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The Fitness for Intended Use of Analytical Equipment and Systems

A Laboratory Guide to the Life Cycle of Analytical Equipment and Systems, their Qualification and Related Topics

First Edition 2025

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Table of Contents

1 Summary

The aim of a measurement process is to obtain a valid reportable result. The fitness for intended use of the equipment in the context of the fitness for purpose of the analytical process is the prerequisite for any further activity in connection with measurements. This prerequisite is achieved by qualifying the equipment and systems and by validating the analytical procedure.

It continues with the development of a new or changed method, leads through the validation of the method to the non-routine and routine uses of the method. The specific performance characteristics of the equipment impact on the validation of the method (e.g. robustness, measurement uncertainty), they are included in the assessment of the transferability of methods to other instruments (internal or external to the laboratory) and in the interpretation of proficiency tests.

The importance of the knowledge about the equipment characteristics and performance increases from routine methods which are used day by day on samples with very little variability to methods which may show unexpected variability (e.g. environmental samples, forensic samples) or to samples with unknown or unexpected compositions and properties (e.g. non-targeted analysis, screening analysis).

This document is a laboratory guide to the life cycle of analytical equipment and systems and their qualification for laboratories working to various standards and regulations. It is designed to help the laboratory management and staff and other users of analytical equipment to find a common nomenclature to meet the requirements efficiently, to do their work efficiently and to better understand the characteristics and limitations of the equipment. The user is responsible for ensuring that the requirements of the quality systems under which their organisation operates are taken into account.

In this guide, the following verbal forms are used:

- “shall”: indicates a requirement, e.g. as defined in a standard;
- “should”: indicates a recommendation;
- “may”: indicates a permission;
- “can”: indicates a possibility or capability.

These definitions correspond to those in ISO/IEC Directives, Part 2 Principles and rules for the structure and drafting of ISO and IEC documents [1].

2 Scope

The definition of the term “equipment” in ISO/IEC 17025 clause 6.4.1 [2] is very broad.
The following restrictive definition is used for this guide:

The term "equipment" covers measuring instruments or instrument systems including control and data processing units, auxiliary equipment and computerized systems with software that are necessary for the correct performance of analytical laboratory activities and that can influence the results.

This document is a guide to the life cycle of analytical equipment and systems, equipment qualification and related topics. It covers the entire lifespan of the equipment. It begins with the design, development and production of new equipment by the manufacturer. At the user's end, it covers all processes from the considerations involved in purchasing new equipment to commissioning, operation, maintenance, requalification and decommissioning. The main focus of attention is on the ***fitness for the intended use*** of the analytical equipment. Standards (ISO 9001, ISO/IEC 17025, ISO 15189 and ISO 17034) are taken into account. The recommendations of the guide are not contradictory to the requirements for regulated (e.g. GLP and GMP) laboratories. This is particularly important for laboratories that work in a mixed environment of quality assurance systems. It is possible to set up a generally applicable quality system.

The focus is primarily on equipment used in laboratories (offline and atline analysis), but the guide also applies to equipment for field measurements. Equipment permanently installed in plants for inline and online analyses may also be treated according to the proposed principles.

The Guide is the basis for the documents that describe the processes in a specific environment. The organization-specific work instructions shall represent the user's quality environment. It takes into account the standards and regulations to be fulfilled, as well as the different requirements of routine analyses or individual case analyses.

The guide is aimed at all persons interested in the quality assurance of analytical equipment and systems. In particular, it is aimed at people who are involved in the life cycle processes of analytical equipment and systems. It supports a common understanding between equipment manufacturers, distributors, users, accreditation and certification bodies and the customers of the laboratory results.

The life cycle management of the equipment and systems, is supported by various processes. These include, for example, document management with archiving, risk assessments, traceability and data integrity. These processes are briefly explained to the extent necessary to understand the overarching process of equipment life cycle management. Reference is made to further literature.

What are the minimum requirements for understanding and implementing the guide? A laboratory employee who has worked with the usual methods (e.g. titration, chromatography and spectroscopy) and is familiar with their theoretical principles can familiarise himself with the subject of equipment and system qualification with the help of this guide.

2.1 How to work efficiently with this guide

Depending on your personal background, your previous experience and the specific question, you can skip parts of the guide. This overview enables the reader to quickly find the information that is relevant to them.

- If you want to know how equipment qualification is integrated in quality assurance in the analytical laboratory, you will find what you are looking for in ***Chapter 3 Introduction***. It also explains where the equipment qualification fits into the overall analytical process, from the object which is sampled to the final analytical information in the given context.
  Sometimes it helps to know the ***historical background***, in particular the reference to the regulated sector (pharmaceuticals), when implementing the qualification of equipment. This is also dealt with in Chapter 3.
- ***Chapter 4 General principles*** examines the normative and regulatory background of equipment qualification, which is particularly interesting if a laboratory has to work according to various quality requirements. Equipment qualification should fulfil all relevant requirements. The supporting processes are also discussed here.
  Appendix A: Standards and regulations lists the relevant requirements in their original wording.
- If you are specifically interested in the core process, the life cycle of equipment, you will find the relevant information in ***Chapter 5 Life cycle of laboratory equipment***, which covers the life of an equipment from the cradle to the grave, so to speak, from the start of the procurement process to the retirement of the equipment.
- Equipment qualification is applied in various sectors. For this reason, different terms are sometimes used to describe related topics. ***Appendix B: Acronyms and Terminology*** provides the definitions of the terms so that they can be compared with each other.

3 Introduction

3.1 The role of the measuring instrument in the measuring process

A measurement is the comparison of a realisation of an SI unit (e.g. certified weight for mass in grams) with a sample of unknown quantity value. In the beginning, the base units of the SI system were partly defined by physical artefacts (e.g. the International Prototype Kilogram). Since 2019, all SI units have been defined by natural constants.

The following examples show measurements with varying complexity, depending on the method and the requirements.

Example 1

The distance between two points in space is measured by direct or indirect comparison with a unit of length (**quantity**) such as the meter. The **measurement** in a carpentry workshop is done with a folding rule, tape measure or ruler or in a precision mechanics workshop with a vernier caliper. The measuring instrument has to be fit for its intended use. The distance to be measured is compared with a multiple (**quantity value**) of the length standard meter (**quantity**). The metre is the basic unit of length in the International System of Units (SI).

Example 2

Mass is determined by indirect comparison with the gram (quantity). The comparison is made by calibrating a balance with a measurement standard traceable to the kilogram of the International System of Units (SI). For everyday mass determinations, no influence quantities are taken into account. If higher demands are made on the measurement result or on its measurement uncertainty, the displayed value shall be corrected with consideration of the influence quantities. Possible **influence quantities** are for example the different acceleration due to gravity at different points on the earth's surface or at different times, the buoyancy of the sample in the surrounding medium (usually air), magnetic interactions of the sample, components of the scale or surrounding objects and electrostatic interactions. The correction of these influencing quantities requires additional measurements with further measuring instruments. In order to achieve metrological traceability, this equipment shall also be calibrated.

Example 3

When determining the content and impurities of a sample by means of HPLC and UV/VIS detection with gradient elution, the relationship between the **indication** of the measuring instrument (photometric absorbance) and the **measurement result** (content) is established by calibration with a suitable calibration material of the main component and impurities if applicable. In reality, either only small amounts of a reference material are available or it is completely missing. In these cases, experimentally determined or estimated factors related to the main component are used. In the case of impurities for which no reference materials are available, only the evaluation in relation to a calibrated component remains. Since the absorption spectra differ from the calibrated component and the components related to it, the results from different measurement processes are only comparable if the properties of the spectrometer (e.g. wavelength, slit width, dark current) do not change. This problem is exacerbated the further one moves from precisely specified directed analytics in the direction of non-targeted analytics and screening, evaluations on the basis of chemometrics or knowledge/deep learning based techniques.

In each case, several influencing quantities are involved in the quantification. These are, for example, the reproducibility of the injected sample or standard quantity, the short and long term flow stability, the reproducibility of the gradient, the gradient dead volume, the temperature of the separation system (equilibrium setting mobile/stationary phase) the wavelength accuracy and its precision, the spectral slit width, energy and noise of the radiation source, contaminations in the beam path and the digital processing of the measured optical absorption. This list is not exhaustive. Some of these influencing quantities only play a role when a method is to be carried out

on equipment from different series or from different manufacturers (e.g. the gradient dead volume). Other influencing quantities can fluctuate in the short term (e.g. the flow rate or the temperature of the separation system) or they can drift in the longer term (e.g. reproducibility of the sample application quantity or the energy of the radiation source). In an analytical method, the effect of the influencing quantities on the measurement result is determined in the robustness section of the method development. With non-targeted analytics and screening, it is much more difficult to estimate the effect of the influencing quantities on the results. The results of the robustness tests also show which requirements equipment shall fulfil if the method is to be transferred. Knowledge of the behaviour of the influencing quantities and their effect makes it possible to calculate realistic measurement uncertainties.

Different objects being examined different questions require suitable measuring equipment (analytical instruments). The analytical equipment shall be fit for their intended use. The influence quantities of the measurement and their variability shall be mastered.

3.2 Historical background

It is a basic requirement of analytical biochemistry and chemistry that equipment shall be suitable for the intended use to which it is applied. These requirements were identified in standards and regulations in the early 1990s [3], [4]. They were not new but they were not clearly defined and therefore the auditing bodies which were increasingly turning their attention to this topic acted inconsistently. In such a situation it is not unusual that industry overreacts uncoordinatedly to certainly fulfil the requirements. To avoid inconsistent and bureaucratic workflows in industry and laboratories in the United Kingdom an opinion-forming group was established. Eurachem-UK and the Royal Chemical Society established with support from the Department of Trade and Industry (DTI) an Instrumentation Working Group. It consisted of representatives of industry, laboratories, equipment manufacturers and auditing bodies. The result of this effort were two position papers on the qualification of analytical equipment [5], [6]. The position papers describe the equipment qualification process in four steps:

1) Design Qualification (DQ)
2) Installation Qualification (IQ)
3) Operational Qualification (OQ)
4) Performance Qualification (PQ)

The origins of equipment qualification according to DQ/IQ/OQ and PQ therefore go back to a co-operation between the regulated sector (GMP/GLP) and the sector defined by standards (e.g. ISO 9001/ISO Guide 25 and EN 45000).

Based on the position paper two papers showing the practical implementation have been prepared with assistance from the Instrumentation Working Group [7], [8].

The 4Qs model was adopted in the regulated sector (GLP, GMP). It was extended to any equipment, also manufacturing and infrastructure equipment. It became the globally accepted standard, adopted by the Pharmaceutical Inspection Co-operation Scheme (PIC/S). Originally, the PIC/S GMP Guide “PIC Basic Standards” of 1972 derives from the WHO GMP Guide and was further developed in order to comply with stringent manufacturing and health requirements in PIC/S countries. In 1989, the EU adopted its own GMP Guide, which – in terms of GMP requirements – was equivalent to the PIC/S GMP Guide.

Since that time, the EU and the PIC/S GMP Guides have been developed in parallel and whenever a change has been made to one, the other has been amended, so that both Guides are practically identical [9]. Annex 15 describes the principles of qualification and validation which are applicable to the facilities, equipment, utilities and processes used for the manufacture of medicinal products and for active substances [10]. As part of a quality risk management system, decisions on the scope and extent of qualification and validation should be based on a justified and documented risk assessment of the facilities, equipment, utilities and processes. The PIC/S Annex 15 is identical to the EU GMP Annex 15 [11].

The 4Q process was not adopted in the ISO standards. But all standards intended for analytical laboratories include the qualification of equipment. The user has a lot of room for interpretation. At the

European Directorate for the Quality of Medicines & HealthCare (EDQM), this led to the parallel introduction of Levels I to IV in connection with ISO/IEC 17025 [12]. Details of these Levels are given in chapter 4.1.1.2.1 *Qualification of Equipment – Core document PA/PH/OMCL (08) 73 R5 of the European Directorate for the Quality of Medicines & Healthcare (EDQM)*

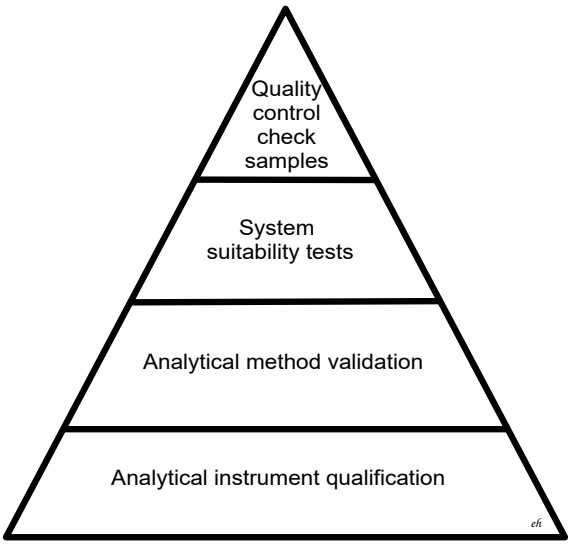

Fig. 1 Components of data quality, USP quality triangle [13], redrawn

In the regulated laboratories the USP general information chapter <1058> Analytical Instrument Qualification [13] is a highly regarded and respected source of information. The qualification of the analytical instruments is understood as the basis for the quality of the analytical data (Fig.1, graphical representation of the quality triangle from USP).

There are four critical components involved in the generation of reliable and consistent data (quality data). These components are shown in the quality triangle as layered activities. Each layer adds to the overall quality. The **equipment qualification** (in USP called Analytical Instrument Qualification, AIQ) forms the basis for generating quality data. The other components essential for generating quality data are **analytical method validation**, **system suitability tests**, and **quality control check samples**.

The USP quality triangle is specifically designed for the GMP environment.

3.3 A general pyramid of quality

This is the attempt to expand the triangle of USP to a more general pyramid reflecting quality supporting processes in analytical methods in a general manner.

3.3.1 Analytical principle, analytical method and analytical process

The **analytical principle** involves physical or chemical interactions, e.g. between light of a certain wavelength and the sample, which leads to interpretable measured values. The analytical principle can be described quantitatively as a partial step of the measurement by the underlying laws of nature. In addition, the **analytical method** also contains parts of the sample preparation and evaluation. It already represents the strategic conception for the achievement of optimal information about the object of investigation or measurement with a given analytical principle. An **analytical process** includes all sub-processes, from sampling to sample preparation, to the measuring arrangement with the analysis function, to the interpretation of the reportable result in relation to the object being examined, Fig. 2 [14].

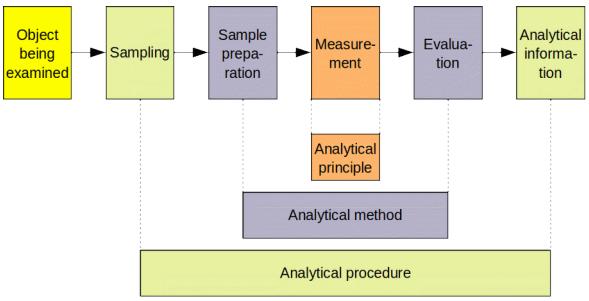

Fig. 2 Analytical principle, method and procedure [14]

3.3.2 The pyramid of quality supporting the reportable result

In principle, the **pyramid of quality** (Fig. 3) includes the **analytical method**. However, it can of course also be used for processes outside the analytical method, e.g. sampling, adapted accordingly.

It is generally applicable to the standards and regulations that cover analytical laboratories. It includes additional aspects.

The purpose of the pyramid of quality is to generate **reportable results** that can be used with confidence. For example the results may be:

- compared against specifications / limit values according to agreed decision rules,
- used to calculate the value (price) of an article, or
- used in scientific studies, legal cases or for further interpretation.

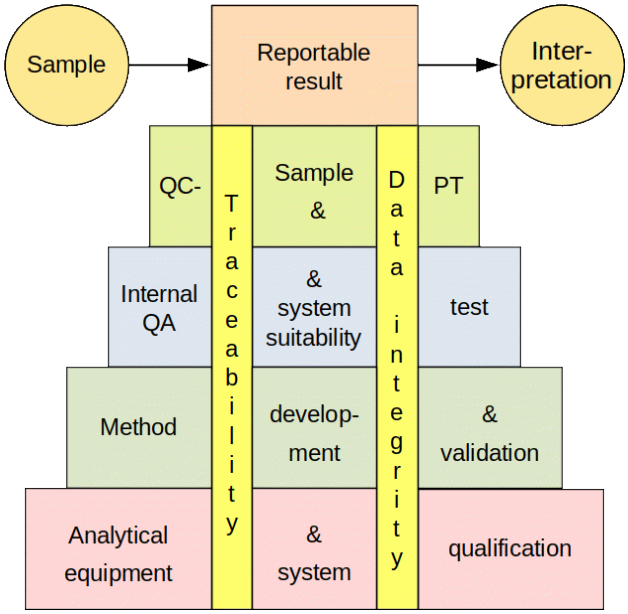

Fig. 3 Pyramid of quality

Various processes are required to generate a report- port- able result: **Analytical Equipment and System qualification**, **Method Development and Validation**, **System Suitability Tests (internal Quality Assurance (QA))**, **Quality Control - QC-Sample and Proficiency Tests (PT, external QA)**, **Traceability** and **Data Integrity**.

A measurement is ideally the comparison of a realisation of an SI unit (e.g. a calibrated mass) with a sample of unknown quantity value.

Different measurement processes and objectives require suitable measuring instruments and systems. The **analytical equipment and systems** shall be **fit for their intended use**. The influence quantities on the measurement and their variability shall be in a state of control.

The **development and validation of** an **analytical method** is carried out using the qualified equipment. In order to keep the characteristics of the measurement results comparable to those of the validation, the equipment shall be maintained in the qualified/validated state.

System suitability tests are performed to verify that the system (equipment, chemicals and reagents, operator, etc.) is performing as it did at the time the method was validated.

In order to demonstrate the comparability of results over longer periods of time or between several participating laboratories, **QC control samples** are regularly analysed and the results are statistically evaluated. Whenever possible, **proficiency tests** are used to demonstrate the comparability of results between different laboratories and/or methods.

Traceability and **data integrity** are required covering all analytical life cycle activities. The term "traceability" includes two aspects:

- **Metrological traceability**, property of a measurement result whereby the result can be related to a reference through a documented unbroken chain of calibrations, each contributing to the measurement uncertainty [15]. This is to be aimed at instrument qualification, method validation and method application. This ensures comparability between different runs of the analytical process and different laboratories.
- **Traceability of processes** means documenting who did what, when and by what means. This is required for processes and workflows to be verifiable and repeatable.

Data integrity is a mandatory requirement for metrology and traceability of processes. Data integrity is summarised by the acronyms **ALCOA** for the original five principles

1. **A**ttributable - Who performed the action and when?
2. **L**egible - Can the data file be read over the entire life cycle?
3. **C**ontemporaneous - Documentation at the time of the activity.
4. **O**riginal - Original record or certified copy.
5. **A**ccurate - No errors or editing without documentation of changes.

The original ALCOA principles have since been updated to ALCOA+. The original principles remain with four additions:

6. Complete - All data, including tests, replicates, or reanalyses performed.
7. Consistent - Elements of the experiment are always performed in a similar manner.
8. Enduring - Recorded in laboratory journals or validated electronic systems.
9. Available - Data can be accessed throughout the life cycle for review, audit, or inspection.

These principles apply to the following types of records:

- Electronically recorded – data recorded using equipment that ranges from simple machines through to complex and highly configurable computerised systems
- Paper-based – a manual recording on paper of a manual observation of an activity
- Hybrid – where both paper-based and electronic records constitute the original record
- Others – this includes photography, images, chromatograms, spectra and more

One element of data integrity is the qualification and validation of the elements of information technology (IT).

In this manner, the equipment qualification and analytical method development and validation contribute to the quality of analysis before analysts conduct the tests. System suitability tests and quality control checks help ensure the quality of analytical results immediately before or during sample analysis.

Since most instrument manufacturers are suppliers to GxP laboratories, they follow the 4Q model.

The determination of the correctness, reproducibility and the drift of the equipment parameters have, in addition to the basic calibration and qualification, an influence on the method validation and the system suitability test and their acceptance criteria.
During the analytical procedure validation, the corresponding values from the equipment qualification should be taken into account as part of robustness testing when defining the measurement range. The actual measured values should also be taken into account when estimating the measurement uncertainty, not general theoretical considerations unrelated to real measurement conditions and equipment.

The criteria and their specifications defined in the equipment qualification have also an influence on the System Suitability Tests (SST) and their acceptance criteria. The SST and specifically the trending of the SST should be the early-warning system to indicate upcoming problems in the analytical process. By the SST the detectability of an incident in the analytical process can be improved.

When transferring a method to equipment with the same measuring principle, the parameters measured and acceptance criteria in the qualification should be maintained. If the acceptance criteria of the qualification are less strict, the successful transfer is not guaranteed. The robustness and the measurement uncertainty shall be redetermined.

The different equipment properties can also have an effect in the results of proficiency tests. For the interpretation of the PT results it may be helpful to consider the equipment property.

All uncertainty components shall be included in the uncertainty of the final result.

The stability of the measurement conditions (influence quantities) and their monitoring are of additional importance in measurement methods that are based on complex mathematical models.
These methods contain multivariate models which are not normally updated frequently, but use results from mathematically complex sets of calibration samples that are stored in a training model. It is essential that the equipment properties have only changed in a controllable manner to a very limited extent since the calibration samples and the measurement samples were analysed.

Complex calibrations often involve multivariate statistical analysis. Examples are NIR spectroscopy or Raman spectroscopy for determining the identity of a sample or for the quantitative analysis of complex mixtures.

It is obvious that activities outside the analytical process, in particular the **sampling process and its uncertainties**, shall be given equal consideration when interpreting the results.

4 General principles

The requirements for handling instruments are defined in standards and regulations. They differ depending on the sector of application and source. Their legal implication differs depending on the authorship and their organizational background. When referred to in a contract, the voluntarily applicable standards become legally binding.

The various requirements are discussed in more detail below. Special attention is paid to digital control and signal processing.

4.1 Requirements in regulations and standards

The development of laws and regulations or standards is fundamentally different. The same applies to checking compliance with the requirements and the consequences of non-compliance.

As a rule, the legislative bodies (e.g. parliament) draw up and pass laws. Detailed legal ordinances are issued for implementation. Depending on the country, different legislative, executive and judiciary bodies are responsible for this. Governmental bodies of the executive branch monitor compliance with laws and regulations. As with other violations of the law, penalties are imposed for non-compliance. Depending on the legal situation, a court gets involved.

Laws and regulations are binding on persons and organisations working in the environment to which the laws apply. Legislation sometimes stipulates that products manufactured outside the actual area of validity shall nevertheless comply with the laws for import of affected goods.

A Standard is a document established by consensus and approved by a recognized body that provides, for common and repeated use, rules, guidelines or characteristics for activities or their results, aimed at achievement of the optimum degree of order in a given context.

Unlike laws, ISO standards are not legally binding. Their use only becomes binding when this is stipulated in legislation or in a contract.

A legal entity can be accredited by a state agency or an agency commissioned by the state according to a standard (e.g. ISO/IEC 17025, ISO 17034 or ISO 15189).

According to other standards (e.g. ISO 9001) legal entities are certified by state-accredited private companies.

4.1.1 ISO Standards

The International Organization for Standardization (ISO) is an international standardisation body composed of representatives from various national standards organizations. Founded on 23 February 1947, the organization promotes worldwide proprietary, industrial, and commercial standards. It works in 165 countries. ISO has formed two joint committees with the International Electrotechnical Commission (IEC) to develop standards and terminology in the areas of electrical and electronic related technologies. It is the world's largest developer of voluntary international standards and it facilitates world trade by providing common standards among nations. More than twenty thousand standards have been set, covering everything from manufactured products and technology to food safety, agriculture, and healthcare.

In the following, those standards are mentioned that particularly affect analytical laboratories and their suppliers. In particular, the aspects relating to the equipment of the laboratories are taken into account.

These requirements are described in such a way that they can be applied in all sectors (e.g. mechanics, electrical engineering or physico-chemical measurements).

Specific requirements which result from the characteristics of atoms and molecules (e.g. isotope distributions, constitutional, conformational and configurational isomerism or the purity as well as the homogeneity and stability of the measurement objects) are not or not sufficiently considered in the ISO standards. These need to be addressed in sector specific guides. Since the standards do not give specific requirements for different types of measurement, sector-specific guides (e.g. for che-

mical and bio-analysis) are beneficial to aid interpretation and implementation of the general requirements.

4.1.1.1 ISO 9001:2015 Quality management systems

ISO 9001 Quality management systems — Requirements [16] describes requirements for a generally applicable quality management system (QMS) that can be introduced regardless of the size and the field of activities of an organization. Other standards address the competence of organisations to carry specific activities, e.g. ISO/IEC 17025 for testing and calibration laboratories.
The need to have an effective and modern approach for a pharmaceutical QMS resulted in the International Conference on Harmonization (ICH) developing in 2008 the quality system guidance for a pharmaceutical Quality System that has the ability to support the regulatory framework for the pharmaceutical industry [17]. ICH Q10 is based on the ISO 9000 series. Therefore for non-pharma specific activities ISO 9001 is a good guide in the life science industry. ISO 9001 is also an adequate basis for QMS for manufacturers of laboratory equipment.
Due to its versatility, the standard is more general in nature. The terms used do not necessarily match the terms normally used in the relevant subject area.

The standard ISO 9001 requires a test equipment management. Test equipment shall be suitable for its purpose and its suitability shall be maintained. Proof of suitability as part of the test equipment monitoring shall be documented [18].

The external procurement of equipment and dealing with the supplier is also handled in ISO 9001 [19]. This also includes external service providers, for example for the service, maintenance and qualification of analytical equipment.
For the manufacturing of equipment the standard is also a highly valuable source to define the appropriate processes [19]. For purchasing this clause is a good source for the qualification of suppliers.
For a lasting and satisfactory relationship with a supplier, the supplier's handling of complaints is of great importance [20]. The fulfilment of these requirements is an important topic in the assessment of suppliers.
For the details of the requirements discussed, please see Appendix A.

4.1.1.2 ISO/IEC 17025:2017 General requirements for the competence of testing and calibration laboratories

This is the main international standard used by testing and calibration laboratories. In most countries, ISO/IEC 17025 [21] is the standard for which most labs shall hold accreditation in order to be deemed technically competent. In many cases, suppliers and regulatory authorities will not accept test or calibration results from a lab that is not accredited. It is the basis for accreditation from an accreditation body.
In some areas, e.g. forensics, doping analysis and food analysis, the standard is the basis and can be required by law. In addition, specific requirements are made.
In ISO/IEC 17025 the resource requirements are defined in clause 6. It is broken down into six subclauses. Clause 6.4 defines the requirements for equipment.
In most cases the laboratory equipment is purchased from an equipment manufacturer.
The external procurement of equipment and dealing with the supplier is handled in clause 6.6.
For the details of the requirements discussed, please see Appendix A.

4.1.1.2.1 Qualification of Equipment – Core document PA/PH/OMCL (08) 73 R7 of the European Directorate for the Quality of Medicines & Healthcare (EDQM)

For analytical laboratories, ISO/IEC 17025 in many aspects largely overlaps with GMP requirements. In the development of active substances and dosage forms, certain aspects are not covered by GMP. ISO/IEC 17025 is used for these areas. Some aspects are less detailed and therefore less clearly defined in the ISO standard than in GMP. An example is the life cycle of the analytical equipment.
For laboratories that are ISO/IEC 17025 accredited and work under GMP, a supplementary document has been issued by EDQM [22]. This guideline

guarantees the harmonized and extended interpretation and application of ISO/IEC 17025 within the Official Medicines Control Laboratory (OMCL) Network.
It is generally used in ISO/IEC 17025 accredited laboratories to fulfil the additional requirements explicitly defined under GMP.
A series of instrument-related annexes is published defining equipment-typical test points and acceptance criteria.
According to EDQM experience showed, that the terms DQ (Design Qualification), IQ (Installation Qualification), OQ (Operational Qualification) and PQ (Performance Qualification) which are not explicitly mentioned by ISO/IEC 17025, have been used in a non-harmonised way by the OMCLs. EDQM does not clarify the 4Q model in the laboratory. These terms have not been used in the documents of EDQM. This does explicitly not exclude their use in OMCL quality systems.
Instead of the terms DQ, IQ, OQ and PQ the terms Level I, Level II, Level III and Level IV are introduced.
Definitions of the levels:

- Level I Selection of instruments and suppliers
- Level II Installation and release for use
- Level III Periodic and motivated instrument checks
- Level IV In-use instrument checks

The 'Level' nomenclature is practically not mentioned in the literature except in the EDQM document and is much less mature than the 4Q model. Since the terms Level I to Level IV are neither mentioned in ISO/IEC 17025 and the 4Q categorisation is allowed by EDQM the Level I to IV nomenclature is not used in this guideline.
This allows the uniform use of the 4Q model in laboratories that work under both ISO/IEC 17025 as defined by EDQM and GMP. The uniform nomenclature is intended to prevent uncertainties and errors and will be used in this document.

4.1.1.2.2 Eurachem/CITAC Guide to Quality in Analytical Chemistry

The Eurachem/CITAC Guide to Quality in Analytical Chemistry: An Aid to Accreditation [23] is a detailed guide for the accreditation of an analytical laboratory. Eurachem/CITAC goes back to the documents of EDQM [12] concerning the qualification of equipment (see above) but without referencing them as literature. Eurachem proposes the general application of the European GMP rules in ISO/IEC 17025 accredited laboratories. The 4Q model is not mentioned in the guideline. The examples in the Eurachem/CITAC guide are taken from the instrument specific documents of EDQM.

4.1.1.3 ISO 17034:2017 General requirements for the competence of reference material producers

ISO 17034 [24] specifies general requirements for the competence and consistent operation of reference material producers. It is intended to be used as part of the general quality assurance procedures of the reference material producer. The requirements for equipment and suppliers are defined in clause 6.3 [25] and clause 7.7 [26].
These requirements apply to all equipment including equipment for material preparation and measuring equipment. The standard includes additional provisions for the operation of measuring equipment: The reference material producer shall ensure that measuring equipment used in reference material production is used in compliance with the relevant requirements of ISO/IEC 17025.
For the details of the requirements discussed, please see Appendix A.

4.1.1.4 ISO 15189:2022 Medical laboratories — Requirements for quality and competence

The standard [27] is based on the details of ISO/IEC 17025:2017 General requirements for the competence of testing and calibration laboratories. The scope of the standard also includes provision of advice to medical laboratory users, including specifics on the collection of patient samples, the interpretation of test results, acceptable turnaround times, how testing is to be provided in a medical emergency, and the lab's role in the education and training of health care staff. While the standard is based on ISO/IEC 17025 and ISO 9001, it is a unique document that takes into consideration the specific requirements of the medical environment and the importance of the medical laboratory to patient care.

For the details of the requirements discussed, please see Appendix A.

4.1.1.5 ISO 10012:2003 Measurement management systems — Requirements for measurement processes and measuring equipment

ISO 10012:2003 [28] specifies generic requirements and provides guidance for the management of measurement processes and metrological confirmation of measuring equipment used to support and demonstrate compliance with metrological requirements. It specifies quality management requirements of a measurement management system that can be used by an organization performing measurements as part of the overall management system, and to ensure metrological requirements are met.

ISO 10012:2003 is not intended to be used as a requisite for demonstrating conformance with ISO 9001 or any other standard. Interested parties can agree to use ISO 10012:2003 as an input for satisfying measurement management system requirements in certification activities. Other standards and guides exist for particular elements affecting measurement results, for example, details of measurement methods, competence of personnel, interlaboratory comparisons.

4.1.2 Regulations

The legal regulations arose because various events occurred in which the life and health of people were threatened. Examples are the Sulfanilamide incident in 1937, also known as the *elixir of death* incident and the Thalidomide scandal in 1960. Such incidents motivated political institutions to create rules to protect their citizens. The result was a collection of regulations designed to protect the life and health of humans and animals. Furthermore, they should also ensure the quality of the data for assessing the risk to the environment. These activities are summarized under the terms GMP and GLP.

4.1.2.1 Good Manufacturing Practice (GMP)

The term was introduced in 1961. GMP is the practice required in order to conform to the guidelines recommended by agencies that control the authorization and licensing of the manufacture and sale of food and beverages, cosmetics, pharmaceutical products, dietary supplements, and medical equipment. These guidelines provide minimum requirements that a manufacturer shall meet to assure that their products are consistently high in quality, from batch to batch, for their intended use.
The most prominent global area of application of GMP is the pharmaceutical industry. In the EU the GMP requirements are compiled in EudraLex. In the USA the corresponding collection is the Code of Federal Regulation (CFR) Volume 21.
Due to the international supply chains and the size of individual markets, individual legislations have an impact all over the world. To achieve a harmonization the PIC (Pharmaceutical Inspection Convention) was founded in October 1970 by the European Free Trade Association (EFTA), under the title of the Convention for the Mutual Recognition of Inspections in Respect of the Manufacture of Pharmaceutical Products. Because of an incompatibility between the Convention and European law, it was not possible for new countries to be admitted as members of PIC. European law did not permit individual EU countries that were members of PIC to sign agreements with other countries seeking to join PIC. As a consequence the Pharmaceutical Inspection Co-operation Scheme was formed on 2 November 1995. Today 56 countries from all continents are members of PIC/S.

The World Health Organization (WHO) version of GMP [29] is used by pharmaceutical regulators and the pharmaceutical industry in over 100 countries worldwide, primarily in the developing world.

The regulations that have a strong impact on GMP laboratories are EU GMP Guide Annex 11 [30] and Annex 15 [31] (respectively Annex 11 and 15 of the PIC/S Guide) [32] and Parts 11 [33] and 211 [34] of US CFR 21.

Although EU GMP Annex 15 discussed qualification of equipment including analytical instruments, there is no such mention in 21 CFR

211, the US GMP regulations. This means that an FDA representative will probably use the descriptive label “calibration” when asking about instrument performance monitoring, but will be referring to the instrument testing carried out under qualification and throughout the instrument’s lifetime of use.

The instrument performance that needs to be satisfied is defined in the corresponding general chapters of the relevant pharmacopoeias.

GMP does not define a comprehensive quality management system. In practice, the ISO 9001 standard is usually used for implementation. ICH Q10 Pharmaceutical Quality System [17] describes a comprehensive model for an effective pharmaceutical quality management system based on the quality concepts of ISO.

A comprehensive Guide on Analytical Instrument and System Qualification is available [35].

4.1.2.2 Good Laboratory Practice (GLP)

The principles of GLP [36] [37] concern non-clinical testing of a chemical or chemical product, examined under laboratory conditions or in the environment, including activities conducted in greenhouses and in the field. It is a set of principles intended to assure the quality and integrity of non-clinical laboratory studies that are intended to support research or marketing permits for products regulated by government agencies. For the Registration, Evaluation, Authorisation and Restriction of Chemicals (REACH) in the EU, the principles of GLP are to be applied.
They include

- physical-chemical testing
- toxicity studies
- mutagenicity studies
- the environmental toxicity studies on aquatic and terrestrial organisms, studies on behaviour in water, soil and air
- bioaccumulation, studies to determine pesticide residues in food or animal feedstuffs
- studies on effects on mesocosms and natural ecosystems
- analytical and non-clinical chemistry testing

Items contained in pharmaceutical products, pesticide products, cosmetic products, veterinary drugs, food additives, feed additives and industrial chemicals are tested under GLP.
Depending on the jurisdiction, the principles of GLP may also be applied to non-clinical safety testing of other regulated products, such as medical equipment.
GLP is very similar to ISO/IEC 17025 in many aspects. The OECD Working Group on GLP has produced a paper comparing GLP and ISO/IEC 17025 [38].
GLP does not define a comprehensive quality management system. In practice, ISO 9001 is usually applied for its implementation. If the organisation concerned performs exclusively analytical laboratory work, ISO/IEC 17025 can also be used.

4.1.2.3 Pharmacopoeias

Pharmacopoeias establish official standards for the quality of medicinal products, active substances and excipients. They are published by the authority of a government or a medical or pharmaceutical society. Important examples with global influence are the European Pharmacopoeia (Ph. Eur.), the United States Pharmacopoeia (USP), the Japanese Pharmacopoeia (JP) and the British Pharmacopoeia (BP). The International Pharmacopoeia (Ph. Int.) is a pharmacopoeia issued by the World Health Organization as a recommendation, with the aim to provide inter-national quality standards for pharmaceutical substances (active ingredients and excipients) and dosage forms, together with supporting general methods of analysis, for global use. Its texts can be used or adapted by any WHO member state wishing to establish legal pharmaceutical quality standards.

As the pharmaceutical market is global, no laboratory working in this field can ignore the requirements of Ph. Eur., USP, BP or JP.

Beside the descriptions of active substances, excipients and pharmaceutical preparations, called monographs, a pharmacopoeia contains in the general chapters descriptions and specifications of laboratory equipment. The qualification of equipment and the validation of analytical methods are important topics. Specifically the General Chapter <1058> - Analytical Instrument Qualification of the United States Pharmacopoeia

(USP) [13] is recognized as a key document. Several general chapters on analytical methods in Ph. Eur. and USP give guidelines on the qualification of the equipment and on the validation of analytical methods.

International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH)

The ICH was founded to harmonize the pharmacopoeias of USA (USP), Europe (Ph. Eur.) and Japan (JP). Today many additional regulatory bodies are members. Beside the harmonisation of the pharmacopoeias also the harmonisation of Good Clinical Practice (GCP) is managed by ICH.

The harmonisation of the general chapters of the pharmacopoeias is not at the same level as the harmonisation of the monographs. ICH is less active in the field of equipment qualification than for example in the field of method development and validation.

The general chapters of the USP on instruments and analytical methods performed with them are commonly used as a reference by instrument manufacturers.

4.1.2.4 Codex Alimentarius

The Codex Alimentarius [39] is a set of food safety and quality standards of the United Nations, first published in 1963 by the Food and Agriculture Organization (FAO) and the World Health Organization (WHO). It is a collection of internationally recognised standards, codes of conduct, guidelines and other recommendations, relating to food, food production, food labelling and food safety. The Codex coordinates fair trade in food at the international level and ensures consumer health protection through uniform standards. The Codex is a reference guide, not an enforceable standard on its own. However, several nations adopt the Codex Alimentarius in their own regulations.

Laboratories shall be in compliance with the general criteria for testing laboratories according to ISO/IEC 17025 for the verification of analytical specifications. Therefore, the requirements for analytical instruments and laboratory equipment specified in the standard shall be met [40].

4.2 Digital control and signal processing

Today's laboratory equipment is controlled by software. The operating and measurement conditions are defined by parameters. Parameters configure the software to get the required conditions and the required behaviour of the equipment.

The programmed control of equipment can be differentiated in three categories:

1. **Control of the operating conditions** (e.g. stability condition, temperature, heating rate, flow rate) The operating conditions can be time-dependent in relation to a process cycle (e.g. temperature ramp, composition of the mobile phase). To achieve comparability of the result the operating conditions shall be reproducible in a predefined scope. Parameters for electronic interfaces (e.g. handshake parameters, network parameters) and for the identification of the equipment and the operator may also be included. They belong to the meta data of the analytical result. The control of the operating conditions is handled by software (programs). The user sets the parameters. The parameters controlling the operating conditions belong to the meta data of the analytical result.

2. **Processing of the signal output of the detector**
   Today the signal processing (e.g. adjustment of the signal gain, filtering of the analogue signal, conversion to digital values) is controlled by digital control units.
   The digital raw data is further processed by mathematical operations of different complexity (e.g. digital filtering, analysing the data stream for peaks or inflexion points, transposing the data from the time to the frequency room by fast Fourier transformation). The parameters of the data processing belong also to the meta data of the analytical result.
   More complex operations like principal component analysis may follow. The signal output of a reference material with well defined properties is correlated by a calibration function to the property of the sample and quality control sample by its signal output. Apart from the property also values for the system suitability

test (e.g. signal resolution, signal shape) are obtained as raw results.

3. The **interpretation of the analytical single result** may include further mathematical treatment (e.g. calculating the average or the standard deviation of multiple determinations or trending). System suitability as well as sample and control sample properties are compared against specifications or further interpreted. This interpretation may lead to an automatic modification of the analytical sequence, e.g. the repetition of a calibration. The comparison of the analytical result of the sample against specifications may lead to a usage decision of the object being examined.
   The interpretation of the single result can be realized in the measuring instrument or in an on-line or off-line linked system (e.g. LIMS, spreadsheet or dedicated software). For complex interpretations complex mathematical procedures (e.g. principal component analysis, search in a database), an expert system or a system based on deep learning may be used.

The software for controlling the equipment and for processing the signal output of the detector is an intrinsic part of the equipment. For equipment procured as a working device this software is developed, documented and validated by the manufacturer. Some equipment offers the possibility to (partially) automate the measurement by user programs. These programs can for example show up in the form of macro programs or spreadsheet-like tables with formulas. These programs are part of the specific analytical process. They are described in the written analytical method and validated with documentation at the validation of the method. The underlying functionality of macro programming or spreadsheet-like tables with formulas is not part of the method validation but of the software validation of the manufacturer of the equipment.

This document does not describe any validation activity of firmware. Firmware is mentioned in the chapter on User Requirements to verify, if appropriate, the activities of the manufacturer of the instrument.

Software is also a topic at Performance Qualification (on-going qualification). To ensure the qualified status of the equipment modifications of the software at maintenance (e.g. software update or upgrade) shall be carefully considered. In particular, with software updates, attention shall be paid to the interaction between components from different generations of equipment and from different manufacturers.

For various reasons, e. g. to correct errors or to expand the functionality, the software can be changed by the manufacturer after the equipment has been delivered. For clarifications, it can be necessary at a later point in time to be able to explain the exact behaviour of the software. For this purpose, the traceability of the software versions is required.

Software is not maintained for an unlimited period. This does not mean that the equipment cannot be used any more. As long as the operation is possible without limitations and as long as the security of the system can be guaranteed, the use is possible. If a vulnerability of the equipment becomes generally known (e.g. a wireless link can be attacked) it shall be considered to replace the equipment.
A possibility is, that after reaching the End of Life the user may get the source code of the application or the structure of the database. It is also possible, that the manufacturer supports the user in a migration to another system. But this procedure is to be defined in the terms and conditions of the ordering contract.

Last but not least, the decommissioning of the equipment is to be considered with software aspects. If data and metadata is saved in a database, the question is: can the information can be accessed without the original equipment? If no further supplier specific data handling (e.g. integration of chromatograms) has to be made, the chance is good to be able to decouple the data from the equipment and its software.

Example: The access to a LIMS based on the database RDBMS running on a DEC Alpha system under the operation system VAX/VMS has to be granted after the decommissioning of the hardware. As a solution the database with a known data structure is transferred to a SQL database running on a current operating system. For retrieving of results and reports programs are written which

access the database in read-only mode. This makes it impossible for the user to modify data. The data migration and the written programs shall be validated.

4.2.1 Software Categories

Software exists in very different forms with many different fields of activity. It is obvious that firmware in a pH meter that controls calibration shall be treated differently than a LIMS with interfaces to instruments and an ERP system. It does not make sense for the user to validate the interpreter of a programming language, e.g. Python, or a spreadsheet software. It is sufficient to qualify them after installation. But the programmes created with it shall be validated. Spreadsheets with simple calculations, without conditional branches and loops, can be treated differently than spreadsheets with complex programmes. In order to coherently define the appropriate level of qualification or validation and the responsibility for it, a classification of the software is appropriate.

The proposed classification is strongly based on GAMP 4 [41] and 5 [42]. In particular, GAMP class 2, which was cancelled in GAMP 5, will be retained for the qualification of analytical equipment and systems. This allows better categorisation of the required work. The proposed classification (Tab. 1) was taken from the literature [43].

Category	**Scope**
Category 1 Infrastructure Software	Commercially available software-based • Operating systems • Databases • Programming languages (interpreter and compiler) • Office software (e.g. text systems, spreadsheet packages)
Category 2 Firmware	Software linked to a specific version of a piece of equipment, supplied by the equipment manufacturer. Software modified by the user or a third party company belongs to category 5. When changing the firmware (e.g. when servicing the instrument), the user shall be oriented. Unexpected problems can occur, especially in measuring system with components from different manufacturers.
Category 3 Non-configured products	Configuration does not change the automation of the business process or the collection and analysis of the data and records generated by the software • software capable of operating and automating the business process without any modification • only run time configuration (e.g. definition of users and user types for authorized individuals, entry of the department or company name into report headers, selection of units to present or report data, default data storage location (either a local or network directory), and the default printer)
Category 4 Configured products	Ability to modify the function of the software to match a business process • Configuration of hardware and software interfaces • Tools provided by the vendor of the product, hence configuration rather than using a programming language to write custom code that is attached to the product

Category	Scope
Category 5 Custom applications	These applications are developed to satisfy specific user requirements. • Commercial programmes modified by the user or a third party • All software written by the user or by a third party, but not the compilers or interpreters used. • Macros written by the user or a third party, on equipment (e.g. macros) or in spreadsheets, etc.

Tab. 1 Software categories

4.3 Traceability

The expression traceability is used in different meanings. It can be the metrological traceability of all parameters and of the measurement result to the corresponding SI-Unit, the traceability of the whole analytical workflow or the traceability of an equipment's life cycle.

4.3.1 Metrological traceability

The metrological traceability is a property of a measurement result whereby the result can be related to a reference through a documented unbroken chain of calibrations, each contributing to the measurement uncertainty.

To avoid confusion, the full term "metrological traceability" is recommended when referring to the property of a result.

4.3.2 Procedural traceability

In the regulated environment the procedural traceability is of very high importance. The question "Who did what, when, and with what means?" is to be answered for any activity. How that is achieved is in the hands of the laboratory. Each support provided by the equipment, e.g. audit trail or log book, is helpful. All manual inputs shall be linked to a unique user identifier and a time stamp. In the case of data transfer between instruments, a unique instrument identifier is to be transferred with the data and saved with the data.

The ISO standards request in cases of nonconformity the execution of defined activities. These activities also cover the investigation of whether other results are affected. If this is the case , the recipient of the results has to be informed. In such an investigation it is necessary to know which instrument was used in which analysis.

4.3.3 Traceability in the life cycle of analytical equipment and systems

For simple equipment without interfaces to other equipment and the development of specific software, the number of generated documents and their linkage is manageable. The documents that are added over time can also be safely classified. The assignment of the requirements from the user requirement specifications in the subsequent documents can be done intuitively.

The more complex a measuring system or piece of equipment becomes, the more confusing the assignment of functions in the various documents becomes. Especially when a system is to be changed or expanded, it is highly recommended to keep a **Traceability Matrix** (TM).

Each individual requirement is given an identifier, which is also mentioned in all subsequent documents. If the requirement demands a modified or newly written program, it is advisable to mention the identifier in the source code as well.

The overview and maintainability of the system is greatly facilitated by the use of a traceability matrix.

Software developers often use libraries they have created themselves for repeatedly used functions. If a function of a library is modified, the re-validation of the software parts in which this function is used should at least be considered. The developer forwards the information about the modification and the affected parts of the software to the testers. The TM can provide support.

Tracking when which changes were made to a system is made possible by a corresponding change management system. It is a good idea to reference the changed or new requirements in the change

management system by the corresponding identifier.

4.4 Documents and documentation required by the laboratory

All equipment qualification activities are controlled by work instructions and protocols. They are documented in reports. The work instructions are based on superordinate external documents, e.g. standards, regulations and generally recognized guidelines. The hierarchical structure shall be specified in the quality assurance system applied in the laboratory.

For qualifications and validations, explicit or implicit **V**alidation (qualification) **M**aster **P**lans (VMP) are specified in the standards and regulations. The VMP describes the basic requirements for equipment qualification and their implementation in the laboratory. If multiple pieces of equipment of a similar type need to be qualified, it is worth creating specific **V**alidation **P**lans (VP). With increasing experience of the laboratory and changing requirements, the VP will continue to develop. A specific VP is created for each piece of equipment. It describes the process of initial qualification and the work that follows from it in detail. The experiences from the implementation of the qualification flow into the VMP and the VPs. This approach represents a circle of continuous improvement.

Depending on the organisation of a laboratory, further documents can be required. Larger purchases in particular are often handled as projects with the corresponding organisation and documents.

All documents are to be managed in accordance with the specified quality assurance system, including traceability (versioning), the release procedure and the archiving of the documents.

It is not specified whether the documentation is based on paper or on electronic media. Both have their advantages and disadvantages. In any case, the data integrity shall be guaranteed.

In the case of electronic systems, this includes their validation and the use of recognized electronic signatures. The local legislation shall be taken into account.

Documents that are output by the equipment in non-electronic form (e.g. printouts) and manually completed logs can be archived as electronic copies (see below).

The work flows are to be defined in work instructions.

4.4.1 Electronic copies

The general principle is, that the original records should be archived. The original record is the first or source capture of data or information e.g. original paper record of a manual observation, printout from equipment or electronic raw data file from a computerised system, and all subsequent data which is required to fully reconstruct the conduct of the laboratory activities. The storage of data on different platforms is not without difficulty. Likewise, searching for information on non-electronic data carriers is time-consuming. All non-electronic data are unique and their loss is of the greatest consequence. Stored data, especially for organisations with multiple locations, should be readily accessible.

The discussion about electronic copies complements discussions about the use of micro-films for archiving [44].

Since the introduction of validated electronic document management systems which support qualified electronic signatures, this is a possible solution for storing any kind of data.

Several guidelines and position papers deal with the handling of electronic copies (true copies or certified copies) in detail [45] [46] [47].

It depends on the characteristics of an organisation whether filing the original documents or electronic filing is to be preferred. The chosen approach shall be described in a standard operating procedure. If information technology is used, it shall be validated.

4.4.2 Retention period

The retention period of the documents depends on the field of activity of the laboratory and therefore on the applied standards and regulations. Note the regional or country-specific requirements.

If the analysed product has an expiry date, the considerations for the retention period are based on

the expiry date. In the case of contract laboratories, the contract with the client shall be taken into account.

The retention periods for the different types of documents should be defined in the VMP.

When defining retention periods the requirements of the relevant regulations or standards, as well as the requirements for business processes, shall be considered.

4.5 Scope of qualification

There are many different types of laboratory equipment ranging from a burette to complex fully automated equipment, e.g. GC-MS or LIMS. The qualification effort is very different. It would be very complicated to treat each piece of equipment differently and set its own qualification requirements. It is also not appropriate to treat all equipment in the same way. Here it makes sense to determine the depth of qualification in a comprehensible way by means of a risk assessment.

A possible example for a risk-based consideration is provided by the USP [13] and the comprehensive guide to analytical instrument and system qualification [35], which divides the instruments into three groups A, B and C:

- **Group A (auxiliary equipment)**
  Group A includes instruments with common prerequisites for calibration or instruments without a measuring function. The manufacturer's specification corresponds to the requirements profile of the user.
- **Group B (simply constructed standard equipment)**
  Group B includes standard equipment and instruments that provide simple measured values as well as equipment for the provision of physical parameters (such as temperature, pressure or flow). Group B equipment requires calibration. The requirements of the users are usually the same as those of the manufacturer's specification. The depth of qualification can be decisively reduced to what is necessary if the critical aspects are determined on the basis of a risk assessment. For example, there is a relatively simple qualification with IQ and OQ, based on a corresponding SOP. In most cases, the main part of the qualification will be a calibration or verification of the measurement parameters.
- **Group C (complex and computer-controlled analysers)**
  Group C includes complex instruments and computer-controlled analytical tools systems where the users have requirements for functionality, operational and performance limits are specific to the analytical application or the equipment for individual questions have to be acquired.
  A full qualification is carried out. The user requirements for the instrument are met by specific functional tests and performance tests. The installation and qualification of these instruments can be a complicated undertaking and require the help of specialists.

The classification of equipment shall be made in connection with the intended use. For example, a stirrer that by default would be put in group A should belong to group B or C if it is part of a dissolution system and stirring geometry, axial fluctuation and exact speed of rotation are important. From this example it is obvious that one should make transparent specifications in one's SOP for the allocation of equipment into the three groups. It would be helpful to have a scheme that leads to the classification into the groups. In any case, the classification should be plausible and comprehensible. It should be documented.

If the type of application (e.g. routine/non-routine analysis or extent of computerisation/automation) or the environment of use of the instrument changes, the categorisation should be reviewed.

4.6 Risk assessment

In recent years the risk-based approach to all processes became increasingly incorporated in standards and in regulations. This forces the applicants of the rules to take more responsibility. It allows the user to target the always limited resources at the critical points.
No risk assessment is carried out for simple equipment (group A). As the complexity of the system increases, the importance of a risk assessment increases. In practice, risk assessments are essential for group B and C equipment.

Risk-based thinking enables a laboratory to determine the factors that could cause its processes and its quality management system to deviate from the planned results, to put in place preventive controls to minimize negative effects and to make maximum use of opportunities as they arise. The introduction of a risk-based thinking is enabling some reduction in prescriptive requirements and their replacement by performance-based requirements.
There are different techniques available for performing a risk assessment. An overview of proven and tested techniques is given for example in [48].

If a risk assessment system is already in use in or around the laboratory, it is recommended to use it and adapt it if necessary.

To give an example of a risk assessment methode and its impact, one possible approach, **F**ailure **M**ode **E**ffects **A**nalysis (FMEA), is outlined. Other simpler methods may also be used.
This outline is only an overview of a risk assessment. The exact procedure and especially the criteria for the assessment should be defined in a SOP.
The risk assessment takes into account three aspects:

1. **Severity**; impact on product quality and/or safety of humans, animals or the environment.
2. **Probability**; likelihood of the defect occurring.
3. **Detectability**; probability that the defect will be noticed before damage occurs

Severity
A risk can be of a direct economic nature or can concern the quality system. A possible classification for the analysis of an incident is:

A) **Business relevant**; the problem leads to extra work and thus to higher financial and human resource requirements, e.g. search for causes, follow-up analyses. There can be limited reputational damage.
B) **Business critical**; the problem leads to substantial additional work and thus to considerably higher financial and personnel resource requirements that cannot be managed with the existing resources. It leads to major reputational damage and loss of trust with customers and can result in the loss of orders. Legal consequences can arise.
C) **Quality relevant**; a violation of the standards or regulations applicable to the laboratory, but which does not pose an immediate risk to the safety of humans, animals or the environment. Legal consequences can arise.
D) **Quality critical**; the problem poses an immediate danger to humans, animals or the environment. Legal consequences arise. There is a high probability that it can lead to exclusion from business areas.

The severity levels ‘business critical’ and ‘quality relevant’ are often treated as equal important in the risk analysis. This leads to a reduction to three levels of severity.

Probability
The likelihood of the occurrence of a fault is estimated. Here, the experience of a process plays an important role. When an error occurs, it shall be checked whether the probability of occurrence shall be corrected in the risk assessment. If a correction is necessary, the previous risk assessment shall be reviewed accordingly.

Detectability
The detectability indicates the probability that the error will be noticed before damage occurs. As long as a falsified reportable result has not left the laboratory or has not been used for conclusions, the harm is not very big. Nevertheless, resources are needed to address the problem.
If the error is only discovered after conclusions have been taken from the result, larger circles are affected and shall therefore be informed. This can lead, for example, to a product recall or the retraction of a published conclusion. If more time elapses between the occurrence of the problem and its discovery, it can be necessary to further investigate downstream products for causing greater harm to humans, animals or the environment. All results generated since the occurrence of the deviation shall be investigated for their validity. The reproducible adherence of the equipment parameters and their control play an important role.

In the first step of the risk assessment (Fig. 4) the possible event is assigned to a **risk class**. The assignment is based on the **severity** and the **probability**.

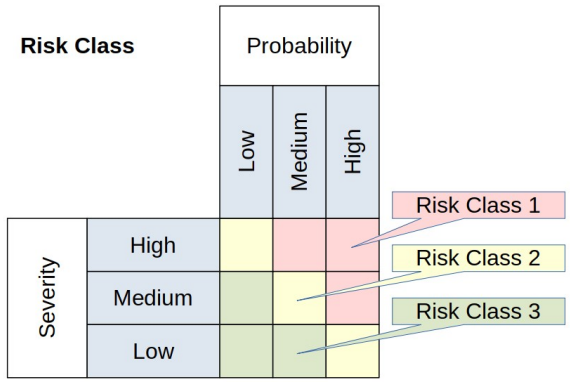

Fig. 4 Risk class

For the assessment of the urgency to reduce the risk (**risk priority**), the probability of timely **detectability** of the occurrence of the event is taken into account as a third factor (Fig. 5).

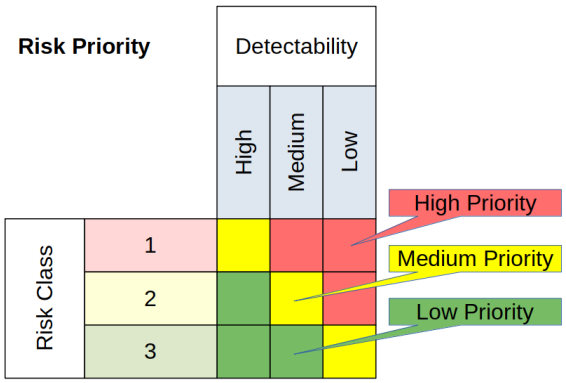

Fig. 5 Risk priority

Incidents classified as "high risk priority" should be prioritised. Precautions should be taken to lower the risk priority. The most potential lies in the probability and the detectability of the incident.

Successful application of this risk assessment depends on the ability to assign realistic meanings of Low, Medium and High to each segment of the assessment. It depends on the business environment and on the applied quality system.

On the equipment side, the scope of qualification and the frequency of re-qualification should be reconsidered. In the overall process of analysis, the possibilities of System Suitability Tests and control samples in terms of detectability of problems, for example, need to be considered.

All processes related to analytical equipment are candidates for risk assessments. The individual test points and the scope of their qualification is determined by a risk assessment. The length of intervals between services and re-qualifications should be based on risk assessments.

The risk assessments shall be archived. In cases of occurrences of incidents, the risk analysis is to be reviewed and possible new findings should lead to a modification, in the sense of continuous improvement, of the risk assessment.

5 Life cycle of laboratory equipment

The life cycle of a piece of equipment (Fig. 6) starts with the necessity of purchasing the equipment for use in an analytical laboratory. The user describes the detailed requirements for the equipment to be procured in the user requirement specifications. The procurement process and the commissioning process are then started.

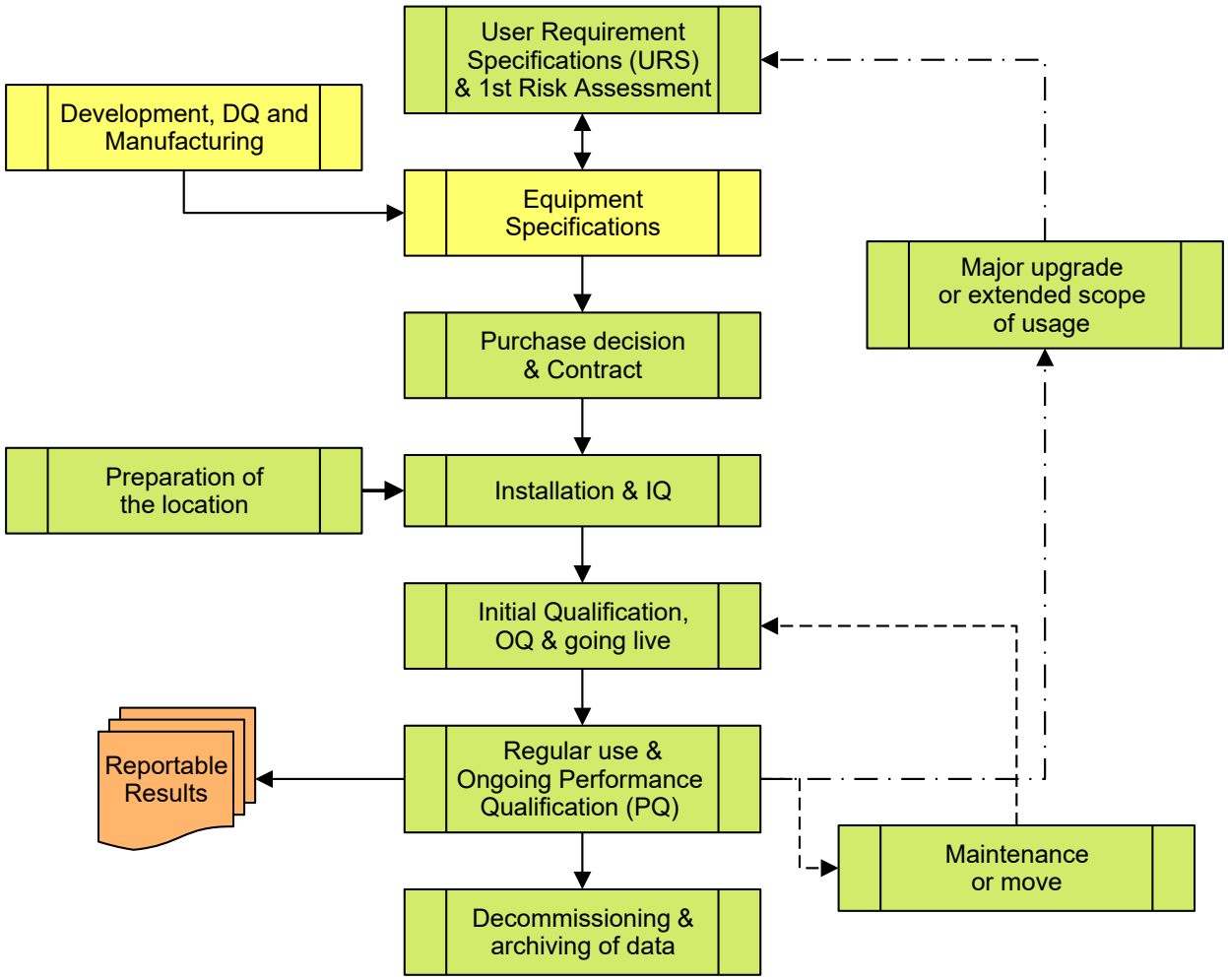

Fig.6 Life cycle of laboratory equipment

It shall be checked at regular intervals whether the equipment is still fit for the intended use. At the end of its life, the equipment shall be disposed of properly and the data and meta data produced shall be archived in a readable format.

It is more important that all required activities are performed in a logical order and scientifically sound manner than the exact allocation within the original DQ/IQ/OQ/PQ framework. The activities may also be performed as an integrated framework [13].

5.1 Design Qualification (DQ) and User Requirement Specifications (URS)

In the first phase of the life cycle of an item of equipment, the manufacturer and the user are in close cooperation. The original DQ process as defined in the 1990s has been refined. The responsibilities between the equipment manufacturer and the buyer have been defined in more detail. The role of the two parties depends on the characteristics of the equipment:

1. Commercial off-the-shelf equipment

2. Customised equipment

   a) Commercial off-the-shelf equipment which is modified by the user to make it suitable for his purposes

   up to

   b) Equipment designed and developed by the user

The most common case is the procurement of off-the-shelf equipment. The second case occurs, for example, when an equipment component does not directly match the other components of a measuring system.

User Requirement Specifications

The key document in the life cycle of a piece of equipment from the perspective of the laboratory is the User Requirement Specification (URS). All properties that are defined in the URS define the further steps up to and including decommissioning of the equipment. The more carefully and far sightedly the URS is written, the fewer the number of unexpected questions that is likely to arise in the course of the equipment's life.

There are two reasons to write detailed URS [49]:

1. Economic efficiency; not buying the right equipment means poor utilisation of financial resources. It can also lead to unexpected follow-on investments or inefficient operation. It does not reflect well on the skills of the people in charge. Writing meaningful and complete URS means protecting investments.

2. Compliance with legal requirements or quality standards: The laboratory shall do this in order to meet requirements from the quality assurance system specified for the activities or quality obligations towards clients.

The two requirements are not in competition with each other. If writing a URS is approached with a business-oriented mindset, but with a compliance or quality gist, both aims will be reached. If the URS are written down and released with adequate document control, then this fulfils both reasons for writing specifications.

Writing the URS supports the following processes:

- It serves as a reference against which commercial products are selected, evaluated in detail and possible extensions are defined. With this approach, you avoid being seduced by the technology or the vendor to buy an inadequate system.
- It identifies gaps between the requirements of the laboratory and the equipment offered by suppliers. This makes it possible to aim for an enhancement of the selected system or to review the requirements and, if necessary, adapt them to the systems on the market.
- It reduces overall system effort and cost, as a careful review of the URS should reveal omissions, misunderstandings or inconsistencies in the specification, and this means they can be easily corrected before an instrument is purchased.
- It provides the input for the DQ, IQ, OQ and PQ test specifications for the qualification of the equipment.
- It defines which documents and procedures shall be written, changed or archived for both the users and those responsible for the system. To make it easier to find and assign the various requirements in the life cycle documents, a traceability matrix can be beneficial for complex equipment.

The writing of the URS is the process before the DQ and the selection of the supplier and the instrument.

All standards and regulations relevant to analytical laboratories require that the equipment is fit for the intended use within the laboratory (see chapter 4.1). The important point is that a laboratory does not have to follow the supplier’s specification and proposed usage.
The crucial question is: what does the laboratory require from the instrument?
What is the type of application?

- analytical research,

- development of analytical methods for single laboratory use up to official methods
- non-routine analysis, screening, non-targeted analysis
- highly specific analysis, e.g. characterising of reference materials
- routine analysis in industry, pharmaceutical production or clinical laboratory

The specification of the hardware (instrument) contains the external specifications, e.g. maximum dimensions and weight, specifications of the connections for media and data connections and environmental compatibility.

The most obvious specifications are the physical parameters of the equipment. In the case of an isocratic HPLC equipment, these are for example the flow rate, the maximum achievable pressure, the injection volume, the temperature range and the reproducibility of the column temperature control, the wavelength range and the dynamic range of the UV detector, etc. These requirements should reflect the needs of the future user of the instrument. They are not identical to the instrument specifications of the manufacturer. Usually they are a sub-range of the manufacturer's specification. If the scope of application of the equipment is changed, the URS shall be revised and it shall be checked whether the changed requirements can still be met.
Example: The manufacturer specifies for a HPLC pump a flow rate from 0.00 to 10.00 ml/min. In a specific laboratory the flow rate of the analytical methods is from 0.30 to 3.50 ml/min. To allow a reasonable development and validation of new methods, the limits may be set as 0.20 to 4.00 ml/min. These limits are used in the evaluation of the new pump. They are used in the first OQ and in re-qualification as specifications to be tested. If it happens in the future, that the upper limit has to be moved to 5.00 ml/min the URS is to be modified and an OQ protocol for the new scope of application is developed and executed.

In GMP, the general chapters on the analysis methods of the pharmacopoeias, e.g. EP, USP and JP, also contain specifications for the instruments.
If analyses are to be performed according to a pharmacopoeia, the requirements defined in the pharmacopoeia are binding.

A series of 27 reports, between 1984 and 2018, on the evaluation of analytical instrumentation have been published by the Instrumental Criteria Sub Committee of the Analytical Methods Committee (AMC) of the Royal Chemical Society [50]. The publications provide recommendations on the stages that are required for the successful evaluation, purchase (DQ) and installation (IQ) of analytical equipment. These recommendations can be taken into account in the URS. The aspects of later equipment life cycle and in particular the aspects of information technology are not dealt with.

The information and the technical specifications provided by the manufacturer are a source to be considered. The comparison between the given data and the requirements of the laboratory may not be easy, since most manufacturers follow their own pattern of specifications. If the equipment is advertised and sold to regulated laboratories, the specifications from pharmacopoeias may apply, but this has to be confirmed by the supplier.

The requirements shall be carefully and clearly defined. They are the basis for the selection of the instrument and the supplier as well as the IQ and OQ. It is essential that the specified values are also verifiable. When writing the URS it has to be considered how the verification should take place. Extrapolations from the verified range to the range required in the URS are not permissible.

The more complex equipment becomes, the more extensive the URS gets. Especially with complex systems, e.g. LIMS or chromatography data systems, it should be considered whether the URS should be supplemented and extended by a **functional specification** (FS).
The URS becomes a document that describes the functions more generally at a higher level. The FS are detailed descriptions of what exactly the user expects from a particular function.
Example of FS: For a report from the LIMS, it is defined which input shall be made for the query and how they may depend on each other. This results in the criteria with which the database is searched. Finally, it is defined which data is found, how it is formatted and in what form it is output.

With complex equipment, the software plays a major role. The functions for equipment control,

data acquisition, processing, calculation of results, reporting and data interfaces to other systems shall be specified. The applications are configurable and the configuration shall be documented either as part of the instrument binding specification or as a method-specific configuration. Modern systems can be largely automated. This can include result-dependent decisions. Higher-level requirements, e.g. system policies, user roles, use of electronic signatures shall also be defined.

In addition to the immediate characteristics of the instrument, the environment plays an essential role, both commercially and from a quality assurance point of view. This is crucial when choosing the manufacturer, supplier and, if necessary, an external service provider for service and maintenance. Corresponding requirements have also to be recorded in the URS.

An often forgotten question is what happens to the data (e.g. measurement data, metadata) when the equipment is decommissioned. Shall the data remain readable and even evaluable? What options are available?

Design Qualification (DQ)

DQ in the instrument life cycle is the activity that confirms that the instrument(s) which are proposed for purchasing and the suppliers meet the requirements in the URS.

The design of the instrument was carried out by the manufacturer. He defines the specifications for the equipment before development begins. He guarantees compliance with them in the delivered equipment. The manufacturer will work according to a specified quality assurance system, e.g. ISO 9001, in the development and in the manufacture of the instrument.

The customer compares the specifications given by the supplier with his requirements laid down in the URS.

If the requirements are not met by any commercially available instrument, a custom instrument may be considered. On the other hand, the requirements in the URS may need to be revised. However, it shall be very carefully weighed up whether the intended use is still achievable.

5.1.1 Commercial off-the-shelf equipment

This is the standard case. Most laboratories will buy equipment without any mechanical or electrical modification. A piece of equipment or system can be composed of a basic configuration and different options. Likewise, a measuring system can be made up of different components. As long as all components come from the same manufacturer and from the same generation of equipment, no particular problems are to be expected when the individual parts interact. If the components come from different manufacturers or from different product lines, caution is advised. Especially if not only simple electrical signals (e.g. start/stop) but data is exchanged via electronic interfaces (e.g. RS-232, USB, Ethernet, WLAN or Bluetooth), care shall be taken. In the case of further development of the software (including firmware), it is not guaranteed that third-party equipment can still be addressed without problems.

5.1.1.1 Manufacturer

The ISO 9001 standard is a suitable document to control equipment development. Clause 8.3 of the standard [51] deals with the design and development of products and services (see appendix A). It requests that the organization shall establish, implement and maintain a design and development process that is appropriate to ensure the subsequent provision of products and services.
The detailed sub-clauses are:

- Design and development planning
- Design and development inputs
- Design and development controls
- Design and development outputs
- Design and development changes

The manufacturer defines the specifications for equipment based on the requirements of the market (e.g. feedback from customers, legal and normative requirements, competing products, commercial prospects and research results) as well as new technical developments.

The manufacturer checks compliance with the manufacturing and product specifications in the course of production and before delivery. In the case

of very complex equipment, which often involve strong customisation, it is not unusual for the manufacturer to assemble and fully test the equipment at his premises in a fully functional state. The customer is informed of the results. The equipment is then disassembled, packed and transported to the customer. This is called a Factory Acceptance Test (FAT).

Selection and Qualification of Manufacturer

An analyst being experienced in a specific analytical method should be familiar with developments in this area and with the potential manufacturers and suppliers. If the experience is lacking, the information can be obtained from literature, published methods, trade magazines, attending international and national meetings and exhibitions, internet searches, by networking with analysts from other laboratories, professional societies and training courses.

If the manufacturer is ISO 9001 certified, a good way to judge is against the requirements of the ISO standard. In a first step, a questionnaire can be sent to the manufacturer in which they can show their organization and processes. To be able to compare the manufacturers and to analyse the enhancement of the manufacturer with time it is advisable to use a standardised questionnaire and to archive the results. In the case of strategically important purchases, an on-site audit is recommended, also taking into account the answers to the questionnaire.

An important question is how long after the purchase (not after the end of production) the equipment will be supported. This concerns, e.g. the spare parts and also the support by the service organisation. It is important that the manufacturer or seller informs the buyer in good time about the end of manufacture and especially about the end of service.

In particular, the duration of support for software is essential. How long are further developments and especially bug fixes offered? Has the supplier defined a software life cycle with time specifications? In the case of changes to software from a third-party source (e.g. operating system, database, device drivers, etc.), how long is the application software maintained?

Even if the manufacturer is not certified, the requirements of ISO 9001 are a good starting point for assessing the supplier.

A high weighting is also given to requirements that are more difficult to qualify vis-à-vis the manufacturer and supplier. If equipment has already been procured from the same manufacturer in the past, there is valuable experience in dealing with each other. In particular, trustworthiness can be better assessed. Keeping promises made in earlier procurements will have a great influence on further cooperation. On the other hand, comments on manufacturers, e.g. on the internet by unknown persons, should be treated with caution.

With regard to the total cost and speed of introduction of a new instrument, the effort required in the laboratory shall be taken into account. The similarity of operation, layout and design (including software) with instruments already in the laboratory plays an essential role.

A general impression of the manufacturer is provided by the company's innovative spirit. If novel beneficial innovations are regularly included in the product updates, and the existing products are further developed, this is a sign of the manufacturer's capabilities and that it pays attention to the future wishes of the customers.

It is a sign of fairness and creates trust for possible future purchasing processes if the equipment manufacturer is informed about the evaluation process. In any case, the manufacturer should be informed of the result and the reasons for it. Of course, possible confidentiality agreements with competitors shall be taken into account.

5.1.1.2 Buyer, user

In an order, business factors, e.g. payment modalities, delivery dates and possible contractual penalties, shall always be regulated in addition to the technical requirements and the procedures for deliveries.

In larger companies and institutions in particular, general rules are laid down for the purchase of

equipment and services. These rules are binding in the form of general terms and conditions in contracts. The supplier shall be informed about these conditions. Conversely, most suppliers also have defined general terms and conditions. They shall be carefully checked before signing the order contract.

If the general terms and conditions of the supplier and the purchaser contain incompatible statements, an agreement shall be reached in writing at the latest when the contract is signed.

In case of uncertainty, it is recommended to consult the purchasing department or the legal department.

5.1.1.2.1 User Requirement Specification (URS)

In the URS the buyer defines the requirements for the equipment, the associated procurement and maintenance processes in detail. This covers the specifications but also the aspect of cooperation between supplier and buyer. The requirements defined in the URS shall be measurable. They are the requirements that are checked in IQ and OQ.

It is advisable to clearly mark the individual chapters and subsections with an abbreviation (label). It facilitates traceability through all documents. The structure of the abbreviations should be defined in writing. These abbreviations are used for cross-references in further documents, e.g. risk assessments, documentation of IQ, OQ and PQ.

5.1.1.2.2 Initial risk assessment

An initial risk assessment needs to be performed to determine the correct approach to qualifying an item of laboratory equipment.

The classification of instruments into groups proposed by the USP is an example of risk-based thinking by classification (see Chapter 5.4 Scope of qualification).

As a result of the risk assessment, the inspection points and the scope of their inspection in IQ and OQ are defined.

5.1.1.3 Quality assurance / Quality unit

The role of the quality unit in equipment qualification remains the same as for any other standardised or regulated activity. Quality personnel are responsible for ensuring that the EQ process meets the defined requirements, that processes are being followed, and that the intended use of the equipment is supported by complete, valid, and documented data.

5.1.2 Commercial equipment modified by the user after arrival and In-House designed and constructed equipment

The tasks and the responsibility for their implementation are partly transferred from the external manufacturer to the final user of the equipment. This also applies to the processes after procurement.

5.1.2.1 Manufacturer

In the DQ process the role of the manufacturer remains the same as for the off-the-shelf equipment.

If the equipment is modified by the user, the warranty may become void.

The documentation loses its validity for the changed parts.
Services can no longer be provided by the manufacturer of the original equipment.

The delivery of original spare parts should be contractually defined.

For in-house constructed equipment the same rules apply to purchased components as to purchased equipment. Also for mass products, trustworthy suppliers shall be selected. For critical components (e.g. monochromator, electronic circuits) it is strongly desirable that the manufacturer works according to ISO 9001. The same selection procedure is applicable as for off-the-shelf equipment.

5.1.2.2 Buyer, user

The equipment or equipment components purchased from an external manufacturer are handled as any other purchased unit. At goods receipt the delivered material is compared with the order and if possible with the specifications. It is not always possible to check all specifications of a unit since the control needed for testing may not be possible without the integration in the finished equipment.

The part of the planning and of the implementation steps of the final equipment is the responsibility of the future user.

The User Requirement Specification contains also the modifications of the purchased instrument.

In the case of in-house designed equipment the user is at the same time the developer and also the manufacturer of the equipment.
Even if the user is not ISO 9001 certified, it is a good decision to follow the principles of the standard, especially clause 6.3.

5.1.2.3 Quality Assurance / Quality Unit

The role of the quality unit in equipment qualification remains the same as for any other standardised or regulated activity. Quality personnel are responsible for ensuring that the EQ process meets the defined requirements, that processes are being followed, and that the intended use of the equipment is supported by complete, valid, and documented data.

5.2 Prearrangements before delivery and Installation Qualification (IQ)

It is not easy to define the boundary between Installation Qualification and Operational Qualification in a general and abstract way. The delimitation can shift depending on the equipment type and supplier.

In this document Installation Qualification (IQ) covers all activities after the contract for the order has been sent, up to and including the equipment's response to the initial application of power in the selected environment. IQ establishes that the 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 and use of the instrument.

For very complex instruments, which often involve heavy customisation, it is not unusual for the manufacturer to set up the instrument at the customer's premises in a fully functional state, test it completely and hand it over ready for operation. This is called S**ite Acceptance Test** (SAT). In this case IQ and OQ are integrated in the same process. When a SAT is carried out, its functionality was usually tested in a **Factory Acceptance Test** (FAT) at the manufacturer's premises before the unit was delivered.

IQ is the first documented activity starting at the arrival of the equipment at the future user. The division of labour between supplier and user is defined in the tender and the contract for the order. It is to be defined who unpacks the delivery and controls it for completeness. IQ does not have to be executed by the user, it can be delegated to the supplier. But the user is always responsible for the appropriate implementation of IQ according to the requirements of the applied quality system. If the IQ is executed by the supplier, the user shall check the written procedure on compliance with his rules. The acceptance is documented.

The consignement of goods received is checked for visual damage. If damage is observed the freight forwarder and the supplier are informed. Depending on the previously agreed procedure, the service is to be contacted.

IQ applies to an instrument that is new or was pre-owned. For any equipment that is on site but has not been previously qualified, or has not been qualified to current industry standards applied in the laboratory, existing documents should be collated and a risk assessment should be undertaken to determine the best course of action. These activities and their consequences should be documented and archived instead of the standard IQ.

An IQ is also carried out if the instrument is purchased second-hand.

Relevant parts of IQ would also apply to a qualified instrument that has been transported to another location or is being reinstalled for other reasons, such as prolonged storage.

The IQ is carried out against tender, order and URS.

5.2.1 Prearrangements before delivery

Before the instrument is delivered and installed, the installation location has to be prepared. Many manufacturers supply the customer with an information document which defines the environment required for the equipment. The preparations have to be completed before the arrival of the equipment.

The manufacturer wants to show his product in the best light. Therefore the measurements by the manufacturer are carried out under well controlled conditions. If the conditions are less well controlled at the selected environment in the laboratory the equipment may not give the best possible performance. This applies for example to balances.

How well a supplier supports these prearrangements before the delivery of the equipment is also a criterion for supplier selection.

Characteristic items to be considered are:

- **Health and safety**; the information provided by the manufacturer relating health and safety is considered and followed. The general safety considerations of a laboratory are to be followed
  - The handling of toxic and unstable waste solvents, liquids and solutions (e.g. eluents in LC)
  - toxic and explosive waste exhaust gases (e.g. split vents at gas chromatography) should not be discharged into the laboratory atmosphere.
  - explosive gases and compressed gases like hydrogen, acetylene and oxygen shall be treated with care.
- **Environment**; the installation site shall satisfactorily meet the requirements specified by the supplier of the equipment.
  - For most instruments, the temperature and the air humidity are specified as a range. In particular, the humidity and its stability shall be kept in mind. Especially at low outside temperatures and low humidity, the relative humidity in the lab gets very low very quickly. Without artificial humidification, the relative humidity drops below the permitted limit. This can lead to problems with electrostatic charges, for example. These occur very frequently, especially in weighing processes.
  - Waste heat from furnaces, especially if they are cooled cyclically (e.g. gas chromatographic ovens), should not be discharged into the laboratory atmosphere. Otherwise it is very difficult to control the overall temperature in the laboratory. There will be temperature gradients in the laboratory. Due to the sluggishness and hysteresis of the room air conditioning, temperature fluctuations cannot be avoided.
  - Vibrations and shocks
    Fine mechanical and optical instruments in particular shall be protected from vibrations and impacts. These can cause misalignment and loosening of mechanical and electrical connections. For sensitive instruments, special bases with absorbent properties shall be used. Special attention should be paid to periodic vibrations. These can be caused by traffic in the vicinity of the installation site or intermittent resonance vibrations. The disturbances can vary within a building depending on the floor and the location in the room.
    In the case of mobile equipment, e.g. in vehicles, particular attention shall be paid to mechanical disturbances.
  - Room for installation, operation and servicing; The room for routine operation of the instrument shall be large enough. Heat radiation and obstruction of the circulation of cooling air shall be prevented. Accessibility to the instrument for service, maintenance and re-qualification shall be ensured easily and safely. A service corridor at the rear of the instrument should be considered.

- **Services and utilities**
  - Electricity, Water, Gases
    Basic instruments may be operated from a standard electrical socket. More complex instruments may need special power supplies (e.g. three phase or higher current than usual). If the stability of the voltage meets the usual standards, no problems arise.
    In order to protect the units from short over-voltage surges, appropriate filters shall be provided in the laboratory's power supply. Overvoltage surges can be caused, for example, by lightning strikes or switching operations in the high-voltage network. If several units that are connected to each other via electrically non-insulated signal lines are operated on different phases of the power supply, interfering current flows can occur. These are caused by different voltages of the phases involved.

For all systems with electronic data processing, from microprocessor-controlled equipment to computer-controlled complex systems, the possible consequences of a power failure shall be assessed with a risk assessment. A possible risk reduction is the introduction of an uninterruptible power supply (OPS).

Water is often used as a coolant. In addition to security of supply, attention shall be paid to quality. There shall be no blockages due to solids in the inlet or microorganisms growing in the system.

If the water is used in the analytical process, the quality and functioning of the treatment shall be ensured.

Gases are either delivered with pressure cylinders (e.g. acetylene, helium) or generated on site with gas generators (e.g. hydrogen, nitrogen, zero air).

In the case of gases, the quality, in particular the purity, shall be ensured in accordance with the specifications provided by the equipment manufacturer.

Common compressed air always contains oil. High purity compressed air cannot be achieved simply by purification.

High-quality gases shall not be contaminated by insufficient connection lines. Particular attention shall be paid to tight connections. Welded connections are best. Before use, the piping system shall be carefully cleaned with a flushing process.

Care shall be taken with plastic pipes and tubing. Various polymers, e.g. Poly-tetrafluoroethylene (PTFE, Teflon) are not gas diffusion tight. Oxygen diffuses very easily through PTFE.

In the case of non-continuous supply, it shall be ensured that no pressure drop occurs due to small line cross-sections during switching operations.

- Control computer

  Many instruments are controlled by computers. Ordinary personal computers are often the basis for the control computer. In most companies a standardised configuration for PCs is defined by the IT department. Due to safety and support reasons non standard PCs are not allowed to be linked to the company's IT network. On the other hand the instrument manufacturer defined for the development and the validation of the instrument software a specific hardware and software setup of the computer. These two requirements shall be brought into line. The procedure and the delimitation of responsibility shall be laid down in writing.

  More and more often, the instrument manufacturer wants to have access to the computer for remote maintenance or software upgrade from outside the customer's company. This is a security problem for the laboratory and the whole company. The exact procedure, the parameters set and the software used shall be agreed in writing between the supplier and the customer's IT department at an early stage. The access may already be used at the IQ of the equipment.

- IT network

  The components of a measuring system communicate among themselves via a suitable data network. This can be a cable-based or wireless network.

  The equipment often also communicates with higher-level systems, e.g. a LIMS or a central server.

  Especially in the case of cable-based data connections, the infrastructure (from the connection via the cabling to the network node) shall be available to a sufficient extent. With most networks, performance decreases above a certain transmission density. The data capacity shall be planned sufficiently high.

5.2.2 Installation Qualification

The IQ may be carried out either by the supplier and/or the user. The complexity of the instrument and the lack of knowledge of the user may preclude the user performing IQ. It is also possible that the unpacking of the equipment by the user may invalidate the warranty. The unpacking and the assembly of the equipment shall be undertaken by a competent individual and in accordance with the supplier's instructions and procedures. The responsibility and the details of the process are to be defined in the contract for the order. The IQ checks

performed should be formally recorded. Where these have been carried out by the supplier, the results of these tests shall be communicated to the user. They are carried out according to a procedure approved by the client.

- On arrival the instrument is checked and verified as undamaged. In case of damage, the carrier and the supplier shall be informed immediately. The delivery note and the packaging list are available and correspond with the order. The process is documented.
- Fixed parameters: These reviews measure the non-changing parameters of the unit such as dimensions, weight, voltage inputs, connection types, allowable pressures and loads. If the specifications provided by the manufacturer for these parameters satisfy the user, the review requirements can be waived. However, if the user wishes to confirm the parameters, the measurements can be carried out in the laboratory on delivery. Fixed parameters do not change during the life of the unit and therefore never need to be retested.
- IQ documentation packages purchased from a supplier should be reviewed to ensure that the protocol and the resulting report are acceptable to the user before and after execution.
- The instrument including all modules, software, cables, supplies, and any other instrument accessories arrive as specified by the user in the order.
  All required documentation (e.g. manuals, training material and service manuals) has been supplied and is of correct issue corresponding to the versions of installed hardware and software. All manuals should also include their issue number and date of issue.
- Software installation, network, and data storage: Some analytical systems require the installation of software on a qualified computer and need to be connected to a network for communications and data storage at the installation site. Information technology involvement is often required with computerized laboratory systems. The correct hardware, firmware and software has been supplied and is it of correct issue and uniquely identified by part number.
- Assembly and installation: Assemble and install the instrument, and perform any preliminary diagnostics and testing.
  Assembly and installation may be done by the supplier, service agents, specialized engineers, or qualified in-house personnel.
- Any abnormal event observed during assembly and installation merits documentation.
- The information on consumables required during the normal operation of the instrument system has been provided.
- The response of the instrument to the initial application of power is as expected or any deviations are recorded. If the equipment is designed to perform any automatic diagnostic or start-up procedures the response to these should also be observed and documented.
- In computerised systems, a user shall log in. When the system is started for the first time, no personal user account is defined. The account specified by the manufacturer (e.g. SYSTEM) is used. For further use, including further qualification, at least one personal user account shall be created immediately. This ensures the identification of the operator for the accumulated data and metadata.

5.2.3 Documentation

All activities and all decisions taken during IQ should be documented. They become part of the equipment qualification documentation.

Decisions and experiences can possibly have an influence on future IQ. The VMP and, if available, the type-specific validation plan should be adapted accordingly.

These equipment records shall include, but not be limited to, the following [21], [27]:

- unique identity of the equipment, including software (e.g. operating system, database, device driver and application software) and firmware version, the manufacturer's name, type identification, and serial number or other unique identification
- the current location

- condition when received (e.g. new, used or re-conditioned)
- date of receipt and date of completing IQ
- contact information for the supplier or the manufacturer
- records (e.g. reports, completed check lists and printouts of self tests) that confirmed that the equipment passed successfully the IQ

5.3 Operational Qualification (OQ)

OQ is the documented collection of activities necessary to demonstrate that a piece of equipment will function according to its operational specification testing in the selected environment. OQ demonstrates fitness for the selected use, and should reflect the requirements defined in URS.

In OQ, it is checked whether the equipment meets the user requirements. The user requirements do not have to match the manufacturer's specifications. If the user requirements are stricter than the manufacturer's specifications, no recourse can be taken.

- If a site acceptance test (SAT) is run by the supplier, it concludes the IQ and is documented there.
- Fixed parameters have been, if applicable, verified in IQ.
- For OQ test packages purchased from a service provider or supplier, the user shall review the material to assure themselves of the scientific soundness of the tests and compliance with applicable regulations. The user should review the documents before execution and approve the tests after execution to ensure completeness and accuracy of the completed document and the test data generated.
- The scope of qualification may be defined by categorising the equipment. Therefore OQ testing of the equipment depends on its intended applications. No specific OQ tests for any instrument or application can be offered.
- The specifications for the tests are defined in the URS. If specifications from the manufacturer are adopted, it is advisable to either have them checked by the manufacturer or to adopt the methods from the manufacturer. If the methods are adopted by the manufacturer, communication with the manufacturer in case of problems is more efficient.
  The manufacturer's service documentation is a good source of information for testing to verify the manufacturer's specifications and for diagnoses of the unit.
- It is rarely possible to perform an OQ test in the strict sense on a single system module. Testing a module usually requires other modules of the system or additional test equipment. OQ tests can be modular or holistic. Modular testing of individual components of a system may facilitate the replacement of such components without full re-qualification of the full measuring system but requires a risk assessment to justify it. Holistic tests, which involve the entire system, demonstrate that the whole system complies with URS. The boundary between OQ and PQ cannot always be clearly defined.
- OQ is a check of the key operational parameters performed following installation and following repairs and/or maintenance.

5.3.1 Instrument function tests

Instrument functions should be tested to verify that the instrument operates as intended and defined in the URS. If there is any uncertainty about the proper functioning of the instrument, selected tests of the OQ can be repeated during routine use of the instrument.

Example: As with any spectrometric device, a UV-Vis spectrophotometer shall be qualified for both wavelength (x-axis) and photometric (y-axis, or signal axis) accuracy and precision, and the fundamental parameters of stray light and resolution shall be established. OQ is carried out across the operational ranges required within the laboratory and defined in the URS for both the absorbance and wavelength scales.

The first time the equipment parameters are checked, their trending is started. Trending is the early-warning system to indicate upcoming problems in the analytical equipment.

If one or more parameters are not within the specifications, the equipment shall not be used. The

problem shall be discussed with the manufacturer and a solution shall be documented.

5.3.2 Software functionality

The software provided with the instrument has been validated by the instrument manufacturer. If a customisation of the instrument software was requested in the order contract, the modification shall be installed and documented at IQ. Any configuration shall occur before the OQ and be documented. Method-specific configurations such as detector wavelength settings, flow rates, flow or temperature gradients and evaluation parameters are excluded here. Unless changes are needed for specific component tests, the OQ should be performed using the software configuration that will be used for routine analysis. If configuration is required, OQ testing should include critical elements of the configured application software to show that the whole system works as intended. Functions to test would be those applicable to data capture, analysis of data, and reporting results under actual conditions of use as well as security, access control, and audit trail. The user can apply risk assessment methodologies and can leverage the supplier's software testing to focus the OQ testing effort.

When applicable, test secure data handling, such as storage, backup, audit trails, and archiving at the user's site, according to written procedures. The user can carry out a risk assessment. In particular, attention shall be paid to data integrity and procedural traceability.

The log files of archiving, backups and audit trails should be meaningful and easy to analyse.

5.4 Performance Qualification (PQ)

The PQ is the documented collection of activities necessary to demonstrate that a piece of equipment consistently performs according to the specifications defined by the user and is suitable for its intended use. The PQ verifies the fitness for use of the equipment under actual conditions of use. It maps an analytical procedure as it is applied in normal use of the instrument.

After IQ, OQ and the initial PQ have been performed, the continued suitability of the equipment for its intended use is verified by a continued PQ.

PQ complements the System Suitability Test (SST) which is executed as part of the analytical method. The SST is limited to the expected events which may occur in the method. While the PQ provides a more holistic view of the instrument.

It is not always easy to define the boundary between OQ and PQ in a general and abstract way. The delimitation can shift depending on the equipment type and supplier. This document provides general considerations and guidelines for definition. The effective separation between OQ and PQ is made in the specific case in the qualification plan.

In traditional methods a reference material is analysed along with unknown samples. The performance of these methods is confirmed and assured during each test. By contrast, multivariate model-based methods or library based methods often do not use reference materials during analysis. This makes robust development, validation and proper maintenance of such methods as well as the use of continuously qualified equipment, of highest importance for reliable analytical results throughout the method life cycle.

The user shall define the PQ protocols, including test procedures, acceptance criteria and frequency. Preventive maintenance plans and documentation of repairs and other modifications are also a necessary part of the overall equipment qualification.

Performance testing is a test or series of tests to verify the acceptable performance of the unit for its intended use. PQ tests are usually based on typical applications of the equipment in the field and may consist of analysis of known components or standards. Tests should be based on good science and reflect the general intended use of the equipment.

The test should be sufficient robust to allow trending over the life of the instrument. The samples, control samples, reference materials and their preparations should be stable within the required time period.

If the characteristics of the analytical system may change over time and with the samples analysed,

these changes can also be determined in the PQ. Especially in analytical systems where the analysis exploits the distribution between a stationary and a mobile phase, e.g. chromatography, the properties of the stationary phase change with time. Components of the sample can permanently change the stationary phase and its selectivity. In gas chromatography, for example, the Grob-Test [52] can be used to characterise column selectivity and absorption properties.
Instead of a general test, a test specific to the requirements of the laboratory's field of activity may preferably be used.

Whether such tests are used in PQ or more commonly in the analytical method itself depends on the specific use and methods.

5.4.1 Initial PQ

The initial qualification process shall be completed by completing the Performance Qualification before the equipment produces reportable results for the first time.

The initial PQ is carried out according to the accepted protocol. The report compares the experimental results with the specifications.

If the specifications are not met, the cause shall be investigated. If modifications or repairs are required, the OQ or at least part of the OQ may need to be repeated. All activities shall be documented and justified.

When the equipment has successfully passed the initial performance qualification, it has shown its fitness for the intended purpose. This marks the official placing into operation. From this point on, the time interval for re-qualification runs.

All documents are archived as part of the equipment documentation.

5.5 Maintaining the qualified condition of laboratory equipment

Standards and legal regulations require that laboratory equipment is kept in a qualified condition.

The calibration ensures that the displayed value corresponds to the measured quantity. In addition to calibrating the actually measured variable, it shall be ensured that the parameters critical for the measurement are effective and traceable. In the case of a spectroscopic measurement, for example, the set wavelength shall correspond to the effective wavelength in a specified range. This range was used, for example, for the validation of the robustness of the method and for measurement uncertainty considerations. In contrast to direct calibration of the measured variable, the correctness of the critical parameters is not checked as often. In all of the quality assurance systems considered here, in addition to calibration, a periodic review of the critical parameters is required. Depending on the quality assurance system, additional checks are required when certain events occur. These events can be predictable and therefore projectable, e.g. relocation of equipment, or they can come as a surprise, e.g. a result falling out of the expected series or, at GMP, a so-called "out of specification result" (OOS result). All of these checks serve to maintain the qualified condition and shall be documented accordingly. All tests for re-qualification are compared against given specifications. The procedure for non-compliance with the specification should be defined.

The susceptibility to changes is taken into account in the scope of the parameters to be checked. With mechanically controlled systems (e.g. load cells, optical banks), mechanical loads (e.g. vibrations, shocks) can lead to misalignments. This can occur, for example, in a monochromator with a dispersing element. In contrast, dichroic bandpass filters are very wavelength stable with regard to mechanical stability. Optical systems in particular can change their properties as a result of environmental contamination. The influence of stray light, reduced reflection or radiation transmission can change over time. These changes can also occur depending on the wavelength.

Also the influence of reagents can slowly and almost unnoticed alter the surface of materials. Examples: alkaline solutions can etch glass; UV light may cause photochemical reactions which lead to precipitations on the measuring cells.

System suitability tests are prescribed in the pyramid of quality. The SSTs verify that the system will perform in accordance with the criteria set forth

in the analytical procedure. These tests are performed along with the sample analyses to ensure that the system's performance is acceptable at the time of the test.
If the specification of the SST is not met, an investigation is started. It is of advantage, if the process of the investigation is standardised.
It is of great advantage if emerging problems can be identified at an early stage by evaluating the SST with statistical methods. The measured variables, in chromatography for example the retention time of a reference peak, signal resolution, signal asymmetry etc., are evaluated in quality control charts. In this way, emerging problems can be detected before the acceptance criteria of the SST are violated. In the case of multiple determinations of the same analyte, the standard deviation can be compared across the analytical sequences. For example, if the standard deviation increases, this may indicate problems with the stability of the mobile phase flow. Continuous monitoring of instrument data can also be indicators of emerging problems. If the back preassure increases progressively in LC methods, this can mean that either the separation system becomes increasingly clogged with insoluble material or that the stationary phase is crushed due to insufficient stability at high preassure.

In particular, methods that are not regularly re-calibrated require long-term stable measurement conditions. Examples are multivariate model-based methods or library based methods. The identification of materials with NIR spectroscopy and principal component analysis is one example. Both the wavelength and the intensity of the signals are essential for the accuracy of the result.

Depending on the purpose and the reason of the re-qualification it consists of a mixture of experiments of the OQ and PQ step.

5.5.1.1 Time-dependant re-qualification

In the case of equipment that has demonstrated long term stability of operation there is no need for requalification unless required by regulation. In a risk assessment, the probability of detection of the occurrence of an event is also considered. If a change occurs gradually, the probability of detection is low (see risk assessments). Thus, the risk shall be reduced by periodic checks. If it turns out that a large number of measurements have to be checked for validity over a long period of time, this is a very big expenditure of resources. These resources are missing in the daily work. This shows that the frequency of re-qualification should be determined by a risk assessment.

If there is no prior experience of possible gradual changes, shorter intervals should be chosen. The likelihood of instrument degradation also depends on the instrument's environment. In a clean laboratory without vibrations, instruments are stressed differently than in a contaminated factory laboratory close to a dusty production plant or an instrument set up in an off-road vehicle, with corresponding mechanical stresses. These factors shall be taken into account in a documented manner when determining the service and re-qualification intervals.

If sufficient measured values are available that, statistically evaluated, show that the equipment runs unchanged over a longer period of time, the intervals for re-qualification can be extended in a documented manner. If unexpected events show that the intervals were too long, they shall be shortened in a documented manner. If samples with different properties (e.g. different matrix) are measured, a shortening of the intervals may also be necessary, possibly until it can be statistically shown that no effect can be observed.

ILAC and OIML have developed a guideline for the determination of calibration intervals of measuring instruments discussing different methods of reviewing calibration intervals [53]

The qualification of equipment shows that the equipment currently has the expected properties. If major work is carried out on the equipment without first checking the equipment, e.g. the annual service, it cannot be proven that the equipment still ran as expected at the end of the period. It is therefore necessary that at least a selected part of the re-qualification is carried out before the start of planned work. It follows that the longest possible interval between periodic re-qualifications is determined by the service interval of the equipment. If problems arise here, all results since the last successful qualification shall be checked. This process is to be documented. After service, the

equipment shall be re-approved for use with a re-qualification.

The re-qualifications can either be carried out by the laboratory or by external persons. In any case, the procedure, the scope, the values to be achieved and the reporting shall be defined in writing. The procedure to be applied if the specifications are not achieved shall also be specified in writing. The entire process shall be documented in writing (protocol and report).

If external contractors are commissioned to carry out the work, the person responsible for the laboratory shall agree to the scope and specifications in advance. Changes are subject to change management.

In any case, the laboratory is responsible for performing the re-qualification. The work can be delegated, but not the responsibility. All documents are to be archived.

5.5.1.2 Event-driven re-qualification

In addition to time-dependent re-qualification, re-qualification shall also be carried out for certain events. Certain activities are only required in certain systems, e.g.:

Relocation of the equipment
The extent of re-qualification depends on the distance of the move and the mechanical stress involved. The extent of re-qualification is determined with a risk assessment.

If the unit is relocated within the same room, large mechanical stresses are not to be expected. In addition it is unlikely that individual parts will be lost. It will usually be adequate if part of the OQ and the PQ are carried out after the move.

If the unit is moved long distances to another location, it is necessary to update the inventory at the old location and perform an IQ at the new location. OQ and PQ are carried out in full.

Replacement of components or modules
If the replacement is a 1:1 replacement, an IQ for the new component and a decommissioning for the replaced component is carried out. The OQ is repeated in the parts relevant to the component. The extent of re-qualification is determined with a risk assessment. The PQ is carried out completely. The documentation shall be kept up to date.

Extension of intended use the equipment for new areas of application
The intended use of an equipment may be extended by expanding the parameter range of an existing equipment defined in the URS or by adding additional hardware or software components.

If the intended use of the equipment changes, the URS shall be revised. This results in changes in all subsequent documents and in the training of personnel. New software functionalities are to be taken into account.

The extent of re-qualification is determined with a risk assessment.

An OQ protocol for a new component of a system is developed and executed. The OQ is repeated, if necessary in a modified form, for the parts relevant to the new component. The PQ adapted to the extended functions is fully executed. The documentation shall be kept up to date.

Under GMP, if an out-of-specification (OOS), out-of-trend result (OOT) or generally an unexpected result occurs, the instrument shall be checked for correct functioning. In these cases, it is advisable to proceed according to a predefined checklist. Selected parts of OQ and PQ are executed.

If an equipment has not been used for a long time, part of the OQ and the PQ shall be repeated after a documented risk analysis.

5.6 Decommissioning

Equipment does not stay in use forever. There are various reasons why it is taken out of service. The most unfavourable case is the unplanned decommissioning after a defect. Proper functioning up to the last analysis can no longer be guaranteed. By analysing the data since the last requalification of the equipment, in particular the SSTs, the highest possible documented certainty is created that all results are valid.

Decommissioning of equipment can also mean that it is sold rather than being disposed of. From the perspective of the future user, this is an acquisition of a piece of equipment. The donor laboratory has the role of the equipment supplier.

Before the unit is scheduled to be taken out of service, the qualification status shall be confirmed in the last period of use. For this purpose, at least a selected part of the re-qualification tests will be carried out. The procedure is analogous to that before planned service and maintenance work.

The decommissioning of the equipment involves various aspects, e.g.

- Privacy protection
- Environmental Protection
- Readability of the data and their integrity
- Later re-evaluation of measurements
- Retention period of the measurement and meta data as well as the evaluations

The equipment shall be disposed of in an environmentally friendly manner. Old devices may contain environmentally harmful components, e.g. asbestos or radioactive sources. The legal regulations for the disposal of special components shall be observed.

In order to be able to read the acquired data, the associated metadata and, if necessary, to evaluate them again, the original software is usually required. Most equipment uses proprietary data formats.

One possibility is to keep the original computer system with the installed software. Over time, however, it becomes more difficult or practically impossible to obtain spare parts for the original computer. This limits the life of the hardware.
In the case of old operating systems, auxiliary programs such as database systems and drivers for peripherals such as input and output devices, it is no longer possible to obtain updates and error corrections. As long as a system is operated as an isolated island, this alone is not a major problem. In a network, however, such systems are very vulnerable to malware attacks. They represent a security risk.

One way to keep old software running and to access old data is to transfer it to new hardware. Often, old operating systems are not directly executable on new hardware. One possibility to consider is operation in a virtualised environment under a current operating system, whereby there are various types of virtualisation.

Not all software can be virtualised. It is of great advantage if this point has already been addressed and tested in the URS.

Both the setup of the virtual system and the data migration shall be validated.

The retention period of the data may be specified sector-specifically in regulations, standards or customer contracts. These periods shall be complied with.

When disposing of old mass storage devices and old mass storage media, data protection and the protection of business secrets shall be strictly observed.

For hard disks, there are programmes that write random numbers to all sectors, including the boot sector. Reconstruction of the data is no longer possible.

With Solid State Disks (SSD), the situation is more problematic. In order to increase the life span and data security, there are reserve areas on the data carrier. These cannot be reached with normal programmes and thus cannot be safely erased. However, they can be read with special programmes.

In any case, mechanical destruction, e.g. multiple drilling through the device and the chips, is the safest way.

Appendix A: Standards and regulations

The copyright on the ISO standards does not permit the verbatim quotation of the standards in this guide. As a workaround, ISO suggests rephrasing the texts in a manner that reflects their meaning.
Appendix A therefore cites the names of the ISO standards and the chapter headings in their original form. The texts have been reworded. The reworded parts are printed in italics and indigo blue.
Only the original wording of the standards is legally binding.

ISO 9001:2015 Quality management systems — Requirements

The standard [16] defines the requirements for measuring equipment, their properties and the traceability of the measurement results.

7.1.5 Monitoring and measuring resources [18].

- **7.1.5.1 General**
  When monitoring or measuring is used to confirm that goods and services meet requirements, the organization must identify and supply the resources required to guarantee accurate and trustworthy results.
  The organization must guarantee that the available resources:
  a) are appropriate for the particular monitoring and measurement tasks being carried out.
  b) are kept up to guarantee that they remain suitable for their intended use.
  As proof of suitability for the monitoring and measurement resources, the organization must keep the relevant documentation.

- **7.1.5.2 Measurement traceability**
  Measurement equipment must be the following when measurement traceability is required or deemed by the organization to be a crucial component of ensuring confidence in the validity of measurement results:
  a) at predetermined intervals or before use, calibrated or verified, or both, against measurement standards traceable to national or international measurement standards; in the absence of such standards, the basis for calibration or verification must be preserved as documented information.
  b) recognized to ascertain their current status
  c) protected against alterations, harm, or degradation that could render the calibration status and ensuing measurement results void.
  When measuring equipment is discovered to be unsuitable for its intended use, the organization must assess whether the validity of earlier measurement results has been compromised and take the necessary corrective action.

For the manufacturing of equipment the standard is also a highly valuable source to define the appropriate processes [19]. For purchasing this clause is a good source for the qualification of suppliers.

8.3 Design and development of products and services

- **8.3.1 General**
  The organisation must create, carry out, and maintain a suitable design and development process to guarantee the ensuing delivery of goods and services.
- **8.3.2 Design and development planning**
  When deciding on design and development stages and controls, the organization must take into account:
  a) the character, length, and difficulty of the design and development processes
  b) the necessary steps in the process, such as the relevant design and development reviews
  c) the necessary activities for design and development validation and verification
  d) the responsibilities and powers associated with the process of design and development
  e) the requirements for both internal and external resources in the design and development of goods and

services
f) the necessity of managing interfaces amongst those engaged in the process of design and development
g) the necessity of incorporating users and clients into the design and development process
h) the specifications needed to provide goods and services in the future
i) customers and other pertinent interested parties' expectations regarding the degree of control over the design and development process
j) the supporting documentation required to prove that the design and development specifications have been fulfilled.

- **8.3.3 Design and development inputs**
  The organization is responsible for identifying the necessary requirements for the design and development of the particular product and service types. The organization must take into account:
  a) requirements for performance and functionality;
  b) data from earlier, comparable design and development projects;
  c) legal and regulatory obligations;
  d) the organization's pledged implementation of standards or codes of practice;
  e) possible outcomes of failure brought on by the characteristics of the goods and services.
  For the purposes of design and development, inputs must be sufficient, comprehensive, and clear. Design and development inputs that disagree must be reconciled. The organization will keep track of all design and development input documentation.
- **8.3.4 Design and development controls**
  The organization must implement design and development process controls to make sure that:
  a) the intended outcomes are specified;
  b) evaluations are performed to assess whether design and development outcomes satisfy requirements;
  c) verification procedures are carried out to guarantee that the outputs of design and development satisfy the input specifications;
  d) validation procedures are carried out to guarantee that the final goods and services fulfill the specifications for the designated application or intended use;
  e) any necessary measures are implemented to address issues identified during the reviews or activities related to verification and validation;
  f) records pertaining to these activities are kept.
- **8.3.5 Design and development outputs**
  The organization must guarantee that the results of design and development:
  a) fulfill the input specifications;
  b) are sufficient for the ensuing procedures for manufacturing goods and rendering services.
  c) incorporate or make reference to acceptance criteria and, if applicable, monitoring and measuring requirements;
  d) outline the features of the goods and services that are necessary for both their safe and appropriate provision and their intended use.
  Documentation of design and development outputs must be kept on file by the organization.
- **8.3.6 Design and development changes**
  To guarantee that there is no negative effect on requirement compliance, the organization must detect, evaluate, and regulate any changes made during or after the design and development of goods and services.
  The organization must maintain records of:
  a) design and development modifications;
  b) the findings from reviews;
  c) approval of the alterations;
  d) the measures implemented to avoid negative effects.

The external procurement of equipment and dealing with the supplier is also handled in ISO 9001 [19]. This also includes external service providers, for example for the service, maintenance and qualification of analytical equipment.

8.4 Control of externally provided processes, products and services

- **8.4.1 General**

  The organization will make sure that processes, goods, and services from outside sources meet the requirements.
  The organization will decide which controls should be implemented for processes, goods, and services that are supplied by outside parties when:
  a) the organization's own products and services are meant to be integrated with those of external providers;
  b) goods and services are delivered directly to the client or clients by outside vendors acting on the company's behalf;
  c) the organization decides to have an external provider provide a process, or a portion of a process.
  In order to assess external providers' ability to deliver processes, products, and services in compliance with requirements, the organization must establish and implement criteria for evaluation, selection, performance monitoring, and re-evaluation. The organization will keep records of these activities and any necessary follow-up actions that result from the assessments.

- **8.4.2 Type and extent of control**

  The company must make sure that processes, goods, and services from outside sources don't negatively impact its capacity to regularly provide its clients with compliant goods and services. The company will:
  a) guarantee that its quality management system maintains control over processes that are supplied by outside parties.
  b) specify the controls it plans to implement for an outside supplier as well as those it plans to implement for the end product.
  c) take into account:
  1) how the company's capacity to continuously satisfy client and relevant legal and regulatory requirements may be impacted by externally supplied procedures, goods, and services;
  2) the efficiency of the measures taken by the outside supplier;
  d) ascertain the verification or other actions required to guarantee that the procedures, goods, and services supplied by third parties satisfy requrements.

- **8.4.3 Information for external providers**

  Before informing the external provider of the requirements, the organization must make sure they are adequate.
  The organization will let outside vendors know what it needs for:
  a) the procedures, goods, and services that must be offered;
  b) acceptance of:
  1) goods and services;
  2) equipment, procedures, and methods;
  3) the release of goods and services;
  c) competence, including any qualifications that individuals may need;
  d) interactions between the organization and its external providers;
  e) the organization's use of performance monitoring and control over external providers;
  f) the organization's or its client's planned verification or validation tasks at the external providers' location.

For a lasting and satisfactory relationship with a supplier, the supplier's handling of complaints is of great importance [20]. The fulfilment of these requirements is an important topic in the assessment of suppliers.

10.2 Nonconformity and corrective action

10.2.1 *The organization must do the following in the event of a deviation, including one that results from complaints:*

a) as appropriate, respond to the deviation by:

1) Take steps to regulate and rectify it

2) deal with the repercussions

b) get rid of the cause or causes of the deviation so that it doesn't happen again by:

1) Examining and evaluating the deviation

2) identifying the nonconformity's causes

3) figuring out whether comparable deviations already exist or might happen

c) take any necessary action.

d) evaluate how well any corrective action worked.

e) if required, update the risks and opportunities identified during planning.

f) modify the quality management system if required.

Corrective measures must be suitable for the consequences of the observed deviations.

ISO/IEC 17025:2017 General requirements for the competence of testing and calibration laboratories [21]

*Subclause **6.4 Equipment** of clause **6 Resource Requirements** defines detailed requirements.*

6.4 Equipment

6.4.1 *The laboratory must have access to all necessary equipment for the proper execution of laboratory operations and that can affect the outcomes, such as measuring devices, software, measurement standards, reference materials, reference data, reagents, consumables, or auxiliary apparatus.*

Note 1: Reference standards, calibration standards, standard reference materials, and quality control materials are just a few of the many names for reference materials and certified reference materials. Additional details on reference material producers (RMPs) are provided in ISO 17034. Competent RMPs are those that satisfy ISO 17034's requirements. A product information sheet or certificate that details, among other things, homogeneity and stability for specified properties, as well as, for certified reference materials, specified properties with certified values, their associated measurement uncertainty, and metrological traceability, is provided with reference materials from RMPs that satisfy ISO 17034 requirements.

Note 2: ISO Guide 33 offers recommendations for the choice and application of reference materials. The production of internal quality control materials is outlined in ISO Guide 80.

6.4.2 *The laboratory must make sure that the equipment specifications outlined in this document are fulfilled when using equipment that is not under its permanent control.*

6.4.3 *Equipment handling, transportation, storage, use, and planned maintenance must be done according to a protocol in the laboratory to guarantee correct operation and avoid contamination or deterioration.*

6.4.4 *Prior to placing or resuming operations, the laboratory must confirm that the equipment satisfies the requirements.*

6.4.5 *In order to produce a valid result, the measurement apparatus must be able to achieve the necessary measurement uncertainty and/or accuracy.*

6.4.6 *Calibration of measuring equipment is required when:*

- *The reported results' validity may be impacted by the measurement's accuracy or uncertainty, and/or*
- *To prove the metrological traceability of the reported results, the equipment must be calibrated.*
  - *Equipment types that may impact the reliability of the results reported include:*

- ✗ *those that are employed for the direct measurement of the measurand, such as the mass measurement using a balance.*
- ✗ *those that are employed to adjust the measured value, such as temperature readings*
- ✗ *those employed to compute a measurement result from several variables.*

6.4.7 *To maintain confidence in the calibration status, the laboratory must set up a calibration program that is reviewed and modified as needed.*

6.4.8 *To enable the user to quickly determine the calibration status or validity period, all equipment that needs to be calibrated or that has a specified period of validity must be labeled, coded, or otherwise identified.*

6.4.9 *Equipment that has been misused or overloaded, produces dubious results, or has been found to be flawed or not meeting requirements will be removed from service. It must either be marked as out of service or isolated to prevent use until its proper operation has been confirmed. The laboratory will commence with the management of non-compliant working procedures and assess the impact of deficiencies or deviations from the specified requirements. (see clause 7.10).*

6.4.10 *Intermediate checks must be performed in accordance with a procedure when they are required to preserve confidence in the equipment's performance.*

6.4.11 *The laboratory must make sure that reference values and correction factors are updated and applied as necessary to satisfy requirements when calibration and reference material data contain them.*

6.4.12 *The laboratory must take reasonable steps to ensure that results are not invalidated by inadvertent equipment adjustments.*

6.4.13 *For equipment that can affect laboratory operations, records must be kept. Where appropriate, the following must be included in the records:*

1. *the equipment's identity, including firmware version and software*
2. *the name of the manufacturer, type identification, serial number, or other distinctive identification*
3. *documentation proving that the equipment complies with the requirements*
4. *the present position*
5. *calibration dates, calibration results, adjustments, acceptance criteria, and the next calibration or calibration interval due date*
6. *recording of reference materials, findings, acceptance criteria, pertinent dates, and validity period*
7. *where relevant to the equipment's performance, the maintenance plan and the maintenance completed thus far*
8. *information about any equipment damage, malfunctions, repairs, or modifications.*

In most cases the laboratory equipment is purchased from an equipment manufacturer.
The external procurement of equipment and dealing with the supplier is handled in clause 6.6 'Externally provided products and services' of the standard.

6.6 Externally provided products and services

6.6.1 *Only appropriate externally supplied goods and services that have an impact on laboratory operations may be utilized, and the lab will make sure that these include:*
a) are meant to be integrated into the activities conducted in the laboratory;
b) are supplied to the client directly by the laboratory, either entirely or in part, as obtained from the outside supplier;
c) are employed to assist in the laboratory's operation.

Note: Measurement tools and standards, auxiliary tools, consumables, and reference materials are a few examples of products. For instance, services can include proficiency testing, assessments, auditing, facility and equipment maintenance, calibration, sampling, and testing.

6.6.2 *The lab must follow a protocol and keep documentation for:*

a) establishing, examining, and approving the laboratory's specifications for goods and services that are externally supplied;

b) specifying the standards for assessing, choosing, tracking, and reassessing the outside suppliers;

c) making certain that, prior to being used or given directly to the client, externally supplied goods and services meet the laboratory's set standards or, if applicable, the pertinent requirements of this document;

d) carrying out any measures brought about by performance reviews, evaluations, and re-evaluations of the outside suppliers.

6.6.3 *The laboratory will inform outside suppliers of its needs for:*

1) the goods and services that will be offered;

b) the criteria for acceptance;

c) proficiency, including any necessary staff qualifications;

d) the tasks that the laboratory or its client plans to complete on the property of the outside supplier.

Qualification of Equipment – Core document PA/PH/OMCL (08) 73 R7 of the European Directorate for the Quality of Medicines & Healthcare (EDQM)

Introduction

The standard ISO/IEC 17025 requires that a laboratory shall have access to equipment that is required for the correct performance of laboratory activities. In particular, calibration programmes shall be established, reviewed and adjusted, including intermediate checks to maintain confidence in the calibration status.

In order to guarantee harmonised interpretation and application of ISO/IEC 17025 requirements within the OMCL Network, the guideline “Qualification of Equipment” has been elaborated.

This document [12] should be considered as a guide to OMCLs for planning, performing and documenting the equipment qualification process. It contains the general introduction and general forms for Level I (Selection of instruments and suppliers) and Level II (Installation and release for use) of qualification, which are common to all types of equipment.

Level III (Periodic and motivated instrument calibration/checks) and Level IV (In-use instrument checks) qualification requirements can be found in separate equipment-related annexes. Level III and IV of qualification must be carried out according to ISO/IEC 17025.Requirements and (if applicable) corresponding typical acceptance limits (given in bold) should be applied; however, other appropriately justified approaches are acceptable. Exemplary procedures provided in the annexes are not binding. They can be helpful when carrying out the required qualification. Nevertheless, other procedures can be applied depending, for example, on the type/model of the equipment.

If the qualification of equipment is done by the manufacturer or an external service provider, it is the responsibility of the OMCL to make sure that this is in line with the requirements set out in this guideline and in the equipment-specific annexes. The following four levels of Equipment Qualification should be considered by the OMCLs:

Level I. Selection of instruments and suppliers

The selection and purchase of new instruments shall follow a documented decision process, based on the needs related to the intended use of the instrument. An example checklist for setting and documenting such specifications and decisions taken is given.

Level II. Installation and release for use

When receiving an instrument, the OMCL should check its condition and fulfilment of the order, and monitor the installation process in the selected environment. This includes start-up checks and a full qualification (normally carried out by the supplier) which fulfils (at minimum) the requirements given in Level III. The

release for use shall be authorised by qualified staff, in order to verify that the equipment conforms to the requirements. This decision may be based on the documentation provided by the supplier. An example checklist for documenting the instrument installation and release for use and decisions taken is given.

Level III. Periodic and motivated instrument checks
When instruments are installed or moved into a new environment, or after significant repair or maintenance operations, a series of calibrations/checks shall be carried out to maintain confidence in the performance of the equipment, according to a defined procedure. Unless defined in the equipment-specific annexes, the frequency of periodic checks shall be based on pre-defined criteria and documented; where adjustments are made, sound scientific justification shall be provided and documented.

Level IV. In-use instrument checks
During the routine use of the instruments, a series of calibrations/checks shall be carried out to maintain confidence in the performance of the equipment and compliance with the system suitability criteria, according to a defined procedure, e.g. specific analytical method, Ph. Eur. chapter/monograph or manufacturer dossier. In the case of OMCLs performing routine testing (e.g. batch release of vaccines and blood products), the use of control charts can provide supplementary information on equipment performance, which can also be used in this context.

NOTE: From experience, the terms DQ (Design Qualification), IQ (Installation Qualification), OQ (Operational Qualification) and PQ (Performance Qualification) (not explicitly mentioned by ISO/IEC 17025) have been used in a non-harmonised way by the OMCLs. Therefore these terms have not been used in this document. This does not exclude their use in OMCL quality systems.

ISO 17034:2017 General requirements for the competence of reference material producers

ISO 17034 [24] specifies general requirements for the competence and consistent operation of reference material producers. It is intended to be used as part of the general quality assurance procedures of the reference material producer.

6.3 Provision of equipment, services and supplies

6.3.1 *Procedures for choosing supplies, services, and equipment that impact the quality of the reference materials produced must be in place at the reference material producer (RMP).*

6.3.2 *To guarantee the quality of the reference materials it generates, the RMP must only use tools, services, and materials that meet certain standards.*

6.3.3 *The RMP will make sure that consumables and equipment are not used until they have been examined, calibrated, or otherwise confirmed to meet the standards or specifications established for the production activities of reference materials.*

6.3.4 *The RMP must keep track of all equipment, service, and supply purchases, including information about the selection criteria applied, the acceptance confirmation, and any commissioning data.*

Note: 6.3 covers all equipment, including measuring and material processing equipment. Additional instructions on how to use measuring equipment are included in 7.7 [25].

The standard ISO 17034 adopts the requirements for equipment from the standard ISO/IEC 17025:2017.

Measuring equipment

The RMP shall ensure that measuring equipment used in RM production is used in compliance with the relevant requirements of ISO/IEC 17025.
Note: Additional information on the management of measurement systems, including information on equipment that is found to drift outside acceptable limits, can be found in ISO 10012.

The standard pays special attention to data integrity.

7.8 Data integrity and evaluation

7.8.1 *All computations and data transfers must pass the necessary checks, according to the RMP.*

7.8.2 *The RMP will make certain that:*

a) computer programs created internally or commercially that are further customized for a particular purpose are verified and proven to be suitable for use;

NOTE A computer-based spread sheet calculation that is verified manually or with test data sets that have known solutions are examples of software validation.

b) methods for safeguarding data integrity are developed and put into place; these methods will cover, among other things, data processing, data storage, data transmission, and data entry and capture integrity;

c) The environment and operating conditions required to preserve data integrity are provided, and the equipment and software are maintained to guarantee correct operation;

d) Appropriate protocols are created and put into place to maintain data security, which includes guarding against illegal access and modifications to documents, including computer records. [26]

ISO 15189:2022 Medical laboratories — Requirements for quality and competence

The standard ISO 15189:2022 [27] refers to the standard ISO/IEC 17025:2017.

Clauses supporting instrument management:

- Clause 6.8 "Externally provided products and services" *describes the requirements for externally provided products and services and the corresponding processes.*
- Clause 8.4 "Control of records" *deals with the creation, modification and archiving of data records.*

6.4 Equipment

6.4.1 General

Processes for equipment selection, acquisition, installation, acceptance testing (including acceptability criteria), handling, transportation, storage, use, maintenance, and decommissioning must be in place in the laboratory to guarantee correct operation and avoid contamination or deterioration.

NOTE: Any equipment that affects the outcomes of laboratory operations, such as sample transportation systems, is considered laboratory equipment. This includes the hardware and software of instruments, measuring devices, and laboratory information systems.

6.4.2 Equipment requirements

a) The equipment necessary for the proper performance of laboratory work must be available in the laboratory.

b) The laboratory management is responsible for ensuring that the functional specifications of the equipment manufacturer or the laboratory's ongoing checks are complied with when the equipment is used outside the laboratory.

c) A registry must be maintained, and each piece of equipment that may affect laboratory operations must be clearly labeled, marked, or otherwise identified.

d) The laboratory must keep equipment maintenance and replacement up to date to ensure the quality of test results.

6.4.3 Equipment acceptance procedure

Before the equipment is installed or put back into service, the laboratory must confirm that it satisfies the required acceptability standards.

Measurement equipment must be able to achieve the measurement uncertainty, measurement accuracy, or both necessary to produce a valid result (for more information, see 7.3.3 and 7.3.4).

NOTE 1 This includes equipment that is used in the lab, that is loaned out, or that is used in point-of-care settings or in related or mobile facilities that the lab has approved.

NOTE 2: Where applicable, the calibration certificate of the returned equipment may be used to verify the equipment acceptance testing.

6.4.4 Equipment instructions for use

a) The laboratory must be equipped with the necessary safety precautions to prevent accidental device settings that could distort the test results.

b) The equipment must be operated by trained, authorized, and competent personnel.

c) The instructions for use of the equipment, including those provided by the manufacturer, must be readily available.

d) Unless verified by the laboratory, the equipment must be used in accordance with the manufacturer's instructions (see 7.3.3).

6.4.5 Equipment maintenance and repair

a) *In accordance with the manufacturer's instructions, the laboratory must have preventive maintenance programs. Any deviations from the manufacturer's instructions or schedules must be documented.*

b) *The equipment needs to be kept in a safe and functional state. Electrical safety, emergency stop devices, and the safe handling and disposal of hazardous materials by authorized personnel are all included in this.*

c) *Equipment that is flawed or does not meet requirements will be removed from service. Until its proper operation is confirmed, it must be conspicuously labeled or marked as out of service. When non-conforming work occurs, the laboratory will take action and assess the impact of the defect or deviation from the specified requirements (see 7.5).*

d) *The laboratory must, if applicable, provide adequate space for repairs, provide the proper personal protective equipment, and decontaminate equipment prior to service, repair, or decommissioning.*

6.4.6 Equipment adverse incident reporting

Unfavorable events and mishaps that are directly related to particular pieces of equipment must be looked into and reported, if necessary, to the relevant authorities as well as the manufacturer, supplier, or both. The laboratory must have protocols in place for reacting to recalls and other notifications from manufacturers and carrying out their suggested actions.

6.4.7 Equipment records

A record must be kept for every equipment that influences the results of laboratory work.

When applicable, these records must contain the following information:

a) information about manufacturers and suppliers, as well as sufficient data such as serial numbers, including software and firmware versions, to uniquely identify each equipment;

b) the dates of delivery, acceptance testing, and service start;

c) proof that the apparatus satisfies the established acceptability standards;

d) the present location;

e) the state in which it was received (new, used, or reconditioned);

f) instructions from the manufacturer;

g) the preventive maintenance program;

h) any maintenance tasks carried out by the lab or an authorized outside service provider;

i) equipment damage, malfunction, alteration, or repair;

j) records of equipment performance, including reports, certificates of calibration or verification, or both, that include dates, times, and outcomes;

k) the equipment's condition, including whether it is in-service, active, out of service, quarantined, retired, or obsolete.

As stated in 8.4.3, these records must be kept up to date and easily accessible for the duration of the equipment's life or longer.

6.5 Equipment calibration and metrological traceability

6.5.1 General

The laboratory must outline sufficient requirements for traceability and calibration in order to sustain consistent reporting of test results over time. Calibration and metrological traceability requirements are part of the specifications for quantitative methods of a measured analyte. Both qualitative and quantitative approaches that use characteristics as opposed to discrete analytes must identify the characteristic being evaluated and include the specifications required for long-term reproducibility.

NOTE Red cell antibody detection, antibiotic sensitivity evaluation, genetic testing, erythrocyte sedimentation rate, flow cytometry marker staining, and tumor HER2 immunohistochemical staining are a few examples of qualitative and quantitative techniques that might not permit metrological traceability.

6.5.2 Equipment calibration

The laboratory must have procedures in place for calibrating equipment that directly or indirectly influences test results. The protocols must contain the following:

a) usage guidelines and calibration instructions provided by the manufacturer;

b) records of metrological traceability;

c) confirmation of the functionality of the measuring system at specified intervals and of the required measurement accuracy;

d) a note of the date of recalibration and the calibration status;

e) assurance that, where correction factors are used, these are updated and documented during recalibration;

f) management of situations where calibration may have failed, in order to reduce the risk to patients and service operations.

ISO 10012:2003 Measurement management systems — Requirements for measurement processes and measuring equipment [28]

Clauses supporting instrument management:

4 General requirements

Specific metrological requirements must be met, and this will be ensured by the measurement management system.

Directions
The requirements for the product are used to determine the specific metrological requirements. Both measurement processes and equipment must meet these specifications. Maximum allowable error, allowable uncertainty, range, stability, resolution, environmental conditions, or operator skills are some examples of requirements.

Measurement procedures and equipment that are subject to this International Standard's provisions must be specified by the organization. The risks and repercussions of noncompliance with metrological requirements must be considered when determining the scope and extent of the measurement management system.

6.2.2 Software

To guarantee its suitability for ongoing use, software used in measurement procedures and result computations must be identified, tracked, and controlled. Before being used for the first time, software and any updates must be tested and/or validated, authorized for use, and stored. Testing will only be done as much as is required to guarantee accurate measurement results.

Directions
There are various types of software, including programmable, off-the-shelf, and embedded packages. Off-the-shelf software may not need to be tested. To get the desired measurement result, testing may involve checking for viruses, checking user-programmed algorithms, or a combination of both. The validity and integrity of software-based measurement procedures can be preserved with the aid of software configuration control. Making backup copies, storing data off-site, or using any other method to protect programming, guarantee accessibility, and offer the required degree of traceability are all examples of archiving.

6.2.3 Records

It is necessary to keep records containing the data required for the operation of the measurement management system. The identification, storage, security, protection, retrieval, retention period, and disposal of records must be ensured by documented procedures.

Directions
Examples of records include purchases, operating data, data on nonconformities, customer complaints, training, qualifications, verification results, measurement results, and any other historical data that is useful for the measurement processes.

6.2.4 Identification

The technical processes and measuring instruments of the measurement management system must be properly labeled, either individually or in combination. The status of the metrological confirmation of the devices is specified. To prevent unauthorized use, devices that are demonstrably used exclusively in a specific measurement process or specific measurement processes must be properly labeled or otherwise controlled. It must be possible to distinguish the devices used in the measurement management system from other devices.

6.3 Material resources

6.3.1Measuring equipment

The measurement management system must list and identify all of the measuring tools required to meet the given metrological requirements. Before being verified, measuring apparatus must be in a valid calibration state. In order to guarantee reliable measurement results, measuring equipment must be used in an environment that is sufficiently controlled or understood. The measurement management system must include the measuring tools used to track and document the influencing quantities.

Directions
Due to varying metrological requirements, measuring equipment may be approved for use in specific measurement processes but not for use in other measurement processes. The metrological specifications for the measuring apparatus are based on the requirements for the calibration, verification, and confirmation of the product or apparatus.
The metrological function or the published specification of the manufacturer of the measuring equipment may be used to determine the maximum allowable error.
An organization other than the metrological function carrying out the metrological confirmation may calibrate the measuring apparatus.
The calibration requirement may be satisfied by the characterization of reference materials.

Measurement equipment must be received, handled, transported, stored, and dispatched according to documented procedures that are established, maintained, and used by the metrological function management to avoid misuse, abuse, damage, and alterations to its metrological properties. Measurement equipment added to or removed from the measurement management system must be processed according to certain protocols.

7 Metrological confirmation and realization of measurement processes

7.1 Metrological confirmation

7.1.1 General

The purpose of metrological verification is to ensure that the metrological characteristics of the measuring device comply with the metrological specifications for the measurement procedure. The calibration and verification of measuring devices are part of metrological verification.

Directions
If the measuring device is already in a valid calibration state, recalibration is not necessary. Metrological validation procedures should include means of verifying that the measurement uncertainties and/or errors of the measuring devices are within the permissible ranges specified in the metrological requirements.

All restrictions or special requirements regarding the metrological confirmation status of measuring instruments must be easily accessible to the operator.

Measuring instruments must have metrological characteristics that are suitable for their intended use.

Directions
The following are some examples of characteristics of measuring instruments:

- *range,*
- *bias,*
- *repeatability,*
- *stability,*
- *hysteresis,*
- *drift,*
- *effects of influencing quantities,*

- *resolution,*
- *discrimination (threshold),*
- *error, and*
- *dead band.*

To obtain metrological confirmation, the metrological requirements can be compared directly with the metrological characteristics of the measuring instruments, which are factors that contribute to measurement uncertainty.

Avoid qualitative descriptions of metrological characteristics, such as "required accuracy of measuring instruments."

7.1.2 Intervals between metrological confirmation

….

Directions
The intervals between metrological verifications can be determined based on information from calibration and metrological verification histories, as well as new findings and technologies. Records collected for measurements using statistical process control techniques can be helpful when deciding whether to adjust metrological verification intervals.
The measurement verification interval and the calibration interval may be identical.

7.1.3 Equipment adjustment control

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Directions
Zero adjusters and other devices that are meant to be adjusted by the user without the assistance of outside references are exempt from the sealing requirement.
Write-protection strategies should receive extra consideration in order to stop unwanted modifications to firmware and software.
The metrological function typically makes the decisions regarding which measuring devices should be sealed, which controls or adjustments will be sealed, and what sealing materials—such as labels, solder, wire, or paint—should be used. The metrological function's implementation of a sealing program ought to be recorded. Not all measuring devices are suitable for sealing.

7.1.4 Records of the metrological confirmation process

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Directions
The minimum period of time that records must be kept is determined by a number of factors, such as manufacturer liability, statutory or regulatory requirements, and customer requirements. It might be necessary to keep records pertaining to measurement standards for an extended period of time.

Each item of measuring device's compliance with the established metrological requirements must be shown in the records of the metrological confirmation procedure.

The following will be included in the records, if needed:

a) the manufacturer, type, serial number, and other unique identifiers of the equipment;

b) the completion date of the metrological confirmation;

c) metrological confirmation's result;

d) the designated time frame for metrological verification;

e) determining the metrological verification process (refer to 6.2.1);

f) the specified maximum allowable error or errors;

g) the pertinent environmental circumstances and a declaration regarding any required adjustments;

h) the unknowns associated with equipment calibration;

i) specifics of any upkeep, including any adjustments, fixes, or alterations made;

j) any restrictions on usage;

k) identifying the individual or individuals carrying out the metrological confirmation;

l) identifying the person or people in charge of ensuring that the data recorded is accurate;

m) the distinct identification, e.g. by serial mumbers, of any calibration reports and certificates, as well as other pertinent documents;

n) proof of the calibration results' traceability;

o) the metrological specifications for the purpose;

p) the calibration results acquired preferable before and after any alterations, repairs, or adjustments.

Directions
In order to demonstrate the traceability of all measurements and to replicate the calibration results under conditions that are similar to the original conditions, it is necessary to record the calibration results.
A verification result that indicates whether the equipment satisfies (or does not) specified requirements is sometimes included in the calibration certificate or report.
The records could be on microfilm, typescript, manuscript, electronic, magnetic, or another type of data medium.

The metrological function or the published specification of the measuring equipment manufacturer can be used to determine the maximum allowable error.

8.3.3 Nonconforming measuring equipment

Any verified measurement apparatus that is suspected or known

a) to have sustained harm,

b) to have been overloaded,

c) to experience a malfunction that renders its intended use invalid,

d) to yield inaccurate measurement findings,

e) to exceed the metrological confirmation interval that has been set,

f) to have been improperly managed,

g) to possess a broken or damaged safeguard or seal,

h) to have come into contact with influencing quantities that could negatively impact its intended use (such as dust or electromagnetic field),

must be identified by conspicuous labeling or marking, or removed from service by segregation. A nonconformity report will be created after the nonconformity has been confirmed. Such equipment cannot be put back into service until the causes of its nonconformance have been fixed and verified once more.
When nonconforming measuring equipment is not restored to its intended metrological properties, it must be

properly marked or identified in some other way. For such equipment to be used for other purposes, metrological confirmation must guarantee that the changed status is obvious and that any usage restrictions are noted.

Directions
Equipment that is determined to be unfit for its intended use may be downgraded or its intended use changed if it is not feasible to modify, repair, or overhaul it. Reclassification should only be applied very carefully because it can lead to misunderstandings about the permissible uses of seemingly identical pieces of equipment. This includes limited metrological confirmation of only a few of the multiranged equipment's ranges or functions.

The equipment user must assess the possible repercussions and take any required action if the results of a metrological verification conducted before any adjustment or repair show that the measuring apparatus did not satisfy the metrological requirements to the extent that the accuracy of the measurement results may have been jeopardized. Re-examining the product made using measurements made with nonconforming measuring equipment may be one way to do this.

Good Manufacturing Practice (GMP)

In GMP, no distinction is made between laboratory equipment and equipment for the production of pharmaceutical products with regard to the qualification of the various devices. The DQ/IQ/OQ/PQ process is generally binding. The general requirements for the qualification process are defined by PIC/S Annex 15. There are very few and not detailed requirements in laws or regulations.
Detailed requirements for equipment of analytical laboratories can be found in the pharmacopoeias.

ICH Harmonised Tripartite Guideline Good Manufacturing Practice Guide for Active Pharmaceutical Ingredients Q7
12.8 Validation of Analytical Methods
12.82 Appropriate qualification of analytical equipment should be considered before starting validation of analytical methods.

CFR 21: Food and Drugs, Part 211—Current Good Manufacturing Practice for Finished Pharmaceuticals; Subpart I - Laboratory Controls
211.160 General requirements.
(a) The establishment of any specifications, standards, sampling plans, test procedures, or other laboratory control mechanisms required by this subpart, including any change in such specifications, standards, sampling plans, test procedures, or other laboratory control mechanisms, shall be drafted by the appropriate organizational unit and reviewed and approved by the quality control unit. The requirements in this subpart shall be followed and shall be documented at the time of performance. Any deviation from the written specifications, standards, sampling plans, test procedures, or other laboratory control mechanisms shall be recorded and justified.
(b) Laboratory controls shall include the establishment of scientifically sound and appropriate specifications, standards, sampling plans, and test procedures designed to assure that components, drug product containers, closures, in-process materials, labelling, and drug products conform to appropriate standards of identity, strength, quality, and purity. Laboratory controls shall include:
(1) Determination of conformity to applicable written specifications for the acceptance of each lot within each shipment of components, drug product containers, closures, and labelling used in the manufacture, processing, packing, or holding of drug products. The specifications shall include a description of the sampling and testing procedures used. Samples shall be representative and adequately identified. Such procedures shall also require appropriate retesting of any component, drug product container, or closure that is subject to deterioration.

(2) Determination of conformance to written specifications and a description of sampling and testing procedures for in-process materials. Such samples shall be representative and properly identified.
(3) Determination of conformance to written descriptions of sampling procedures and appropriate specifications for drug products. Such samples shall be representative and properly identified.
(4) **The calibration of instruments**, apparatus, gauges, and recording devices **at suitable intervals in accordance with an established written program containing specific directions, schedules, limits for accuracy and precision, and provisions for remedial action in the event accuracy and/or precision limits are not met. Instruments,** apparatus, gauges, and recording devices **not meeting established specifications shall not be used.**

Good Laboratory Practice (GLP)

The minimal requirements for GLP are defined by the Organization for Economic Co-operation and Development (OECD) and by the World Health Organization (WHO). WHO covers with GLP the quality practices for regulated non-clinical research and development.

OECD Series on Principles of Good Laboratory Practice and Compliance Monitoring
Number 1 OECD Principles on Good Laboratory Practice
(as revised in 1997) ENV/MC/CHEM(98)17

These principles of GLP, as defined in the OECD document, should be applied to the non-clinical safety testing of test items contained in pharmaceutical products, pesticide products, cosmetic products, veterinary drugs as well as food additives, feed additives, and industrial chemicals. These test items are frequently synthetic chemicals, but may be of natural or biological origin and, in some circumstances, may be living organisms. The purpose of testing these test items is to obtain data on their properties and/or their safety with respect to human health and/or the environment.

Section II Good Laboratory Practice Principles

4. Apparatus, Material, and Reagents
1. Apparatus, including validated computerised systems, used for the generation, storage and retrieval of data, and for controlling environmental factors relevant to the study should be suitably located and of appropriate design and adequate capacity.
2. Apparatus used in a study should be periodically inspected, cleaned, maintained, and calibrated according to Standard Operating Procedures. Records of these activities should be maintained. Calibration should, where appropriate, be traceable to national or international standards of measurement.
3. Apparatus and materials used in a study should not interfere adversely with the test systems.

The EU adopted the OECD principles by the Directive 2004/10/EC on the harmonisation of laws, regulations and administrative provisions relating to the application of the principles of good laboratory practice and the verification of their applications for tests on chemical substances.

WHO GLP Handbook
Chapter 2 • Good Laboratory Practice Training
Facilities and equipment

The GLP Principles emphasise that facilities and equipment must be sufficient and adequate to perform the studies. The facilities should be spacious enough to avoid problems such as overcrowding, cross contamination or confusion between projects. Utilities (water, electricity etc.) must be adequate and stable.

All equipment must be in working order; a programme of validation/qualification, calibration and maintenance attains this. Keeping records of use and maintenance is essential in order to know, at any point in time, the precise status of the equipment and its history.

Facilities: Buildings and Equipment

Equipment

For the proper conduct of the study, appropriate equipment of adequate capacity must be available. All equipment should be suitable for its intended use, and it should be properly calibrated and maintained to ensure reliable and accurate performance. Records of repairs and routine maintenance and of any non-routine work should be retained. Remember that the purpose of these GLP requirements is to ensure the reliability of data generated and to ensure
that data are not invalidated or lost as a result of inaccurate, inadequate or faulty equipment.

Suitability

Suitability can only be assessed by considering the tasks that the equipment is expected to perform: there is no need to have a balance capable of weighing to decimals of a milligram to obtain the weekly weight of a rat, but a balance of this precision may well be required in the analytical laboratory. Deciding on the suitability of equipment is a scientific responsibility and is usually defined in SOPs.

Calibration

All equipment, whether it is used to generate data (e.g. analytical equipment or balances), or to maintain standard conditions (e.g. refrigerators or air conditioning equipment), should work to fixed specifications. Proof that specifications are being met will generally be furnished by periodic checking.
In the case of measuring equipment this is likely to involve the use of standards. For example, a balance will be calibrated by the use of known standard weights. In the case of analytical equipment a sample of known concentration will be used to ensure that the equipment is functioning as expected, as well as providing a basis for the calculation of the final result. Other equipment, such as air conditioning systems for animal facilities or constant temperature storage rooms, will be checked periodically by the use of calibrated instruments (probes, thermometers...). Verifications should be performed at a frequency that allows action to be taken in time to prevent any adverse effect on the study should it be discovered that the equipment is not operating within specifications.

Maintenance

The requirement that equipment be properly maintained is based on the assertion that this ensures the constant performance of equipment to specifications and that it reduces the likelihood of an unexpected breakdown and consequent loss of data.
Maintenance may be carried out in two quite distinct ways:

• Preventive maintenance; when parts are changed regularly based upon the expected life of the part concerned. Planned maintenance of this type may be a useful precaution for large items of equipment or items that do not possess suitable backup or alternatives.
Regular preventive maintenance therefore reduces the risk of breakdown.

• Curative maintenance; when repairs are made in the case of a fault being detected. This approach particularly applies to equipment such as modern computer driven analysers or electronic balances that do not easily lend themselves to preventive maintenance. It is good practice to adopt contingency plans in case of failure; these may include having equipment duplicated or assuring that there is immediate access to a maintenance technician or an engineer.

Back up for vital equipment should be available whenever possible as well as back up in the event of service failures, such as power cuts. A laboratory should have the ability to continue with essential services to prevent animals or data being lost, and studies irretrievably affected. For example, a laboratory carrying out animal studies may, as a minimum, need a stand-by generator capable of maintaining the animal room environment, even if it does not allow the laboratory to function completely as normal; for example test item analysis could wait until power is restored.

Early warning that equipment is malfunctioning is important; hence the checking interval should be assigned to assure this. Alarms are very valuable, particularly if a problem occurs at a time when staff are not present in the laboratory.

Documentation

Routine maintenance should be documented in such a way that users of equipment can be assured that it is reliable and not outside its service interval. A label attached to equipment or the provision of a clear service plan may ensure this.

Records of equipment calibration, checking and maintenance demonstrate that the respective SOPs have been followed and that equipment used was adequate for the task and operating within its specifications.

The records should also demonstrate that the required action was taken as a result of the checks that had been made, for example when parameters exceeded acceptable limits staff were aware of this and took appropriate remedial action.

Pharmacopoeias

Since in GMP the equipment qualification is handled in a very broad sense (see chapter 4.1.2.1), specific advice for the analytical laboratory is given in the pharmacopoeias as EP and USP. In the general chapters the requirements are defined for specific methods and their equipment. A key document for the equipment qualification or analytical instrument qualification is the general chapter <1058> Analytical Instrument Qualification in USP.

Appendix B: Acronyms and Terminology

Adjustment of a measuring system	Set of operations carried out on a measuring system so that it provides the prescribed indications corresponding to the given values of a quantity to be measured. [VIM3, 3.11]
Audit trail	The audit trail is a form of metadata containing information associated with actions that relate to the creation, modification or deletion of GXP records. An audit trail provides for secure recording of life-cycle details such as creation, additions, deletions or alterations of information in a record, either paper or electronic, without obscuring or overwriting the original record. An audit trail facilitates the reconstruction of the history of such events relating to the record regardless of its medium, including the “who, what, when and why” of the action. Outside of GxP and generally in the world of software, the audit trail is called a log file. [21 CFR Part 11]
Business Continuity Plan	A Business Continuity Plan (BCP) is a document that describes how a company will continue to operate in the event of an unplanned business interruption. It is more comprehensive than a disaster recovery plan and includes contingencies for business processes, assets, personnel and business partners - every aspect of the business that could be affected.
Calibration	Operation that, under specified conditions, in a first step, establishes a relation between the quantity values with measurement uncertainties provided by measurement standards and corresponding indications with associated measurement uncertainties and, in a second step, uses this information to establish a relation for obtaining a measurement result from an indication Note 1: A calibration may be expressed by a statement, calibration function, calibration diagram, calibration curve, or calibration table. In some cases, it may consist of an additive or multiplicative correction of the indication with associated measurement uncertainty. Note 2: Calibration should not be confused with adjustment of a measuring system, often mistakenly called “self-calibration”, nor with verification of calibration. Note 3: Often, the first step alone in the above definition is perceived as being calibration. [VIM3, 2.39]
Calibration material / Calibrator	A material of known composition or properties which can be presented to the analytical instrument for calibration purposes. [IUPAC Goldbook] Ideally, it is a primary standard. Secondary CRMs are second choice, as the uncertainty contribution of CRMs sometimes makes them unsuitable.
Certified reference material	Reference material (RM) characterized by a metrologically valid procedure for one or more specified properties, accompanied by an RM certificate that provides the value of the specified property, its associated uncertainty, and a statement of metrological traceability [ISO Guide 30:2015]

Cooperation on International Traceability in Analytical Chemistry	Cooperation on International Traceability in Analytical Chemistry; The CITAC initiative aims to promote cooperation between existing organisations to improve the international comparability of chemical measurements. Membership is open to both individuals and companies/institutions. https://www.citac.group
Codex Alimentarius	The Codex Alimentarius is a collection of internationally recognized standards, codes of practice, guidelines, and other recommendations published by the Food and Agriculture Organization (FAO) relating to food, food additives, food production, food labelling, and food safety (e.g. food contaminants). http://www.fao.org/fao-who-codexalimentarius/en/
Data integrity	Data integrity is the degree to which data are complete, consistent, accurate, trustworthy, reliable and that these characteristics of the data are maintained throughout the data life cycle. The data should be collected and maintained in a secure manner, so that they are attributable, legible, contemporaneously recorded, original (or a true copy) and accurate. Assuring data integrity requires appropriate quality and risk management systems, including adherence to sound scientific principles and good documentation practices.
Disaster recovery	A disaster recovery (DR) plan is a formal document created by a company that provides detailed instructions on how to respond to unplanned incidents such as natural disasters, power outages, cyber attacks and other disruptive events. The plan includes strategies to minimise the impact of a disaster so that a company can continue operations - or quickly resume important operations.
Equipment	The laboratory shall have access to ***equipment*** *(including, but not limited to, measuring instruments, software, measurement standards, reference materials, reference data, reagents, consumables or auxiliary apparatus)* that is required for the correct performance of laboratory activities and that can influence the results. [ISO/IEC 17025, clause 6.4.1] The definition of the term “equipment” in ISO/IEC 17023 clause 6.4.1 is very broad. The following restrictive definition is used for this guide: ***The term "equipment" covers measuring instruments or instrument systems including control and data processing units, auxiliary equipment and computerized systems with software that are necessary for the correct performance of analytical laboratory activities and that can influence the results.***
European **D**irectorate for the **Q**uality of **M**edicines & HealthCare	The EDQM is the European Pharmacopoeia Commission and is based in the Council of Europe in Strasbourg. https://www.edqm.eu
EudraLex	It is the collection of rules and regulations governing medicinal products in the European Union https://en.wikipedia.org/wiki/EudraLex https://ec.europa.eu/health/documents/eudralex_en
Eurachem	Eurachem is a network of organisations in Europe, having the objective of establishing a system for the international traceability of chemical measurements and the promotion of good quality practices. It provides a forum for the discussion of common problems and for developing an informed and considered approach to both technical and policy issues. https://www.eurachem.org/
Food and **D**rug **A**dministration	FDA is a federal agency of the Department of Health and Human Services of the United States of America. The FDA is responsible for protecting and promoting

	public health through the control and supervision of food safety, tobacco products, dietary supplements, prescription and over-the-counter pharmaceutical drugs (medications), vaccines, biopharmaceuticals, blood transfusions, medical devices, electromagnetic radiation emitting devices (ERED), cosmetics, animal foods & feed and veterinary products. https://www.fda.gov/
Good **L**aboratory **P**ractice	The Principles of **G**ood **L**aboratory **P**ractice (GLP) have been developed to promote the quality and validity of test data used for determining the safety of chemicals and chemicals products. It is a managerial concept covering the organisational process and the conditions under which laboratory studies are planned, performed, monitored, recorded and reported. Its principles are required to be followed by test facilities carrying out studies to be submitted to national authorities for the purposes of assessment of chemicals and other uses relating to the protection of man and the environment. Globally, GLP is under the auspices of the OECD.
Good **M**anufacturing **P**ractice	**G**ood **M**anufacturing **P**ractice (GMP); the practices required in order to conform to the guidelines recommended by agencies that control the authorization and licensing of the manufacture and sale of food and beverages, cosmetics, pharmaceutical products, dietary supplements, and medical devices. Globally, GMP is under the auspices of the WHO.
Guide to the Expression of **U**ncertainty in **M**easurement	**GUM**, a metrology guide pertaining to measurement uncertainty [JCGM 100:2008]
Influence quantity	Quantity that, in a direct measurement, does not affect the quantity that is actually measured, but affects the relation between the indication and the measurement result Note: In the GUM and in the second edition of the VIM, the term “influence quantity” is used for referring not only to the quantities affecting the measuring system, as in the definition above, but also to those quantities that affect the quantities actually measured. Also, in the GUM influence quantities are not restricted to direct measurements. [VIM3, 2.52]
International **C**ouncil for **H**armonisation of Technical Requirements for Pharmaceuticals for Human Use	An initiative that brings together regulatory authorities and pharmaceutical industry to discuss scientific and technical aspects of pharmaceutical product development and registration. https://www.ich.org
International **L**aboratory **A**ccreditation **C**ooperation	**ILAC** is the international organisation for accreditation bodies operating in accordance with ISO/IEC 17011 and involved in the accreditation of conformity assessment bodies including calibration laboratories (using ISO/IEC 17025), testing laboratories (using ISO/IEC 17025), medical testing laboratories (using ISO 15189), inspection bodies (using ISO/IEC 17020), proficiency testing providers (using ISO/IEC 17043) and reference material producers (using ISO 17034). https://ilac.org
Instrumental drift	Continuous or incremental change over time in indication, due to changes in metrological properties of a measuring instrument Note: Instrumental drift is related neither to a change in a quantity being measured nor to a change of any recognised influence quantity. [VIM3, 4.21]

Intermediate check	Intermediate check is the process of verifying the calibration status and the qualification status of the equipment in between calibration and the planned requalification. This is done to verify whether there is any drift in the measurement indicated by the instrument over a period of time [ISO/IEC 17025 clause 6.4.10] See also: System Suitability Test. The intermediate test is part of the System Suitability Test.
International **U**nion of **P**ure and **A**pplied **C**hemistry	IUPAC members, the National Adhering Organizations, can be national chemistry societies, national academies of sciences, or other bodies representing chemists. There are fifty-four National Adhering Organizations and three Associate National Adhering Organizations. https://iupac.org
Laboratory **I**nformation **M**anagement **S**ystem	A LIMS is a software-based solution with features that support the operation of an analytical laboratory. Key features include workflow and data tracking support, data interfaces that fully support deployment in regulated environments, among others. The capabilities and uses of a LIMS have evolved over the years from simple sample tracking to an enterprise resource planning tool that manages multiple aspects of laboratory informatics.
Log file	A log file contains the automatically kept log of all or specific actions of processes on a computerized system. Important applications can be found above all in automation. In principle, all actions that are or could be necessary for later traceability are recorded. Essential information that a log file contains is who did what, when, with what data, why and how, or what problems or errors occurred when and where. Audit trails are GxP relevant log files.
Measurement	Process of experimentally obtaining one or more quantity values that can reasonably be attributed to a quantity [VIM3] 2.1
Measurement method	Method of measurement; generic description of a logical organization of operations used in a measurement [VIM3] 2.5
Measurement principle	Principle of measurement; phenomenon serving as a basis of a measurement EXAMPLE 1 Thermoelectric effect applied to the measurement of temperature. EXAMPLE 2 Energy absorption applied to the measurement of amount-of-substance concentration. [VIM3] 2.4
Measurement result	Set of quantity values being attributed to a measurand together with any other available relevant information. [VIM3, 2.9]
Measurement standard	Realization of the definition of a given quantity, with stated quantity value and associated measurement uncertainty, used as areference. [VIM3, 5.1]
Metrological traceability	Property of a measurement result whereby the result can be related to a reference through a documented unbroken chain of calibrations, each contributing to the measurement uncertainty. [VIM3, 2.41]
Medicinal product	Any substance or combination of substances which may be used in, or administered to, human beings, either with a view to restoring, correcting or modifying physiological functions by exerting a pharmacological, immunological or metabolic action, or to making a medical diagnosis.
OIML	International Organization of Legal Metrology (French: **O**rganisation **I**nternationale de **M**étrologie **L**égale) The OIML is an intergovernmental organization that was created in 1955 to promote the global harmonization of the legal metrology procedures that underpin and

	facilitate international trade. https://www.oiml.org/
OMCL	**O**fficial **M**edicines **C**ontrol **L**aboratory is the term used in Europe for a public institute in charge of controlling the quality of medicines and, depending on the country, other similar products (for example, medical devices). https://www.edqm.eu/en/omcl-background-and-mission
OECD	**O**rganisation for **E**conomic **C**o-operation and **D**evelopment Following Decision C(97),186/Final of the OECD Council, data generated in the testing of chemicals in one OECD Member Country, in accordance with OECD Test Guidelines and the Principles of GLP are accepted in all other OECD Member Countries. https://www.oecd.org/chemicalsafety/testing/oecdguidelinesforthetestingofchemicals.htm https://www.oecd.org/
Pharmacopoeia	In its modern technical sense, it is a book containing directions for the identification of compound medicines, and published by the authority of a government or a medical or pharmaceutical society (see Ph. Eur. and USP)
Ph. Eur.	The European Pharmacopoeia is a major regional pharmacopoeia which provides common quality standards throughout the pharmaceutical industry in Europe to control the quality of medicines, and the substances used to manufacture them. It is a published collection of monographs which describe both the individual and general quality standards for ingredients, dosage forms, and methods of analysis for medicines. These standards apply to medicines for both human and veterinary use. https://www.edqm.eu/en/news/european-pharmacopoeia
PIC/S	**P**harmaceutical **I**nspection **C**onvention and **P**harmaceutical **I**nspection **C**o-operation **S**cheme The Pharmaceutical Inspection Convention (PIC) and Pharmaceutical Inspection Co-operation Scheme (PIC/S) are two international instruments between countries and pharmaceutical inspection authorities. The PIC/S is meant as an instrument to improve co-operation in the field of GMP between regulatory authorities and the pharmaceutical industry. https://picscheme.org
Proficiency test	Evaluation of participant performance against pre-established criteria by means of interlaboratory comparisons [ISO 17043:2023]
Qualification	The act of planning, carrying out and recording the results of tests which is performed on equipment to confirm its working capabilities and to display that it will perform routinely as intended use and against predefined specification or acceptance criteria which are mentioned in supplier's recommendation / design specification / manual / supplier's documents / guidelines etc. Validation and qualification are essentially components of the same concept. The term qualification is normally used for equipment, utilities and systems, and validation for processes. [WHO TRS 937, 2006]
Quality assurance	Part of quality management focused on providing confidence that quality requirements will be fulfilled [ISO 9000:2015] Quality Assurance (QA) relates to a set of planned activities which are defined in standard operating procedures, within the product manufacturing process that ensure the safety and the quality of the product. It is a process oriented mainly proactive activity.
Quality control	Part of quality management focused on fulfilling quality requirements [ISO 9000:2015] QC usually involves

	- assessing the suitability of incoming components, in-process materials, and the finished products; - evaluating the performance of the manufacturing process to ensure adherence to proper specifications and limits; and - determining the acceptability of each batch for release. It is a product oriented mainly retrospective activity
Quality management	Coordinated activities to direct and control an organization with regard to quality (degree to which a set of inherent characteristics of an object fulfils requirements). Quality management can include establishing quality policies and quality objectives and processes to achieve these quality objectives through quality planning, quality assurance, quality control and quality improvement. [ISO 9000:2015]
Quality management system	A Quality management system (QMS) comprises activities by which the organization identifies its objectives and determines the processes and resources required to achieve desired results. The QMS manages the interacting processes and resources required to provide value and realize results for relevant interested parties. It enables top management to optimize the use of resources considering the long and short term consequences of their decision. A QMS provides the means to identify actions to address intended and unintended consequences in providing products and service [ISO 9000:2015]
Reference material	Material, sufficiently homogeneous and stable with respect to one or more specified properties, which has been established to be fit for its intended use in a measurement process [ISO Guide 30:2015]
SI unit	The International System of Units consists of a set of defining constants with corresponding base units, derived units, and a set of decimal-based multipliers that are used as prefixes. [Bureau International des Poids et Mesures]
System suitability test	Verifies that the system will perform in accordance with the criteria set forth in the procedure. These tests are performed along with the sample analyses to ensure that the system's performance is acceptable at the time of the test.
Traceability	- Ability to trace the history, application or location of an object When considering a product or a service, traceability can relate to: • the origin of materials and parts; • the processing history; • the distribution and location of the product or service after delivery [ISO 9000:2015] - metrological traceability: property of a measurement result whereby the result can be related to a reference through a documented unbroken chain of calibrations, each contributing to the measurement uncertainty [International vocabulary of metrology – Basic and general concepts and associated terms (VIM3, 2.41]
United **S**tates **P**harmacopoeia	The USP is a pharmacopoeia (compendium of drug information) for the United States published annually by the United States Pharmacopeial Convention (usually also called the USP), a non-profit organization that owns the trademark and also owns the copyright on the pharmacopoeia itself. https://www.usp.org
Validation	Confirmation, through the provision of objective evidence (data supporting the existence or verity of something), that the requirements (need or expectation that is stated, generally implied or obligatory) for a specific intended use or application have been fulfilled [ISO 9000:2015] Validation and qualification are essentially components of the same concept. The term qualification is normally used for equipment, utilities and systems, and validation for processes. [WHO TRS 937, 2006] Verification, where the specified requirements are adequate for an intended use.

	[VIM3, 2.45]
Verification	Confirmation, through the provision of objective evidence (data supporting the existence or verity of something), that specified requirements (need or expectation that is stated, generally implied or obligatory) have been fulfilled [ISO 9000:2015] Provision of objective evidence that a given item fulfils specified requirements EXAMPLE 1 Confirmation that a given reference material as claimed is homogeneous for the quantity value and measurement procedure concerned, down to a measurement portion having a mass of 10 mg. EXAMPLE 2 **Confirmation that performance properties or legal requirements of a measuring system are achieved.** EXAMPLE 3 Confirmation that a target measurement uncertainty can be met. NOTE 1 When applicable, measurement uncertainty should be taken into consideration. NOTE 2 The item may be, e.g. a process, measurement procedure, material, compound, or measuring system. NOTE 3 **The specified requirements may be, e.g. that a manufacturer's specifications are met.** NOTE 4 Verification in legal metrology, as defined in VIML, and in conformity assessment in general, pertains to the examination and marking and/or issuing of a verification certificate for a measuring system. NOTE 5 **Verification should not be confused with calibration.** Not every verification is a validation . NOTE 6 In chemistry, verification of the identity of the entity involved, or of activity, requires a description of the structure or properties of that entity or activity. [VIM3 2.44]
VIM	**V**ocabulaire **i**nternational de **m**étrologie – Concepts fondamentaux et généraux et termes associés, English: International vocabulary of metrology – Basic and general concepts and associated terms. VIM is an attempt to find a common language and terminology in metrology across different fields of science, legislature and commerce. It is published by the Joint Committee for Guides in Metrology (JCGM) https://www.bipm.org/en/committees/jc/jcgm/
VIML	The VIM was used by the OIML as a basic source for its International Vocabulary of Terms in Legal metrology. http://viml.oiml.info/en/index.html
World **H**ealth **O**rganization	The WHO is a specialized agency of the United Nations responsible for international public health. The WHO Constitution, which establishes the agency's governing structure and principles, states its main objective as "the attainment by all peoples of the highest possible level of health". The WHO version of GMP is used by pharmaceutical regulators and the pharmaceutical industry in over 100 countries worldwide, primarily in the developing world. https://www.who.int/medicines/areas/quality_safety/quality_assurance/production/en/

Appendix C: Abbreviations

Abbreviation	Meaning
ALCOA	Attributable, Legible, Contemporaneous, Original, Accurate
BCP	**B**usiness **C**ontinuity **P**lan
CITAC	**C**ooperation on **I**nternational **T**raceability in **A**nalytical **C**hemistry
CRM	**C**ertified **r**eference **m**aterial
DQ	**D**esign **Q**ualification
DR	**D**isaster **R**ecovery
EDQM	European Directorate for the Quality of Medicines & HealthCare
ERP	**E**nterprise **R**esource **P**lanning
EudraLex	It is the collection of rules and regulations governing medicinal products in the European Union
FDA	**F**ood and **D**rug **A**dministration
GLP	**G**ood **L**aboratory **P**ractice
GMP	**G**ood **M**anufacturing **P**ractice
GUM	**G**uide to the Expression of **U**ncertainty in **M**easurement
GxP	GxP is a general abbreviation for the "good practice" quality guidelines and regulations. The "x" stands for the various fields, including the pharmaceutical and food industries, for GMP and GLP.
HPLC	**H**igh **p**erformance **l**iquid **c**hromatography
ICH	**I**nternational **C**ouncil for **H**armonisation of Technical Requirements for Pharmaceuticals for Human Use **I**nternational **C**onference on **H**armonisation (1990 – 2015)
IEC	**I**nternational **E**lectrotechnical **C**ommission
ILAC	**I**nternational **L**aboratory **A**ccreditation **C**ooperation
IUPAC	**I**nternational **U**nion of **P**ure and **A**pplied **C**hemistry
IQ	**I**nstallation **Q**ualification
ISO	**I**nternational **O**rganization for **S**tandardization
LIMS	**L**aboratory **I**nformation **M**anagement **S**ystem
OECD	**O**rganisation for **E**conomic **C**o-operation and **D**evelopment
OIML	International Organization of Legal Metrology (French: **O**rganisation **I**nternationale de **M**étrologie **L**égale)
OMCL	**O**fficial **M**edicines **C**ontrol **L**aboratory
OQ	**O**perational **Q**ualification
Ph. Eur.	European Pharmacopoeia
PIC/S	**P**harmaceutical **I**nspection **C**onvention and **P**harmaceutical **I**nspection **C**o-operation **S**cheme
PQ	**P**erformance **Q**ualification
PT	**P**roficiency **T**est

Abbreviation	Meaning
QA	**Q**uality **A**ssurance
QC	**Q**uality **C**ontrol
QMS	**Q**uality **M**anagement **S**ystem
SST	**S**ystem **S**uitability **T**est
URS	**U**ser **R**equirement **S**pecification
USP	**U**nited **S**tates **P**harmacopoeia
VIM	**V**ocabulaire **I**nternational de **M**étrologie – Concepts fondamentaux et généraux et termes associés, English: International vocabulary of metrology – Basic and general concepts and associated terms.
VIML	**V**ocabulaire **I**nternational des Termes de **M**étrologie **L**égale; English: International Vocabulary of Terms in Legal Metrology
WHO	**W**orld **H**ealth **O**rganization
4Q	Summary of the qualification steps DQ, IQ, OQ and PQ of devices

Bibliography

[1] ISO/IEC Directives, Part 2 Principles and rules for the structure and drafting of ISO and IEC documents, Geneva: ISO Central Secretariat, 2021.
[2] ISO/IEC 17025:2017 General requirements for the competence of testing and calibration laboratories, Clause 6.4.1, Geneva: ISO Central Secretariat, 2017
[3] ISO 9001:1994, Quality systems — Model for quality assurance in design, development, production, installation and servicing; clause 4.11 Control of inspection equipment. Geneva: ISO Central Secretariat, 1994
[4] Commission Directive 91/356/EEC of 13 June 1991 laying down the principles and guidelines of good manufacturing practice for medicinal products for human use
[5] Freeman HM, Leng M, Morrison D, Munden RP, Position paper on the qualification of analytical equipment, 1995 Pharm Tech Europe 40–46
[6] Bedson, P., Sargent, M. The development and application of guidance on equipment qualification of analytical instruments. Accred Qual Assur 1, 265–274 (1996). https://doi.org/10.1007/s007690050083
[7] Bedson, P., et al., Guidance on equipment qualification of analytical instruments: High Performance Liquid Chromatography (HPLC), LGC/VAM/1998/026, 1998
[8] Holcombe, D., et al., Guidance on Equipment Qualification of Analytical Instruments: UV-Visible Spectro(photo)meters (UV-Vis). Valid Analytical Measurement (VAM) Programme, LGC/VAM/2000/079, 2000
[9] PIC/S Guide to Good Manufacturing Practice for Medicinal Products, Part 1, PE 009-16 (Part I), Geneva: PIC/S Secretariat, 2022
[10] PIC/S Guide to Good Manufacturing Practice for medical products - Annexes, PE 009-16 (Annexes), Geneva: PIC/S Secretariat, 2022
[11] EudraLex Volume 4 EU Guidelines for Good Manufacturing Practice for Medicinal Products for Human and Veterinary Use Annex 15: Qualification and Validation, 2015
[12] PA/PH/OMCL (08) 73 R7 Qualification of Equipment – Core Document, 2023

[13] USP General Chapter <1058>, Analytical Instrument Qualification, https://doi.org/10.31003/USPNF_M1124_01_01
[14] Georg Schwedt, The essential guide to analytical chemistry, page 7, 1997. ISBN: 978-0-471-97412-3. Copyright Wiley-VCH GmbH and affiliated companies. All rights reserved, including those for text and data mining and training of artificial intelligence or similar technologies.
[15] BIPM, IEC, IFCC, ILAC, IUPAC, IUPAP, ISO, OIML (2012) The international vocabulary of metrology—basic and general concepts and associated terms (VIM), 3rd edn. JCGM 200:2012.
[16] ISO 9001:2015, Quality management systems - Requirements, Geneva: ISO Central Secretariat, 2015
[17] ICH Q10: ICH harmonised tripartite guideline, Pharmaceutical Quality System, 4 June 2008
[18] ISO 9001:2015 Quality management systems – Requirements, Clause 7.1.5 Monitoring and measuring resources, Geneva: ISO Central Secretariat, 2015
[19] ISO 9001:2015 Quality management systems – Requirements, Clause 8.4 Control of externally provided processes, products and services, Geneva: ISO Central Secretariat, 2015
[20] ISO 9001:2015, Quality management systems – Requirements, Clause 10.2 Nonconformity and corrective action, Geneva: ISO Central Secretariat, 2015
[21] ISO/IEC 17025:2017 General requirements for the competence of testing and calibration laboratories, Geneva: ISO Central Secretariat, 2017
[22] PA/PH/OMCL (08) 73 R5 Qualification of Equipment – Core Document, 2003
[23] V. Barwick (Ed), Eurachem/CITAC Guide: Guide to Quality in Analytical Chemistry: An Aid to Accreditation (3rd ed. 2016). ISBN 978-0-948926-32-7.
[24] ISO 17034:2017, General requirements for the competence of reference material producers, Geneva: ISO Central Secretariat, 2017.
[25] ISO 17034:2017 General requirements for the competence of reference material producers, Clause 6.3 Provision of equipment, services and supplies, Geneva: ISO Central Secretariat, 2017.
[26] ISO 17034:2017 General requirements for the competence of reference material producers, Clause 7.7 Measuring equipment, Geneva: ISO Central Secretariat, 2017.
[27] ISO 15189:2022 Medical laboratories — Requirements for quality and competence, Geneva: ISO Central Secretariat, 2022.
[28] ISO 10012:2003 Measurement management systems — Requirements for measurement processes and measuring equipment, Geneva: ISO Central Secretariat, 2003
[29] WHO Good Manufacturing Practices for Pharmaceutical Products: Main Principles; Annex 2, WHO Technical Report Series 986, 2014
[30] EudraLex, Volume 4, EU Guidelines for Good Manufacturing Practice for Medicinal Products for Human and Veterinary Use Annex 11: Computerised Systems
[31] EudraLex, Volume 4, EU Guidelines for Good Manufacturing Practice for Medicinal Products for Human and Veterinary Use Annex 15: Qualification and Validation
[32] Pharmaceutical Inspection Convention / Pharmaceutical Inspection Co-operation Scheme; PE 009-17 (Annexes), 25 August 2023, Guide to Good Manufacturing Practice for Medical Products - Annexes
[33] CFR - Code of Federal Regulations Title 21 Food and Drugs, Chapter I—Food and Drug Administration, Department of Health and Human Services, Subchapter A – General; Part 11 Electronic Records; Electronic Signatures
[34] CFR - Code of Federal Regulations Title 21 Chapter I—Food and Drug Administration, Department of Health and Human Services, Subchapter C - DRUGS: General Part 211 Current Good Manufacturing Practice for Finished Pharmaceuticals
[35] Christopher Burgess, Bob McDowall, Guide on Analytical Instrument and System Qualification - A Lifecycle Approach, 2023, European Compliance Academy; https://www.gmp-compliance.org/
[36] Directive 2004/9/EC of the European Parliament and of the Council of 11 February 2004 on the inspection and verification of good laboratory practice (GLP), 2004.

https://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=OJ:L:2004:050:0028:0043:EN:PDF
[37] Directive 2004/10/EC of the European Parliament and of the Council of 11 February 2004 on the harmonisation of laws, regulations and administrative provisions relating to the application of the principles of good laboratory practice and the verification of their applications for tests on chemical substances, 2004. https://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=OJ:L:2004:050:0044:0059:EN:PDF
[38] OECD Position Paper Regarding the Relationship between the OECD Principles of GLP and ISO/IEC 17025, ENV/JM/MONO(2016)47, 2016
[39] Codex Alimentarius - International food standards; https://www.fao.org/fao-who-codexalimentarius/about-codex/en/
[40] Guidelines for the assessment of the competence of testing laboratories involved in the import and export control of food, CAC/GL 27-1997
[41] Good Automated Manufacturing Practice Guidelines version 4, International Society for Pharmaceutical Engineering, Tampa, FL, 2001
[42] Good Automated Manufacturing Practice Guidelines version 5, International Society for Pharmaceutical Engineering, Tampa, FL, 2008
[43] McDowall, R.D., Understanding and Interpreting the New GAMP 5 Software Categories, Spectroscopy 2009, 24(6), 22–31.
[44] FDA Guidance Document CPG Sec. 130.400 Use of Microfiche and/or Microfilm for Method of Records Retention, FDA, CPG 7150.13, November 2004
[45] Medicines & Healthcare products Regulatory Agency (MHRA) GxP Data Integrity Guidance and Definitions; Revision 1, March 2018.
[46] Digitalisation of Documents in a GxP-regulated Environment, 2nd Edition, Publisher: German Quality Management Association e.V. (GQMA), March 2017.
[47] Working Group on Information Technology (AGIT), Position Paper regarding: Is it acceptable to destroy the paper originals of raw data and related study documentation, if an image of the paper is captured in an electronic form (e.g. scanned)? Revision 2, 2018.
[48] ICH Q9(R1): ICH harmonised tripartite guideline, Quality risk management, 18 January 2023
[49] McDowall, R.D., How do you write user requirements for Chromatographs and chromatographic data systems?, LCGC Europe 2020, 33(5), 257–263.
[50] Potts, Philip J., Evaluation of analytical instrumentation. Part XXVII: a guide to good practice in the purchase of analytical instrumentation, Anal. Methods, 2018, 10, 3303-3309.
[51] ISO 9001:2015 Quality management systems - Requirements; clause 8.3 Design and development of products and services, Geneva: ISO Central Secretariat, 2015.
[52] Grob, K., Grob, G., & Grob, Jr., K., Testing capillary gas chromatographic columns, Journal of Chromatography, 1981, 219, 13-20. https://doi.org/10.1016/S0021-9673(00)80568-3
[53] ILAC G24, Guidelines for the determination of calibration intervals of measuring instruments, 2022

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