemicals).
– The improvement of the laboratory standard provides dependability and mutual recognition of laboratory data.
– The guidelines also refer to the organization and the personnel, e.g. management of the test equipment and test director.
– Monitoring/checking by GLP inspectors and by an internal quality assurance unit (QAU) independent of the management of the testing equipment.
– No statement regarding the accuracy and precision of the results or the suitability of a method used.
– Repeated checking every four years. The inspection is associated with a huge technical effort.

GMP: "Good Manufacturing Practice"

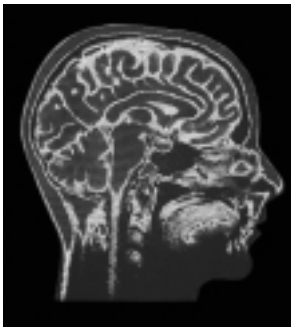
This quality management system is used for the production and analysis in the legally regulated area of the pharmaceutical industry. The basic principles of "Good Manufacturing Practice" are very similar to those of GLP.

The quality assurance is responsible for the:

– Definition of the areas of responsibility for the application of GMP in drug manufacture
– Performance of the validations and inprocess controls
– Release of every production lot
– Performance of self-inspections

The following are required:
– Defined and validated manufacturing processes
– Sufficiently qualified and trained personnel
– Suitable rooms and equipment
– Approved descriptions of methods and instructions
– Comprehensive manufacturing documentation

This QM system also places particular emphasis on the documentation.



GCP: "Good Clinical Practice"

GCP refers to clinical trials of pharmaceuticals in connection with man.

In principle, preclinical experimental laboratory tests in the development of pharmaceuticals have a duty to conform with GLP. If the experiments proceed to the clinical phase, the QM system GCP applies, whereas during the manufacture of the approved drug GMP regulations are in force.

HACCP: "Hazard Analysis of Critical Control Points"

HACCP ensures food quality in food manufacture and in the equipment for communal feeding. In general, a risk analysis and an error avoidance strategy should assure absolute safety of the food as regards health. HACCP is a sub-system within a quality management system that deals with the processes of food processing.

Critical control points (CCP) in the food processing are identified, the specific risk of these critical control points assessed and preventive measures to solve them defined.

HACCP essentially follows the following basic principles:

1. Determination and evaluation of conceivable hazards at all stages of food manufacture.
2. Identification of the critical control points (CCP).
   Example: Estimation of the risk at different points in meat butchery that contamination by bacteria could occur.
3. Determination of all those points, handling or processing stages at which the potential hazard can be eliminated or lowered.
4. Definition of the critical limit values, compliance with which ensures that the critical control point is under control.
5. Establishment of a system for monitoring of the CCPs through planned tests or observations.
6. Definition of corrective measures which must be implemented as soon as the monitoring shows that a certain CCP is no longer under control.
7. Establishment of confirmation procedures with supplementary tests or measures which ensure perfect functioning of the HACCP system.
8. Establishment of documentation which encompasses all procedures and reports associated with these basic principles and their application.

The HACCP concept requires hygienic and test plans for product and production hygiene in each operation, plant and personnel hygiene, cleaning, disinfection and pest control. Moreover, the personnel must be adequately trained.

Legal regulations

	Drug act	PharmBetrV	Pharmacopoeia	Verification ordinance	91/356 EEC	EC guide	PIC guide	PIC-PH 4/93 (SMF)	WHO guideline	FDA CFR 211	OECD-GLP	ISO 9000 ff
Instrument selection by process												x
Method qualification		x			x	x	x	x	x	x	x	x
Colibration instructions			x		x	x	x	x	x	x	x	x
Acceptance criteria (precision, trueness)										x		x
Planned corrective measures										x		x
Records						x	x	x	x	x	x	x
Conclusions (release, blockage)						x	x		x			
Evaluation of preceding Q tests if measuring instrument faulty												x
Log book stipulated						x	x		x	x		
Scheduling									x	x	x	x
Daily check, Check before use									x			
Calibration status of instrument									x			x
Assurance of suitable storage and handling												x
Protection against wrong adjustments												x
Location defined												x
Unambiguous identification of inspection, measuring and test equipment												x

Table following Hörig

3. Proof of suitability for routine operation

At the start of a new process procedure, the requirements with respect to the desired product quality must be defined, e.g. the required reproducibility of a measurement result. If a process comprises several stages, the possible error in each individual stage must be considered and summarized to a total error at the end of a process.

For each individual stage of the entire process the following steps must therefore be performed:

1. Qualification of the instrument

The required performance of a measuring instrument depends on the required quality goal.

– New purchase: Can the instrument theoretically attain the required quality goal (data specifications bulletin)?

– The qualification at the location provides the proof that the instrument actually results in the required quality goal.

2. Validation of the method

Are the measurement results of the method of sufficient quality for the planned use to attain the required quality goal? In practice, the method is frequently tested with the actual instrument which has already been qualified. A separate system suitability test is not needed in this case.

3. System suitability test

After instrument and method have been tested separately, in a further step the so-called system suitability test is performed to determine whether both components also produce the expected performance when used together.

3.1. Qualification of the instruments

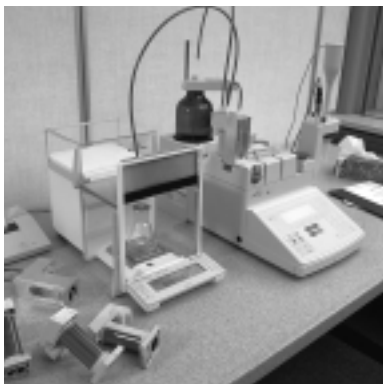
The qualification and calibration of instruments comprises 6 areas. For the user, 4 of these are relevant for quality and their execution must be fully documented.

1. Design qualification
2. Installation qualification
3. Operational qualification
4. Performance qualification

Qualification depends on the location as the measuring instrument can be subject to different influences which depend on the ambient conditions. It is thus practical to define standard operating procedures (SOPs) for the qualification to ensure that it leads to comparable results.

– Same instrument type at different locations

– Qualification of the same instrument by different people



The 6 relevant steps for the qualification of instruments

Qualification	Action	Responsibility	
Specification qualification	S.Q.	Product development	Research and development
Construction qualification	C.Q.	Production and subsequent test	Production
Design qualification	D.Q.	Definition of features	User
Installation qualification	I.Q.	Installation on site	User
Operational qualification	O.Q.	Basic calibration	User
Performance qualification	P.Q.	Testing with known standards	User

Design qualification (D.Q.)

Within the design qualification, the user specifies the requirements the instrument should meet.

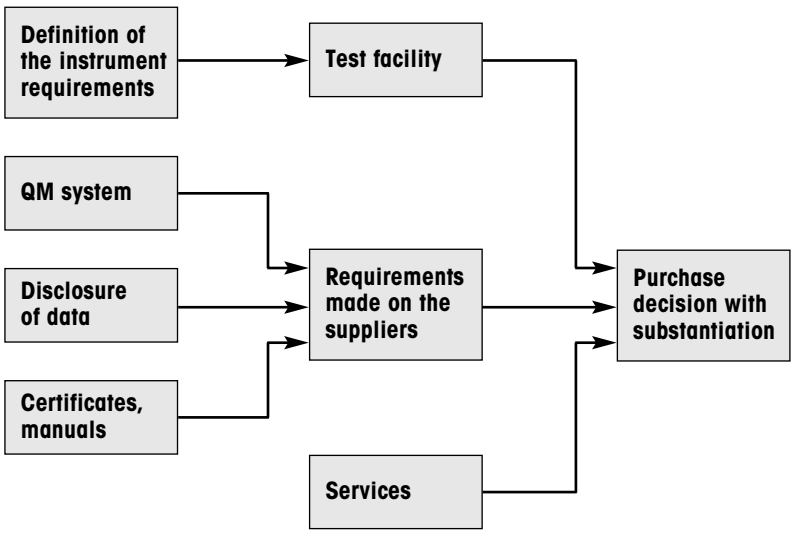
The design qualification requires that the desired accuracy of measurement is defined. The user must inform himself beforehand of the method to be used in order to estimate the magnitude of possible errors. Instruments from several manufacturers can be evaluated using, e.g. data specifications bulletins or in a practical test.

For the substantiated purchase decision, the performances of the supplier which go beyond the measurement performance of the instrument, e.g. warranty and services should always be included.

If the supplier produces according to a QM system, he can support the design qualification of the user. A validation declaration from the manufacturer of the product provides assurance that the product has been developed and produced according to the requirements of the QM system (in general).

The ISO 9001 standard itself says nothing about the defined steps of quality assurance of the manufacturer. The manufacturer can thus provide the procedure certified by ISO 9001 as additional information.

Schematic representation of design qualification



Explanation of the validation of lab balances and their optional equipment

All products of the business unit LabTec from METTLER TOLEDO including internal software and optional equipment are developed and manufactured within the framework of the quality management system certified in compliance with ISO 9001. They include the following models:

Precision balances	B, B-S, BB, GB, GB-S, GG-S, GL, PB, PB-S, PG, PG-S, PJ, PM, PR, SAG, SB, SG, SR
Microbalances and analytical balances	AX, AB, AB-S, AE, AG, AJ, AM, AT, CB, CG-S, M3, MT, MX, UM3, UMT, UMX
Printers	GA, LC-P, HA-P43
Moisture Analyzers	HB, HG, HR, LJ, LP

Design validation is according to in-house standards for the product and software development process (see schematic representation).
The appropriate validation reports of these process procedures and accompanying documentation such as source codes can be examined after prior agreement with METTLER TOLEDO.

Greifensee, 2001

Mario Hochstrasser
General Manager

Markus Gross
Marketing Manager

Product development process at METTLER TOLEDO

Product	Software
Idea phase	
Generation of a product idea	Definition: Software features
Study phase	
Fundamentals of product development	Prerequisites for software/hardware basis
Project start	
Definition: Product requirements, model	Software concept and interfaces for the hardware
Prototype phase	
Functional prototype, test phase	Specification of the requirements and implementation plan
Pilot series	
Functional manufacture under serial conditions, test phase	Preparation of a ß-version of a product, production and service software
Serial production	
Production of planned number of units, test phase	Validation of the software
Release for delivery	
On schedule supply ability	Definition of the form of service

Installation qualification (I.Q.)

The installation qualification describes all steps for the installation of an instrument up to putting into operation. These include the check on completeness and ensuring that the instrument is in operational readiness after installation (SOP).

Many suppliers offer help during the installation or provide detailed information in the operating instructions on proper installation of the instruments. All work steps must be documented and archived by the person performing the installation.

At many places the use of an "instrument log book" has proved its worth. All actions performed on an instrument during the qualification or the routine check in later operation can be entered in the log book and are thus always at hand. The manufacturer can make the specimen log books, which contain the check lists for suggestions for standard operating procedures, available to the user.

Operational qualification (O.Q.)

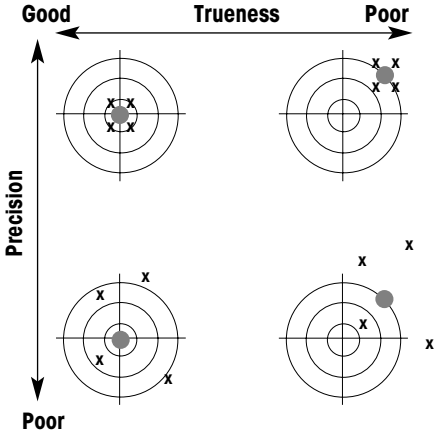
The operational qualification is intimately linked with the current location of the instrument. If the location is changed, this qualification must be performed again.

Before putting into operation, the following work steps must be performed to match the instrument to the specific ambient conditions and to check its performance.

1. Before the start of the actual qualification, adequate acclimatization to the prevailing ambient conditions must be assured. If the ambient conditions fluctuate during the course of a day, it must also be ensured that they have no influence on the performance of the instrument.
2. Checking of all parameters which influence the performance of an instrument and hence can lower the precision of a measurement. The test must be performed according to a standard operating procedure by sufficiently trained personnel and documented by a traceable calibration certificate.

   The following critical parameters should be checked for comparability of the results with respect to time and location.

Scheme to distinguish between trueness and precision



Precision:
Measure of the closeness of agreement of several measured values (individual measurements x), the precision is independent of the position of the true value (center of the disk).

Trueness:
Measure of the closeness of agreement between the average value from a series of measurements and the true value, in the chart the distance between the individual or mean values (●) and the center.

Accuracy, systematic error of measurement
Qualitative term describing the closeness of agreement between the result and a true value. Disturbing influences due, e.g. to a sensor, lead to systematic errors.

Precision, error of measurement with no systematic component
Repeatability. Qualitative term for the closeness of agreement between the results of successive measurements of the same substance, performed under the same conditions. This includes, e.g. the stability of the measurement results with respect to time on changing ambient conditions.
Reproducibility. Qualitative term for the closeness of agreement between results of measurements of the same substance, performed under changed measurement conditions. It includes, e.g. the stability of the measurement results with time when the ambient conditions change.
Limits of determination. Smallest and largest input quantity (measuring range) which can be adhered to with the defined accuracy of measurement (relative probability of occurrence in %).
Linearity. Within the limit of determination a proportional relationship between the input and output quantity should be ensured.

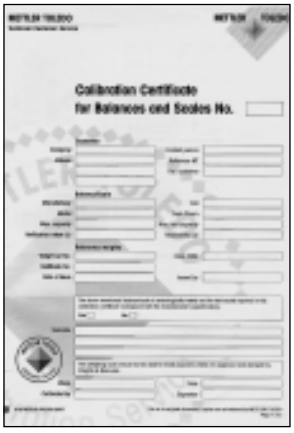
The same parameters are equally critical for the validation of a method.

3. Training. Suitable training measures must be used to provide proof that all users of the instrument can use it properly and without errors.

Example: Basic calibration of electronic balances, accuracy (systematic error of measurement)
The adjustment of the sensitivity ensures that the value shown in the balance display corresponds to the actual weight loaded.

Check the linearity. The linearity ensures the relationship between the readout value and the loaded weight over the entire weighing range.

Repeatability
The repeatability at the location is greatly dependent on the performance of an electronic balance, the prevailing ambient conditions and the experience of the operator. It should therefore be determined by the user himself on site.


Calibration Certificate
for Balances and Scales No.

Reproducibility
Measure of the closeness of agreement between results, for example
– obtained by various users
– at different locations of the balance
– with different balances
– at different times, e.g. after one week.

Limit of determination (minimum sample weight at location)
The accuracy of measurement depends on the absolute sample weight - the lower the sample weight, the greater the relative error. It is thus advisable to define the allowed measurement tolerance in % and determine the corresponding minimum weight.

It is essential that the basic calibration of a balance be performed by adequately trained personnel, e.g. a qualified service engineer.

Example: Operational qualification titrations

Certification and recertification of:
– burettes
– burette drives
– sensor inputs of the electrodes used, e.g. temperature sensor
– training of the personnel

Special application brochures with examples of standard operating procedures for general and specific system suitability tests are available.

Performance qualification (P.Q.)

In order to prove the performance of the instrument for use under operational conditions, a trial run with several in-house substances (usually 3) is performed. The execution of this step depends greatly on the application at hand, but is particularly appropriate in the performance of weighing applications (e.g. piece counting or filling process control). Problems with special substances can appear even in simple weighings. e.g. through electrostatic charging.

Examples of tests performed on electronic balances:
– Determination of the repeatability by a duplicate measurement under conditions mirroring reality for the weighing of typical tare values and sample amounts of a laboratory.
– Determination of the repeatability through multiple loading of the same substance over a relatively long period of time.
– Simple loading of a certified weight to check the sensitivity.

If a test is passed, the instrument is released for routine operation.
The instrument qualification is ended with a final report.

3.2. Validation

The validation includes the systematic check on all essential work steps and the setup for a process or a procedure. The goal of the validation is to ensure the quality of the process when defined production and control procedures are complied with.

The validation is the documented proof that a process, a procedure or a method is suitable to perform a specific task with a high degree of dependability.

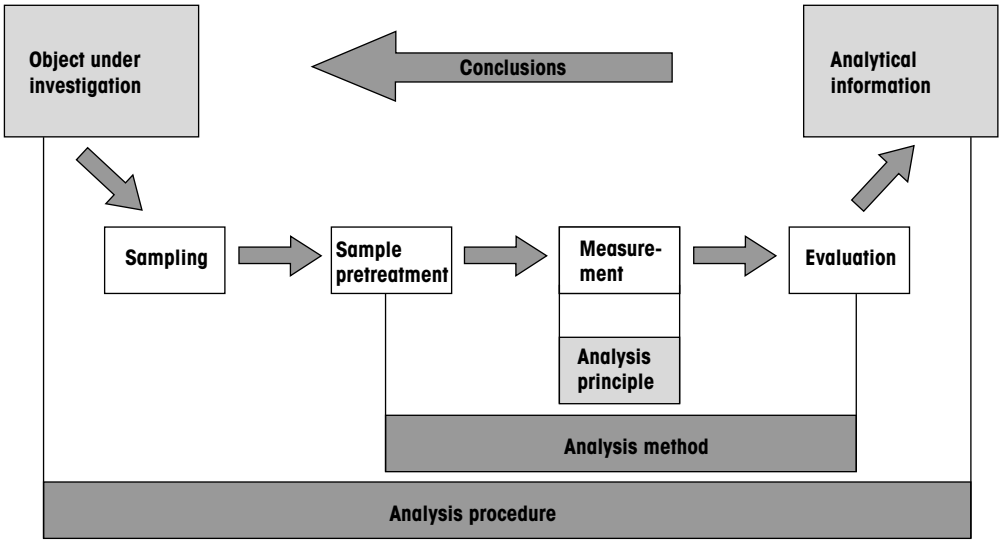
A validation must be planned and the planning must be justified. For example, guidelines exist for the pharmaceutical industry in the US pharmacopoeia for implementing the validation planning.

The method validation proves that an analysis method is suitable for the planned application. To prove that the results lie within a defined error of measurement for a special application, the method must be checked. The validation of a procedure contains the method performed and the handling of the substances used. All work steps must be taken into account and checked separately.

The software of standalone measuring instruments (firmware) usually need not be validated.

To check the analysis method, in principle the same parameters used in the qualification must be checked (see section 3.1.3). The difference is that the parameters refer to the method and not to the performance of the instrument.

The analysis process



1. Accuracy
2. Repeatability
3. Reproducibility
4. Systematic error of measurement
5. Limits of determination
6. Linearity

The following parameters of the method are also investigated:

Selectivity

Ability of an analytical procedure to determine one component in the presence of others without influencing the analysis.

Specificity, robustness

Susceptibility to interfering components. The analysis procedure must not be affected by interfering components.

Limit of detection

The limit of detection is the lowest limit of the measurement system below which no definite value can be determined.

Validation proposals following USP 26 – NF 21

Characteristic	Category I (content determination)	Category II (limit test)	Category II (quantitative determination)	Category III (quantitative determination)
Precision	+	–	+	+
Accuracy	+	+	+	+
Limit of detection	–	+	–	+
Limits of determination	–	–	+	+
Selectivity	+	+	+	+
Range	+	+	+	+
Linearity	+	+	+	+
Robustness	+	+	+	+

The limit values to be defined for the points mentioned depend on the application and the possible consequences if an error appears. In analyses of food or drugs, for instance, limits stricter than those for the analysis of cleaning agents are required. However, the procedure of a validation is basically the same.

Revalidation

A revalidation is usually necessary:

– on change in the composition, the procedure or the sample size
– on equipment changes which influence the process
– on use of new equipment
– after relatively extensive revision of machines or equipment
– on change in the control methods
– in the case of results of the inprocess and final control which appear to indicate a revalidation.

Validation using the example of titration methods

Determination of the accuracy

Performance: Titration of a series with reference substances of known concentration.

Result: The *mean value x.* The difference between the mean value and the true value (the reference substance) is a measure of the accuracy.

Determination of the repeatability

Performance: Titration of multiple series of a sample with the same measurement procedure, the same measuring instrument, by the same user in the same laboratory and within a short space of time.

Result: The *relative standard deviation RSD;* definite outliers are eliminated and each series evaluated statistically. The standard deviation is a measure of the repeatability.

Determination of the reproducibility

Performance: Titration of a multiple series of a sample under changed measurement conditions, e.g. with a different titrator with different chemical influences, by a different user in a different lab and at different times.

Result: The *relative standard deviation RSD;* definite outliers are eliminated and each series evaluated statistically. The standard deviation is a measure of the reproducibility.

Systematic error of measurement (chart 1)

Performance: Titration of a sample series with different amounts of sample under the same measurement conditions. The titrant consumption is plotted against the associated amount of sample and linear regression is used to determine the line $y = a + bx$, where a is the intercept on the y axis and b the slope of the line.

Result: The difference between zero and the *intercept on the y axis a* of the line is the systematic error of measurement.

Linearity (chart 2)

The linearity of a titration method indicates the concentration range for which accurate results are obtained for the sample under investigation.

Performance: Titration of a sample series with significantly different amounts of sample each time under the same measurement conditions. The result is plotted against the amount of sample and linear regression used to determine the line $y = a + bx$.

Result: The *slope b* of the line is a measure of the linearity of the titration method. In the ideal case it should be zero, in other words the result is independent of the amount of sample.

Determination of the limit of determination (chart 3)

Performance: Titration of multiple series under the same measurement conditions, with the amount of sample continuously decreasing for each series.

Result: The *relative standard deviation (RSD)*: The limit of determination is the smallest amount of sample that can be determined with a sufficiently low RSD.

Method validation using the example of electronic balances

Example 1: Weighing of hygroscopic or decomposable substances

A simple weighing operation is unsuitable for hygroscopic or decomposable substances. In this case, the user must define a procedure for the weighing which enables a reproducible and accurate result to be obtained.

A possible measure would be to work under an inert gas (sampling, weighing and further sample processing). The process must be defined as a standard operating procedure and documented accordingly.

The method validation must in this case ensure that the defined procedure is actually suitable.

Example 2: Density determination of a solid with an analytical balance

Density determination following Archimedes' principle can be achieved by two measurements of the same test specimen in two different media of known density (e.g. air and water). The method is supported by special functions in the balance or a control unit.

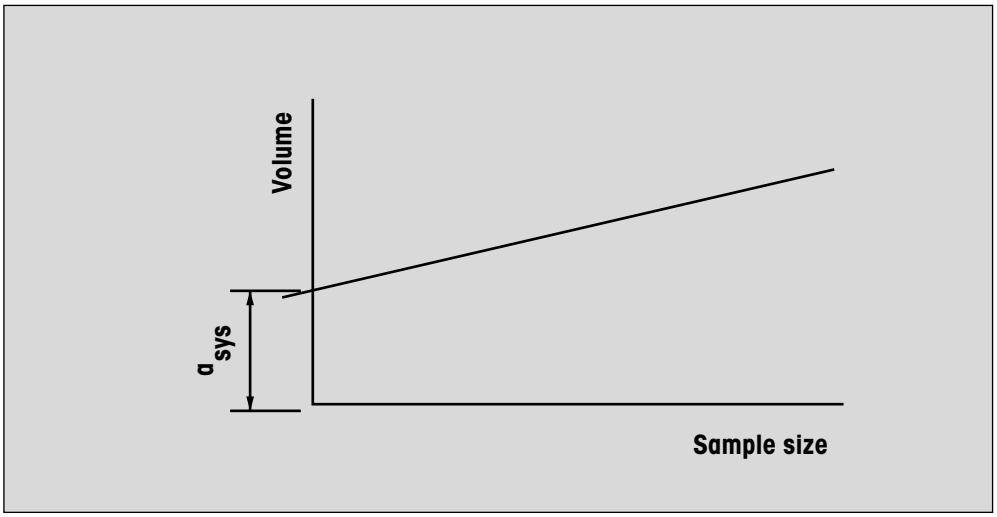
Accuracy. Determination of a reference body of known density by the defined method. Check on the systematic error by manual calculation of the density using the weighing values read off.

Repeatability. Multiple determination of the same body.

Reproducibility. Determination of the same body on different balances or with different auxiliary liquids.

Influence of the sample size on the analytical measurement result

1



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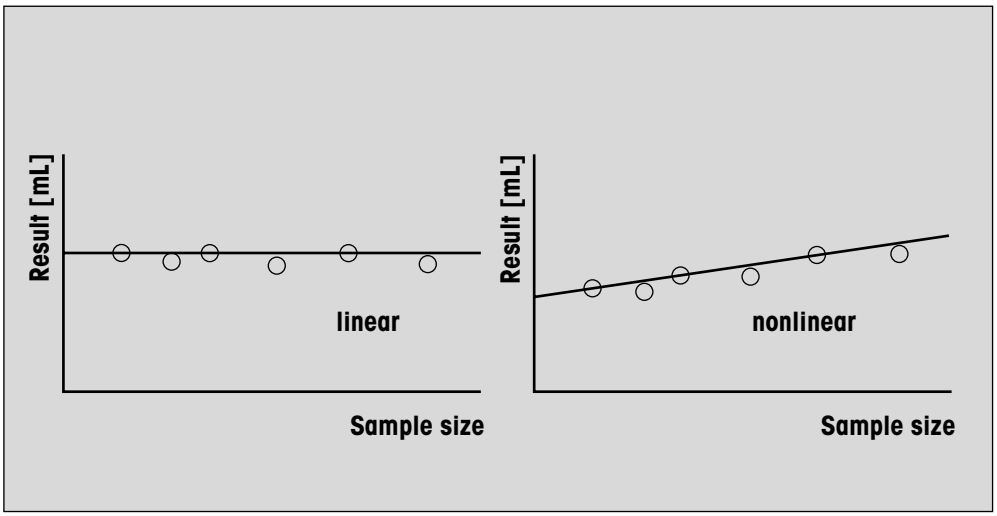

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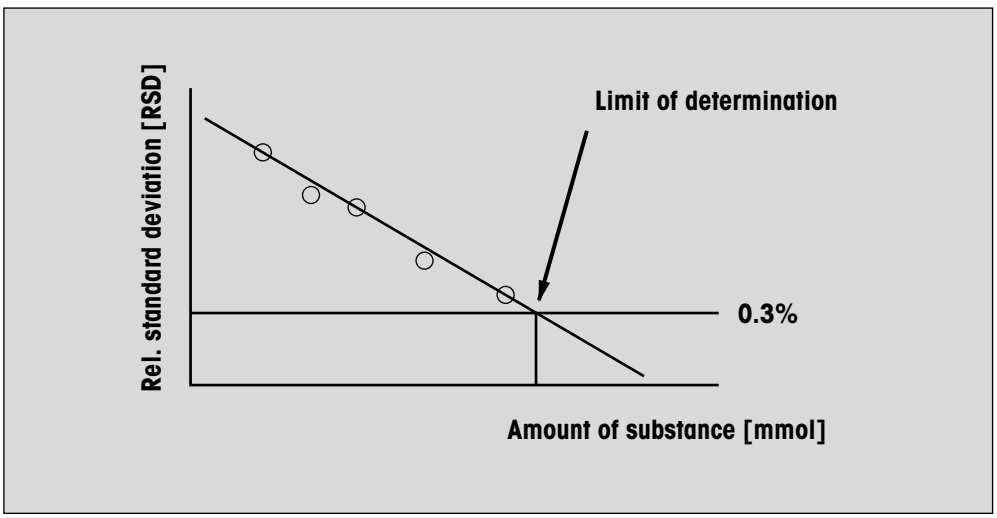


Linearity. The linearity in this case depends on the mass and the volume. It is thus appropriate to use reference bodies of different materials with a known density which differ in regard to mass and volume.

Limits of determination. Determination of the density with different sample sizes (volumes) for determination of the measuring range.

Example 3: Sample handling

Should the sample in a weighing boat be rinsed out with solvent or can the boat simply be emptied?

Validation using the example of instruments to determine moisture

The validation should comprise a combination of a reference method and round-robin experiments of the moisture analyzer.

The main error source in moisture determination is the thermal decomposition of the samples; this can, however, sometimes lead to a stable and reproducible final result. If this effect needs to be excluded, the sample substance for the validation must be investigated *thermoanalytically* (reference method). Other influencing factors are amount of sample, sample distribution or fluctuating atmospheric moisture in the surroundings.

If the drying oven with differential weighing is selected as reference method, first several measurement series must be performed in the drying oven. This method should dependably lead to a stable and reproducible result which can be used as a reference for the method validation.

The result of the reference method should be capable of verification by the method used by the moisture analyzer. If a moisture analyzer offers several methods or switch-off criteria, these can be checked using the reference method. The moisture analyzer can be adapted accordingly.

Should the speed of the process of moisture determination be optimized (e.g. for process control), the accuracy of the result may possibly be immaterial if the results are reproducible and the measured deviation remains constant in proportion to the correct value. The measured value must then be corrected by this constant factor.

3.3. System suitability test

A system suitability test (SST) proves whether the measurement system is suitable for the planned measurement or determination while ensuring compliance with the defined tolerances. An initial test checks the reliability of the measurement system, repeat tests check the current condition in routine operation (control of inspection, measuring and test equipment).

The system suitability test can be part of the method validation and is usually designed as a standard operating procedure, above all when the system is tested at regular intervals. Suitable operating procedures can be used to ensure the system suitability or reliability of the complete measurement system.

In what follows, suggestions for system suitability tests of different instruments are presented.

System suitability tests for titrators

Example: Titer determination

Both the reliability of the measurement system and the accuracy of the method are checked using a reference substance (primary standard).

Appropriate methods for the most important titrants are usually already integrated in titrators.

System suitability tests for electronic balances

Example: Density determination

The system suitability test can here comprise part of the method validation. The density determination of a reference body of known density ensures the reliability of the balance and density determination method.

Example: Moisture determination with a moisture analyzer

The system suitability test for moisture determination can be performed using a reference method with a drying oven. The reference method comprises, e.g. a differential weighing before and after a defined drying operation, usually 2–3 hours at 105 °C. The method validation must first ensure that the reference substance does not decompose during the drying process and supplies reproducible results.

4. Control of inspection, measuring and test equipment in routine operation

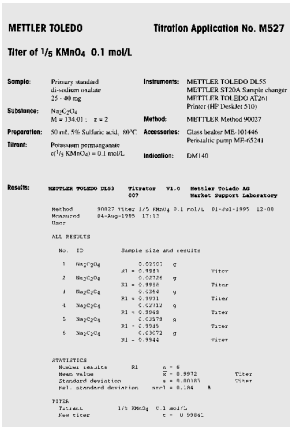
If the system suitability test has been completed successfully, routine operation can be started. A check based on a standardized procedure (SOP) must be made at regular intervals to see whether the particular measurement performance of the instruments is still within the tolerances originally specified. This assures comparability of the test results even if the test is performed by different persons.

4.1. Contents of the test

Depending on the dependability required by the user, the instrument used or the method employed, the contents of the regular testing differ in their extent of detail. For the actual test routine, parts of the qualification already performed, validation or the system suitability test can be adapted or modified slightly. However, the scope of this test is usually considerably less, so that the test can possibly be performed several times a day.

The contents and the performance of the regular test routine must be unambiguously defined and documented. It must be ensured that different persons perform the same manual operations at different locations and a comparable quality of the measurement results is obtained. It is thus imperative to define a standard operating procedure (SOP) for the test.

A relatively extensive calibration which corresponds to the qualification of the instrument and ensures the traceability (section 5) should be performed one or two times a year.



METTLER TOLEDO — Titration Application No. M527

Titer of 1/5 $KMnO_4$ 0.1 mol/L

Sample: Primary standard di-sodium oxalate 25 - 80 mg
Substance: $Na_2C_2O_4$ M = 134.01 ; z = 2
Preparation: 50 ml 5% Sulfuric acid, 80°C
Titrant: Potassium permanganate 0.1 mol/L
Instruments: METTLER TOLEDO DL55, METTLER ST20A Sample changer, METTLER TOLEDO AT261, Printer (HP DeskJet 310)
Method: METTLER Method 90027
Accessories: Glass beaker ME-101446, Peristaltic pump MP-65241
Indication: DM140

Results: METTLER TOLEDO DL55 Titrator V1.0 — Mettler Toledo AG, Market Support Laboratory

Method 90027 Titreg 1/5 KMnO4 0.1 mol/L 01-Jul-1995 12:08
Measured 04-Aug-1995 17:13
User

ALL RESULTS

No.	ID	Sample size and results	
1	$Na_2C_2O_4$	0.03551 g	
		M1 = 0.9883	Titer
2	$Na_2C_2O_4$	0.03724 g	
		M1 = 0.9950	Titer
3	$Na_2C_2O_4$	0.0364 g	
		M1 = 0.9931	Titer
4	$Na_2C_2O_4$	0.03732 g	
		M1 = 0.9948	Titer
5	$Na_2C_2O_4$	0.03579 g	
		M1 = 0.9945	Titer
6	$Na_2C_2O_4$	0.03572 g	
		M1 = 0.9944	Titer

STATISTICS

Number results	N1	n = 6	
Mean value		x = 0.9972	Titer
Standard deviation		s = 0.00181	Titer
Rel. standard deviation		srel = 0.04 %	

TITR

Titrant	1/5 $KMnO_4$	0.1 mol/L
Raw titer		t = 0.99861

4.2. Standard operating procedures (SOP)

The SOP plays an important part in the documentation required by the relevant QM standards. The SOP is always matched to the precise method and the conditions on site.

In practice, an SOP formulated by the user is read and followed much more attentively by fellow employees than one produced by an anonymous authority (often with unfamiliar formulations).

A check list which, in outline, takes the following points into account is helpful in the preparation of an SOP:

Areas of responsibility for the SOP from the field of GLP:

Inspection and testing equipment manager	arranges that SOPs are produced and approves SOPs with date and signature
Inspection and testing director	ensures that SOPs are available and approves SOPs on behalf of the management
Personnel	follows the SOPs
GLP quality assurance	checks whether a valid SOP is available, is followed and whether and how changes are documented.

Administrative matters

1. Use of SOP forms
2. Name of the inspection and testing equipment
3. Date when SOP produced
4. Storage identification (master reference plan) for SOPs
5. Page numbering (1 of n)
6. Title
7. Date of putting into force (first date of validity)
8. Revision information
9. Specification of departments responsible for implementation
10. Date and signatures: authors, checker, person responsible for authorization
11. Distribution list

Contents of the SOP

1. Material needed
2. Description of the work steps
3. Description of the documentation
4. Data processing and evaluation
5. Documents, samples, etc. to be stored
6. Archiving instructions

4.3. Definition of warning and action limits

The maximum admissible error of measurement of the test must be unambiguously defined. On the basis of this definition, warning and action limits for the regular tests can be specified.

A good starting point is to set the warning limit to approx. 1/3 of the maximum error admissible for the test and the action limit to approx. 2/3 of such an error. This has the advantage that even if the action limit is exceeded the intended quality goal can be attained. Cost intensive follow-up measurements or the blocking of entire product lots can thus be avoided.

Example of the definition of warning and action limits in the testing of a balance

Value of the lowest desired sample weight:	240 mg
Test at:	200 mg
Required measurement accuracy:	1%
Maximum admissible error of measurement:	2 mg
– Warning limit	0.7 mg (approx. 1/3 of sample weight)
– Action limit:	1.4 mg (approx. 2/3 of sample weight)

Measures which need to be implemented if the warning or action limit is exceeded should be stipulated in the SOP for testing the balance.

Example: Measures when warning limit reached or exceeded:

– Adjust measuring instrument
– Recalibrate (test)
a) Balance is within tolerance → Decrease test interval
b) Instrument remains outside tolerance → Contact service

Measures when action limit reached or exceeded:

– Immediately take instrument out of operation
– Label instrument as faulty
– Call customer service
– Recalibrate before putting back into operation

4.4. Test intervals

Recommendation: Multiple checks by the user
Perform basic calibration once per year.

The interval between two tests and the test tolerance depends on the dependability required. The following always holds: The greater the importance of the weighing results for the product quality, the more frequently testing should be carried out.

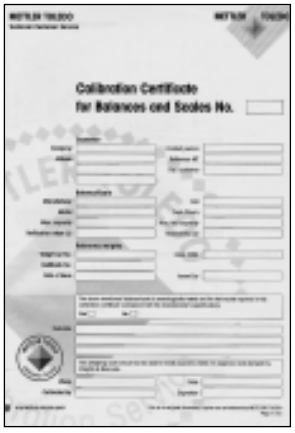
A general rule for defining the test interval can not be formulated owing to the numerous factors which need to be taken into account.

One possibility to find a suitable test interval involves dynamic adaptation of the interval following a defined procedure, depending on the results obtained.

Example. At the start, the defined test is performed at regular time intervals.

– If the measuring instrument lies within the tolerance after three tests, the test interval can be extended, maximum doubled.
– If the measured value of a test is outside the defined tolerance, the test interval is halved.
– If the time for the test is acceptable, the test interval should be retained.

With new measuring instruments with an unknown long-term behavior, it is appropriate to start with short test intervals.



Methods for the revision of the intervals following ISO 10012

	Evaluation	Result	Advantages	Disadvantages	Application
Method 1 Automatic or stepwise adaptation	Tolerance situation of individual inspection measuring and testing equipment	Individual interval change, e.g. ± 0.5 years	Simple method, rapid adaptation	Individual treatment of the measuring devices	Easily surveyed number of measuring devices without special requirements "entry-level method"
Method 2 Quality control-card	Individual control and drift of fixed calibration points for all inspection and test equipment	Individual calculation of confirmation intervals from mean drift of one or more confirmations	Soundly based determination of the intervals	The more complicated the measuring equipment, the more time consuming large data volume	Simple measuring devices and automatic data processing
Method 3 Date	Number of faulty measuring devices per group	Interval adaptation of similar inspection, measuring and test equipment	No interval treatment	Lack of clarity in the assessment, depending on selection of group	Large number of similar measuring devices
Method 4 Period of use	Number of hours in use	Individual interval adaptation according to type of use	Confirmation directly dependent of period of use Monitoring of the load	High initial costs for installation of a counter, etc.	Inspection, measuring and test equipment with high wear and tear
Method 5 Black box (only for intermediate testing)	Test result of critical parameters	Decision wether premature calibration necessary	Testing on site Little work involved	Additional parameters can falsify the results Decision regarding critical parameters Tracing back to black box	Complicated instruments Process measuring chains

Table following Hinn

4.5. Documentation of the test results

The documentation of the regular tests by the user can be implemented very simply using an attached data printer. This prevents transcription errors of the measured values and allows simple integration of the required parameters such as serial number, time, date and user.

Material required for the documentation:

a) Manuals/operating instructions
b) *In-house SOPs* (standard operating instructions)
   e.g. calibration SOP, maintenance/cleaning SOP, etc.

4.6. Control of inspection, measuring and test equipment using the example of electronic balances

The balance can be checked by loading a certified weight in the region of the weighing range in most frequent use, e.g. 100 g (measurement mirroring actual practice).

Example of an SOP (short-form test instructions)

1. Control weight at ambient temperature.
2. Balance is leveled.
3. Balance has been switched on at least 30 minutes before the check or is in the standby mode.
4. Clean weighing pan and check for free clearance (no weighing sample beneath the weighing pan).
5. Adjust balance (if internal adjustment available, otherwise proceed with point 6).
6. Zero.
7. Place control weight in middle of weighing pan, check display value.
8. If a limit value is exceeded, repeat operation. If the limit value is again exceeded, switch off balance, disconnect from power supply, label as out of order and call service.
9. Record the work performed: Name, date, time, instrument type and serial number of the balance, signature.

4.7. Control of inspection, measuring and test equipment using the example of titrators

In order to obtain accurate results with a titrator, the burettes, burette drives and sensor inputs must be calibrated using certified inspection, measuring and test equipment. The condition of the instrument must be traceable to national or international standards.

Testing of the sensor inputs

Here, a test is conducted to establish whether the signal transfer and the impedances of the sensor inputs correspond to the set values within the specified error limits. Certified resistors and a certified voltmeter which allow the traceability of the measurement to the international volt standard are used for the calibration.

Testing of the burette drive

This tests whether the piston travel corresponds to the set value within the specified error limits. A certified micrometer which allows the traceability of the measurement to the international length standard is used for the calibration.

Testing of the burette volume

This test determines whether the discharged volume of the burette corresponds to the set value within the specified error limits. 30%, 50% and 100% of its nominal volume are dispensed and weighed. The mass is compared with that dispensed with a certified reference burette of the same nominal volume and under the same conditions; this allows traceability of the measurement to the international mass standard.

The procedure is based on the DIN 12650 standard, which permits an error limit of 0.3% of the nominal volume of a burette.

4.8. Documentation in the log book

A log book can be extremely helpful as a basis for documentation of the implemented measures (installation, care, maintenance, calibration, etc.). The log book is allocated to a measuring instrument and accompanies it throughout its entire life cycle. As all work performed is entered in the appropriate blank forms of the log book, the history of the instrument is transparent and available at all times.

5. Traceability

For the performance of metrological tests, certified inspection, measuring and test equipment (test standards) must be used. Certification is usually performed by an accredited testing laboratory whose competence is restricted to the individually accredited test procedures. The accreditation provides the testing laboratory with the proof that it has the competence to produce or calibrate special inspection, measuring and test equipment with sufficient accuracy. The accuracy and the limit values of the calibration process are attested to by a certificate. The test standards must be recertified after certain intervals of use.

It must be ensured that the test standards of different accredited testing laboratories match one another, in other words the reported value corresponds to the true value. Traceability means that the measurand of the test standard can be traced to a generally valid basic physical quantity.

Physical base units

Base unit	Name of unit	Symbol	Definition of the universal constants
Length	meter	m	Distance travelled by light in a vacuum during 1/299792458 seconds, practical determination by iodine-stabilized laser.
Mass	kilogram	kg	Not a universal constant, weights are calibrated to the internationl prototype of the kilogram.
Time	second	s	1 second is the duration of 9 192 631 770 periods of the radiation corresponding to the transition between two hyperfine levels of the ground state of the caesium 133 atom.
Electric current	ampere	A	Force equal to 2 x 10^{-7} newton per meter of length induced by an electric current between 2 parallel electrodes placed 1 meter apart in a vacuum.
Thermodynamic temperature	kelvin	K	The fraction 1/273.16 of the thermodynamic temperature of the triple point of water.
Amount of substance	mole	mol	Amount of substance which contains as many elementary entities as there are atoms in 0.012 kilograms of ^{12}C.
Luminous intensity	candela	cd	Luminous intensity of a monochromatic radidator of frequency 540 x 1012 Hz multiplied by 1/683 watt/steradian (normalization constant).

The certification includes a comparison of test standard and traceable base quantities. The error of measurement and tolerances are shown in a calibration certificate. If the traceability of a test standard is ensured, it can be used for the adjustment or calibration of a measuring instrument. The accuracy and reproducibility of the measurement results are thus comparable as the performance of different measuring instruments can be traced back to the same base quantity.

5.1. Traceability of the mass

The mass is an exception as it is the only base unit which to date could not be traced back to a universal constant. Further, the weight force generated in weighing of a mass is dependent on the balance location and decreases with increasing distance from the earth's mid-point. With sensitive balances, this effect is noticeable even on different floors of the same building.

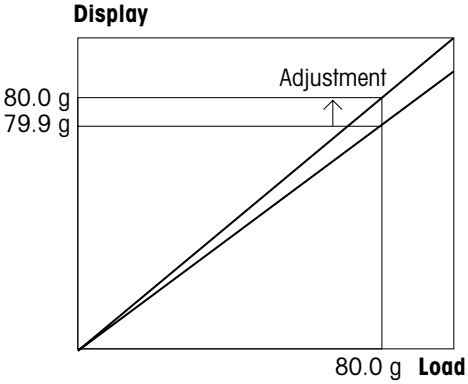
Two requirements for accurate mass determination can be derived from the above comments:
– adjustment of the balance at its location,
  adjustment between loaded mass and displayed weight value.

– The weight used for adjustment must be calibrated against the international prototype of the kilogram via traceability using comparison weighings (shown by certification of the weight). The determined values are documented in a calibration certificate.

Adjustment of the balance at its location

A balance determines the force which is exerted on a loaded weight by the acceleration due to the earth's gravity. In the manufacture of a balance, the relationship between the generated force and the loaded mass is determined.

Adjustment of the sensitivity



Example:
– A mass of 80.0 g is on the weighing pan, 79.9 g are shown in the display.
– After adjustment of the sensitivity, the display shows 80.0 g.
– In contrast to the adjustment, the calibration simply determines the difference between the two values. The displayed value must be corrected by the determined calibration factor.

Adjustment: 80.0 g = 80.0 g
Calibration: 79.9 g x factor = 80.0 g
The calibration factor in this example is 1.0013

Test weights

The traceability of certified weights is ensured by a series of comparison weighings. Each country has its own weight standard which is calibrated against the prototype of the kilogram after certain time intervals by a comparison weighing. The national standards also serve as a standard for the manufacture of additional accuracy classes of weights. The accuracy classes differ in the number of comparison weighings starting from the prototype of the kilogram as an additional measurement error results from the additional weighing.

Weights used for the adjustment or testing of balances must be related to national or international standards (mass standards) via traceability. This proof is provided by an official calibration certificate of an accredited calibration laboratory in which the nominal value and uncertainty of measurement are specified.

Through confirmation of the weight class following OIML (Organisation Internationale de Métrologie Légale) R111 it is also ensured that the error limits corresponding to the weight classification are conformed with and the material and surface quality comply with the international definition.

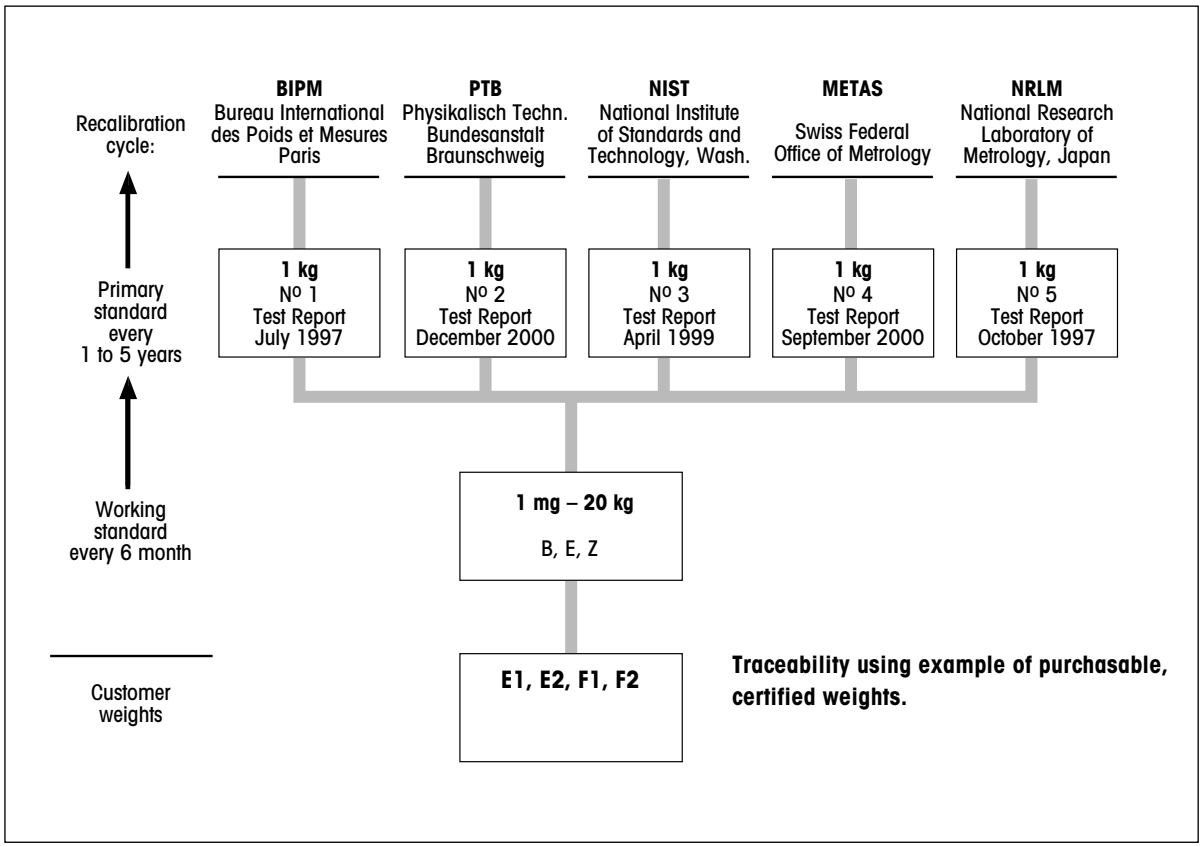
In the selection of the calibration or test weights, the following scheme has proved its worth:

Recommended accuracy class of the weights

Resolution of the balance	Class following OIML R111
up to approx. 6.000 d	M1
up to approx. 30.000 d	F2
up to approx. 100.000 d	F1
over approx. 100.000 d	E2

(resolution = maximum capacity / readability)

Chart for the traceability of certifiable weights from METTLER TOLEDO



5.2. Traceability using the example of titrators

To perform a metrological test of a titrator, certified inspection, measuring and test equipment (test standards) is used: Resistors, micrometers, voltmeters, reference burettes as well as an analytical balance with 0.1 mg readability. The travel of the burette drive, the volume actually dispensed and the measured electronic signals must be traced to the international units kilogram, meter and volt.

Example: The weight of the dispensed volume is determined gravimetrically using a reference liquid of known density.

6. Glossary

Accreditation: Proof of competence issued by a controlling body that an institute or person is competent to perform a particular task.

Accuracy: Ability of a measuring instrument to provide values of the output quantity in the vicinity of the true value (cf. Precision)

Adjustment: Operation which brings a measuring instrument into an operating condition suitable for use. Determination of the difference between a test and actual value. Subsequent adjustment of the measuring instrument with minimization of the error of measurement. An adjustment can be performed automatically, semi-automatically or manually.

Calibration (cf. Testing and Adjustment): Determination of the difference between a displayed value and the true value. The deviation is specified by a calibration factor. Each determined measurement result must be corrected by this factor.

Certification: a) Process in which a neutral authority confirms that a product, a procedure or a service meets the specified requirements.
b) Sum of all calibrations of an instrument.

Control of inspection, measuring and test equipment: Regular check on measuring equipment to ascertain whether the performance capability satisfies the defined requirements.

Drift: Slow change of a metrological characteristic of a measuring instrument.

Error of measurement (rel.): Result of a measurement divided by the true value of the measurand.

Error of measurement: Result of a measurement minus the true value of the measurand (of a measuring instrument)

Limit value of an error of measurement (measurement tolerance): Approved extreme values for a measuring instrument through specifications, regulations, etc., for an error of measurement. The value of the limit values is the error limit. The amount by which the limit value is exceeded is the error of measurement.

Linearity: Constant relationship between output and input quantity (measurand) over the entire measuring range of a measuring instrument.

OECD: Organization for Economic Cooperation and Development.

Pharmacopoeia: List of official drugs and medicinal preparations with regulations for their preparation, properties, analysis, use, etc.

Precision: Closeness of agreement between observed values or independent test results obtained under the same conditions:

Readability: Smallest distinguishable difference between two display values.

Reference material: Material or substance of sufficient homogeneity whose characteristic values are so well defined that they can be used for the calibration of measuring instruments, for the assessment of measurement procedures or for the assignment of material characteristics.

Repeatability: Closeness of agreement between results of successive measurements of the same measurand performed under the same measurement conditions.
– Same measurement procedure
– Same observer
– Identical objects (same sample, same material)
– Repetition over a short period of time
– The same measuring instrument
– The same location.

Reproducibility: Closeness of agreement between the results of measurements of the same measurand performed under changed conditions of measurement (cf. Accuracy).
A valid statement of the reproducibility requires specification of the conditions changed.
The changed measurement conditions can include:
– Measurement principle or measurement method
– Observer
– Measuring instrument
– Reference standard
– Location
– Conditions of use
– Time

Resolution: Number of individual measured values within the measuring range. Measuring range divided by the readability.

Result of a measurement: A value obtained by measurement allocated to a measurand. Corrected measurement result: The measurement result is corrected by the systematic error.

Sensitivity: Change in the output quantity divided by the corresponding input quantity of a measuring instrument.

Stability of a measurement: Ability of a measuring instrument to maintain constant its metrological characteristics with time.

Standard deviation: Measure of the repeatability of a normal distribution (Gaussian bell-shaped curve) in the repeated performance of a measurement.
For a normal distribution (no systematic influence on the error size), the following holds:

$$sd = \sqrt{\frac{1}{n-1}\sum_{i=1}^{n}(x_i - \bar{x})^2}$$

$\overline{n}$ = number of individual results x^i
$\overline{x}$ = arithmetic mean of the individual results xi

Standard operating procedure (SOP): Defined working instructions for an operating procedure whose course is clearly documented. The instructions must be followed as accurately as possible to ensure comparability of the results.

Standard: Material measure, measuring instrument, reference material or measuring system intended to define, realize, conserve or reproduce a unit or one or more values of a quantity to serve as a reference.

Test: Determination of a characteristic (measurement, investigation) for a unit and comparison with the specified requirements. Determination of whether the conformity for the characteristic is attained.

Traceability: Property of the result of a measurement or the value of a standard whereby it can be related to stated references, usually national or international standards, through an unbroken chain of comparison measurements all having stated specified uncertainties.

Trueness: Closeness of agreement between the average value obtained from a large series of observations and an accepted reference value. Ensured by, e.g. adjustment of a balance.

Uncertainty of measurement: Parameter allocated to the measurement result which indicates the scatter of the measured values. The uncertainty of measurement comprises the random and systematic error components of the measurement result.
Random error: Due to the performance limit of the measuring instrument, the uncertainty of measurement can be specified as, e.g. a multiple of the determined standard deviation.
Systematic error: Usually not a normal distribution. Results from the error of measurement minus the random error.

Validation: The requirement for a specially intended use can be met. This is documented by an investigation and suitable proof.

Verification: The verification of a measuring instrument comprises the verification tests and verification identifications which need to be undertaken to comply with the verification regulations (e.g. Metrology and verification act, verification ordinance).

7. Further reading

German and English, publisher: METTLER TOLEDO

"Gute Laborpraxis" im Titrationslabor, Broschüre No. 14

Leitfaden zur Resultatkontrolle, Methodenvalidierung und Gerätezertifizierung, Broschüre No. 15

Validiering von Titrationsmethoden, ein Leitfaden für Benützer von METTLER TOLEDO Titratoren, Broschüre No. 16

Wägetisch-Empfehlungen: Vorschläge zum Bau von stabilen Labor-Wägetischen aus Kunstoffplatten

Eichgesetz und Waagen – ein Leitfaden

Ex-Broschüre: Einführung in den Explosionsschutz in der Budesrepublik Deutschland

SQC guide: For the practice of quality control of filling installations including collection of laws of different countries

School experiments: Natural science laws – Experience "live" – learn easily

Log book Titration

Log book Balances

Log book TA

Balance selection: "Weighing in quality management", new quality brochure for balances

Weighing the right way: Correct working with electronic, analytical, semimicro- and microbalances

Dictionary of Weighing Terms: A practical guide to the terminology of weighing

AT book: the new AT analytical balance from METTLER TOLEDO. Fundamentals of mass determination

German, publishers: various

"GLP-Handbuch für Praktiker: Christ, G.A., Harston, S.J. und Hembeck, H.W., GIT Verlag GmbH, Darmstadt, 1992

Masse, Wägewert, Kraft, Gewichtskraft, Gewicht, Last, Begriffe

Grundbegriffe der Messtechnik

Begriffe im Waagenbau

Metrologische Aspekte nichtselbstätiger Waagen

Praxishandbuch Qualitätsmanagement – Lebensmittel, Kosmetika, Chemie

Statistische Methoden der Qualitätssicherung

Gesetz zum Schutz von gefährlichen Stoffen: (Chemikaliengesetz – ChemG) vom 16. September 1980 in der Fassung vom 14. März 1990 § 19 und Anhang 1 zu °10a Abs. "Grundsätze der Guten Laborpraxis (GLP)"

DAB 10, Deutsches Arzneibuch. 10. Ausgabe 1991, Deutscher Apotheker Verlag, Stuttgart, Germany, Chapter V6.20.4

DIN ISO 10012: Forderung an die Qualitätssicherung für Messmittel

Messunsicherheit und Fähighkeit, Qualität und Zuverlässigkeit: M. Hernla, 1156-62 (1996)

English, publishers: various

The OECD Principles of Good Laboratory Practice: OECD Series on Principles of Good Laboratory Practice and Compliance Monitoring, Number 1, Paris 1992

Guide to Good Manufacturing Practice for Medicinal Products: EC III/2244/87-EN, 1989

USP XXIII, The United States Pharmacopoeia: 23rd edition, United States Pharmacopoeial Convention, Inc. Rockville, MD, 1995, pp 1768–1779

European Pharmacopoeia: 2nd edition, Maisonneuve S.A., 57-Sainte-Ruffine, France 1980, Chapter V.6.20.4 (1987)

ISO/DIN 10012-1, Quality assurance requirements for measuring equipment: Part 1, Management of measuring equipment, Draft Version 1990

Variables affecting precision and accuracy in high performance liquid chromatography: Bakalyar, S.R. and Henry. R.A., J. of Chromatography 126, 327-345, 1976

Automation and validation of HPLC systems: Erni, F,, Seuter, W. and Bosshardt H., Chromatographia 24, 201-207, 1987

Requirements and Tests for HPLC Apparatus and Methods in Pharmaceutical Quality Control: Maldener, G., Chromatographia 28, 85-88, 1989

How to Set Realistic System Suitability Criteria: Wiggins, D.E., LC-GC INT. 2, 44-50,1989

Reproducibility Problems in Gradient Elution caused by Differing Equipment: Snyder, L.R. and Dolan, J.W., LC-GC INT. 3, 28-39, 1990

Liquid reference materials for ultraviolet and visible spectrophotometry: Watson, C., Spectroscopy Europe 7 (3), 27-31, 1995

8. Certificates

SQS

The Swiss Association
for Quality and Management Systems

Mettler-Toledo GmbH

CH-8606 Greifensee

SQS Certificate
ISO 9001:1994 / ISO 14001:1996

Certified area

Whole Company

Field of activity

Balances/scales and weighing systems for laboratories and industry, sensors and measurement systems for chemical and physical analysis and for process measurement technology, customized manufacturing of electronic printed circuit boards, product-related services

This SQS Certificate is valid up to and including 11 May 2004

Scope number 19

Registration number 14072-02

ACCREDITATION

Based on the Accreditation and Designation Ordinance
dated 17th June 1996
the Swiss Federal Office of Metrology grants the

Mettler-Toledo GmbH
Messe Standard Labor
Heuwinkelstrasse
CH - 8606 Nänikon PLZ Ort

accreditation as an

inspection body for agency (type C) for checking the physical properties and the metrological requirements of weight pieces as well as the confirmation of their conformity with the legal regulations

in accordance with SN EN 45004 (Type C)

The accredited scope of inspection is defined in the Official Directory of the Accredited Inspection Bodies in Switzerland. The relevant requirements of the ISO 9001 standard are also covered by this accreditation.

Accreditation number: SIS 034

The accreditation is valid until 30th June 2001.

Wabern, 30th March 1997

Swiss Federal Office of Metrology
The Director

Dr. Wolfgang Schwitz

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