Annex 4

WHO good practices for pharmaceutical quality control laboratories

Contents

Abbreviations

API	active pharmaceutical ingredient
DQ	design qualification
ECSPP	Expert Committee on Specifications for Pharmaceutical Preparations
EQ	equipment qualification
IQ	installation qualification
IT	information technology
LCL	lower content limit
LIMS	laboratory information management system
NAP	normal analytical practice
NMRA	national medicines regulatory authority
NQCL	national quality control laboratory
OQ	operational qualification
PQ	performance qualification
QCL	quality control laboratory
QMS	quality management system
RSD	relative standard deviation
SMART	specific, measurable, achievable, relevant, and time bound
UCL	upper content limit
WHO	World Health Organization

1. General considerations

1.1 In 1999, the World Health Organization (WHO) Expert Committee on Specifications for Pharmaceutical Products (ECSPP) adopted the WHO *Good practices for national pharmaceutical control laboratories*, which were published as Annex 3 of the WHO Technical Report Series No. 902, 2002. These guidelines were subsequently revised as *WHO good practices for pharmaceutical quality control laboratories*, published as Annex 1 of the WHO Technical Report Series No. 957, 2010.

1.2 Since the last revision of the guidelines, the experience from inspections of pharmaceutical quality control laboratories (QCLs) has enabled WHO to identify sections requiring clarification and the need to add new sections. Also, the COVID-19 pandemic made it clear that risk management, crisis management and business continuity are subjects that should be addressed to ensure that laboratories are prepared to face similar situations.

1.3 The present document provides advice on the quality management system (QMS) within which the analysis of pharmaceutical products by QCLs should be performed to ensure that accurate and reliable results are obtained. Compliance with the recommendations provided in these guidelines will help promote international harmonization of good practices for pharmaceutical QCLs and facilitate mutual recognition of test results.

1.4 This guideline is consistent with the requirements of the *WHO good manufacturing practices for pharmaceutical products* (*1*) and international standard ISO/IEC 17025:2017 (*2*), providing detailed guidance for laboratories performing quality control testing of medicines.

1.5 The good practice outlined below is to be considered as a general guide, which may be adapted to meet individual needs, provided that an equivalent level of assurance is achieved. For the items in the following subsections (mainly in the new section 4 on "Planning and strategic management"), a period of adaptation will be given to allow laboratories to implement these new requirements properly:

- 4.3: Performance management
- 4.4: Quality risk management
- 4.5: Crisis management
- 4.6: Communication management
- 6.7: Measurement uncertainty.

1.6 This guideline is applicable to any pharmaceutical QCL, be it a national QCL (NQCL), a commercial QCL, a third-party contract QCL or a QCL of a pharmaceutical manufacturer. However, it does not include guidance for those laboratories involved in the testing of biological products (for example, vaccines and blood products), or for microbiology laboratories. Separate guidance for such laboratories is available, for example, *WHO good practices for pharmaceutical microbiology laboratories* (*3*), which is based on and supplements the requirements described in this document.

1.7 It should be noted that specifications and quality assurance objectives may be different for NQCLs and the QCL of a pharmaceutical manufacturer.

1.1 Pharmaceutical quality control testing

1.8 In a QCL of a pharmaceutical manufacturer, testing usually comprises repetitive testing and analysis of pharmaceutical products. However, an NQCL has to be able to test and evaluate a much wider range of products, requiring the application of a wider range of analytical test procedures and techniques. The same is applicable to commercial and third-party contracted laboratories.

1.9 For the quality of a pharmaceutical product to be correctly assessed, the following should be considered:

- the submission of a sample to the laboratory should be accompanied by a statement indicating the reason why the analysis has been requested;
- the analysis should be correctly planned and executed.

1.10 The test results should be evaluated to determine whether the sample complies with the specifications or other relevant requirements.

1.2 National quality control laboratories (NQCLs)

1.11 A government, normally through the national medicines regulatory authority (NMRA), may establish and maintain an NQCL. Large countries may require several NQCLs to conform with national legislation. The role of NQCLs should be defined in the pharmaceutical legislation of Member States. Appropriate arrangements should, therefore, be in place to monitor compliance with a QMS. Throughout the process of marketing authorization and post-marketing surveillance, the laboratory or laboratories may work closely with the NMRA.

1.12 An NQCL should provide effective support to and collaborate with the NMRA. The analytical results obtained should accurately describe the properties of the samples assessed, permitting correct conclusions as to their quality. Where results from testing of samples show non-compliance with specifications, further investigations should be carried out by the NMRA and, where necessary, the appropriate legal action should be instituted.

1.13 NQCLs usually encompass two types of activity:

- compliance testing of pharmaceutical products employing official methods, which include pharmacopoeial methods, validated analytical procedures provided by the manufacturer and approved by the relevant national or regional authority for marketing

authorization and, whenever necessary, analytical procedures developed and validated by the NQCL;

- investigative testing of suspicious, illegal, or falsified substances or products submitted for analysis, for example by the respective health authorities, customs authorities or police.

1.14 Compliance testing is expected to be performed by NQCLs in accordance with a post-market surveillance testing plan, prepared with the inputs of inspection, assessment and pharmacovigilance and taking into account the criticality of the products, supported by a risk analysis.

1.15 The implementation of these guidelines in NQCLs allows harmonization of laboratory procedures, methodologies and technical competence, enabling mutual trust and recognition among peers.

2. Glossary

2.1 The definitions given below apply to the terms as used in these guidelines. They may have different meanings in other contexts.

acceptance criteria for an analytical result. Predefined and documented criteria by which a result is considered to be within the limits (conforms) or to exceed the limits (does not conform) indicated in the specification.

accuracy. The closeness of agreement between the value that is accepted either as a conventional true value or as an accepted reference value and the value found.

active pharmaceutical ingredient. Any substance or mixture of substances intended to be used in the manufacture of a pharmaceutical dosage form and that, when so used, becomes an active ingredient of that pharmaceutical dosage form. Such substances are intended to furnish pharmacological activity or other direct effect in the diagnosis, cure, mitigation, treatment or prevention of disease, or to affect the structure and function of the body.

analytical acceptance criteria. Performance criteria applied to results obtained from the analysis performed. These criteria are predefined and are dependent on the nature of the product, the analytical procedure, and its original validation, as well as the specification limits given in the compendial monograph or in the marketing authorization, such as precision and accuracy.

analytical test report. An analytical test report usually includes a brief description of the test procedures employed, results of the analysis, discussion (if applicable) and conclusions or recommendations for one or more samples submitted for testing.

analytical worksheet. A printed form, an analytical workbook, or electronic means (e records) for recording information about the sample, as well as reagents and solvents used, instruments and equipment used, test procedure applied, calculations made, results and any other relevant information or comments.

batch (or lot). A defined quantity of starting material, packaging material or product processed in a single process or series of processes so that it is expected to be homogeneous. It may sometimes be necessary to divide a batch into a number of sub-batches that are later brought together to form a final homogeneous batch. In the case of terminal sterilization, the batch size is determined by the capacity of the autoclave. In continuous manufacture, the batch should correspond to a defined fraction of the production, characterized by its intended homogeneity. The batch size can be defined either as a fixed quantity or as the amount produced in a fixed time interval.

batch number (or lot number). A distinctive combination of numbers or letters that uniquely identifies a batch on the labels, its batch records and corresponding certificates of analysis.

calibration. The set of operations that establish, under specified conditions, the relationship between values indicated by an instrument or system for measuring (especially weighing), recording and controlling, or the values represented by a material measure, and the corresponding known values of a reference standard. Limits for acceptance of the results of measuring should be established.

certificate of analysis. The list of test procedures applied to a particular sample with the results obtained and the acceptance criteria applied. It indicates whether or not the sample complies with the specification.

certified reference material. Reference material, characterized by a metrologically valid procedure for one or more specified properties, accompanied by documentation (a certificate) that provides the value of the specified property, its associated uncertainty, and a statement of metrological traceability.

collaborative study. A study performed with a set of laboratories with different purposes, for example to establish a new batch of a reference standard or to validate a new test method to be published with regard to its robustness, which can be used to compare the results between different laboratories.

compliance testing. Active pharmaceutical ingredients, pharmaceutical excipients, packaging material or pharmaceutical products according to the requirements of a pharmacopoeial monograph or a specification in an approved marketing authorization.

confirmed out-of-specification result. A result that has been subjected to a thorough investigation and has been confirmed to be out of specification.

control sample. A sample used for testing the continued accuracy and precision of the procedure. It should have a matrix similar to that of the samples to be analysed. It has an assigned value with its associated uncertainty.

conventional true value. Value attributed to a particular quantity and accepted value.

crisis management. A set of planned strategies defined in advance to assist an organization in managing an unexpected event with a relevant negative impact. These strategies should ensure that business processes, assets and personnel are protected and are able to adapt to function in the event of such a disruption, such as a natural disaster (fire, flood, weather-related events), a cyberattack or a pandemic.

data integrity. The degree to which data are complete, consistent, accurate, trustworthy and reliable, and to which these characteristics of the data are maintained throughout the data life cycle. The data should be collected and maintained in a secure manner, such that they are attributable, legible, contemporaneously recorded, original or a true copy, accurate, complete, consistent, enduring and available (commonly referred to as "ALCOA+"). Assuring data integrity requires appropriate quality and risk management systems, including adherence to sound scientific principles and good documentation practices.

design qualification. A documented collection of activities that define the functional and operational specifications of the instrument and criteria for selection of the vendor, based on the intended purpose of the instrument.

equipment qualification. Action of proving and documenting that any analytical equipment complies with the required specifications and performs suitably for its intended purpose.

expanded uncertainty (*U*). Quantity defining an interval about the result of a measurement that may be expected to encompass a large fraction of the distribution of values that could reasonably be attributed to the measurand. Typically, it is calculated from a combined standard uncertainty and a coverage factor *k*. Estimation of uncertainty from a certain source of variation can already be indicated as an expanded uncertainty (for example, the maximum permissible deviation from the nominal volume of a volumetric apparatus).

good manufacturing practices. That part of quality assurance that ensures that pharmaceutical products are consistently produced and controlled to the quality

standards appropriate to their intended use and as required by the marketing authorization.

installation qualification. The performance of tests to ensure that the analytical equipment or system used in a laboratory is correctly installed in accordance with established specifications, enabling it to operate in the expected range.

interlaboratory comparison or testing. The organization, performance and evaluation of measurements or tests on the same or similar items by two or more laboratories in accordance with predetermined conditions.

level of confidence. A number expressing the degree of confidence in a quoted result, for example, 95%. It represents the probability that the conventional true value of the measurand lies within the quoted range of uncertainty.

management review. A formal, documented review of the key performance indicators of a quality management system performed by senior management on a regular basis.

manufacturer. A company that carries out operations such as the production, packaging, testing, repackaging, and labelling or relabelling of pharmaceuticals.

marketing authorization (product licence, registration certificate). A legal document issued by the competent medicines regulatory authority that authorizes the marketing or free distribution of a pharmaceutical product in the respective country after an evaluation for safety, efficacy and quality. In terms of quality, it establishes inter alia the detailed composition and formulation of the pharmaceutical product and the quality requirements for the product and its ingredients. It also includes details of packaging, labelling, storage conditions, shelf-life and approved conditions of use.

measurement uncertainty. A parameter associated with the result of a measurement that characterizes the dispersion of the values that could be reasonably attributed to the measurand.

metrological traceability. The 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.

operational qualification. Documented verification that the analytical equipment performs as intended over all anticipated operating ranges.

out-of-specification result. A test result that has been investigated and confirmed to fall outside the specifications or acceptance criteria established in product dossiers, drug master files, or pharmacopoeias, or by the manufacturer.

out-of-trend result. A result, from a series of analytical results obtained during a certain period of time, that complies with the acceptance criteria (be it specification, internal limits or analytical acceptance criteria) but falls outside the expected and predicted interval or the statistical process control criteria. It requires performance of trend analysis for test results during stability testing, environmental controls and yields, where applicable.

performance qualification. Documented verification that the analytical equipment operates consistently and gives reproducibility within the defined specifications and parameters for prolonged periods.

pharmaceutical excipient. A substance, other than the active pharmaceutical ingredient, that has been appropriately evaluated for safety and is included in a medicines delivery system to:

- aid in the processing of the medicines delivery system during its manufacture;
- protect, support, or enhance stability, bioavailability, or patient acceptability;
- assist in pharmaceutical product identification; or
- enhance any other attribute of the overall safety and effectiveness of the medicine during its storage or use.

pharmaceutical product. Any material or product intended for human or veterinary use, presented in its finished dosage form or as a starting material for use in such a dosage form, which is subject to control by pharmaceutical legislation in the exporting State or the importing State.

precision. The closeness of agreement among individual results when the procedure is applied repeatedly to multiple samplings of a homogeneous sample. Precision, usually expressed as relative standard deviation, may be considered at three levels: repeatability (precision under the same operating conditions over a short period of time), intermediate precision (within laboratory variations) and reproducibility (precision between laboratories).

primary reference substance (or standard). A substance that is widely acknowledged to possess the appropriate qualities within a specified context, and whose assigned content is accepted without requiring comparison with another chemical substance.

proficiency testing. The evaluation of participant performance against pre-established criteria by means of interlaboratory comparisons. It is common that laboratories are provided with aliquots or portions of a large homogeneous

bulk material to make the necessary tests and measurements within a defined time period, and are provided with a report describing the global performance of the proficiency testing and the individual performance of the laboratory, supported by statistical calculation leading to a Z-score or an equivalent measure, converted into satisfactory, questionable or unsatisfactory results.

quality control. All measures taken, including the setting of specifications, sampling, testing and analytical clearance, to ensure that raw materials, intermediates, packaging materials and finished pharmaceutical products conform with established specifications for identity, strength, purity and other characteristics.

quality management system. An appropriate system, encompassing the organizational structure, procedures, processes and resources, and systematic actions necessary to ensure adequate confidence that a product or service will satisfy given requirements for quality.

quality manager. A member of staff who has a defined responsibility and authority for ensuring that the management system related to quality is implemented and followed at all times.

quality manual. A handbook that describes the various elements of the quality management system for assuring the quality of the test results generated by a laboratory.

quality risk management. A systematic process for the assessment, control, communication and review of risks to the quality of the product during its life cycle.

quality unit. An organizational unit, independent of production, that fulfils both quality assurance and quality control responsibilities. This can be in the form of separate quality assurance and quality control or a single individual or group, depending on the size and structure of the organization.

reference material. Material sufficiently homogeneous and stable with respect to one or more specified properties that it has been established to be fit for its intended use in a measurement process.

reference substance (or standard). An authenticated, uniform material that is intended for use in specified chemical and physical tests, in which its properties are compared with those of the product under examination, and which possesses a degree of purity adequate for its intended use.

risk. Combination of the probability of occurrence of harm and severity of the harm.

secondary reference substance (or standard). A substance whose characteristics are assigned or calibrated by comparison with a primary reference substance. The extent of characterization and testing of a secondary reference substance may be less than for a primary reference substance.

signed (signature). Record of the individual who performed a particular action or review. The record can be initials, a full handwritten signature, a personal seal or an authenticated and secure electronic signature.

specification. A list of detailed requirements (acceptance criteria for the prescribed test procedures) with which the substance or pharmaceutical product has to conform to ensure suitable quality. "Conformance to specification" means that the drug substance and drug product, when tested according to the listed analytical procedures, will meet the acceptance criteria (numerical limits, ranges, or other) and is considered acceptable for its intended use. Specifications are critical quality standards that are proposed and justified by the manufacturer and approved by regulatory authorities as conditions of approval.

standard operating procedure. An authorized written procedure giving instructions for performing operations, both general and specific.

standard uncertainty (U). Uncertainty of the result of a measurement expressed as a standard deviation.

starting material. Any substance of a defined quality used in the production of a pharmaceutical product, including packaging material.

suspected out-of-specification result. The first out-of-specification result obtained for a testing parameter, which has not been investigated and confirmed as out of specification.

system suitability test. A test that is performed to ensure that the analytical procedure fulfils the acceptance criteria that had been established during the validation of the procedure. This test is performed before starting the analytical procedure and is to be repeated regularly, as appropriate, throughout the analytical run to ensure that the system's performance is acceptable at the time of the test.

target uncertainty (U^{tg}). Measurement uncertainty is specified as an upper limit and decided on the basis of the intended use of measurement results. Unless otherwise indicated, U^{tg} is expressed as an expanded uncertainty.

trend analysis. An analysis of sets of data intended to detect patterns or trends, with the purpose of understanding the current behaviour and predicting future behaviours of that same type of data. This analysis enables the implementation of actions to control the trends that are observed.

uncertainty evaluation procedure. The procedure used for estimating the overall uncertainty.

validation of an analytical procedure. The documented process by which an analytical procedure (or method) is demonstrated to be consistently suitable for its intended use.

verification of an analytical procedure. The process whereby a pharmacopoeial method or official method approved by regulatory authorities is demonstrated to be suitable for the samples intended to be tested, and the process whereby a laboratory demonstrates it can adequately operate the pharmacopoeial method or official method approved by regulatory authorities.

verification of performance. A test procedure that is regularly applied to a system (for example, liquid chromatographic system) to demonstrate consistency of response.

3. Organization and management system

3.1 Structural and general requirements

3.1 The laboratory, or the organization of which it is part, should be legally authorized to function and be held responsible for the test results, certificates of analysis and other types of work that it performs.

3.2 Senior management is responsible for the establishment, implementation and control of an effective quality system and data governance system by ensuring that policies, training and technical systems are in place.

3.3 The laboratory should:

- have managerial and technical personnel with the authority and resources (financial, human and infrastructure) needed to carry out their duties;
- have arrangements to ensure that its management and personnel are not subject to commercial, political, financial and other pressures or conflicts of interest that may adversely affect their work or compromise impartiality;
- have procedures in place to declare conflicts of interest, as well as possible measures that should be taken to mitigate risks arising from declared interests, and to evaluate, review and document continuously the declarations of interest with respect to the ongoing work;

- have a policy and procedures to ensure confidentiality of all information (oral, paper and electronic) shared with or generated by the laboratory during the performance of laboratory activities, including information contained in marketing authorizations, analytical methods, and the transfer of results or reports;
- be responsible, through legally enforceable commitments, for the management of all information obtained or created during the performance of laboratory activities;
- ensure that all personnel, including contractors, personnel of external bodies or individuals acting on the laboratory's behalf, keep confidential all the information obtained or created during the activities (except as required by law), act impartially and competently, and work in accordance with the laboratory's QMS;
- define, with the aid of organizational charts, the organization and management structure of the laboratory, its place in any parent organization (such as the ministry of health or the NMRA in the case of an NQCL), and the relationships between management, technical operations, support services and the QMS;
- specify the responsibility, authority and interrelationships of all personnel who manage, perform, verify, review or approve work that affects the results of laboratory activities, for instance, in the job description;
- ensure the precise allocation of responsibilities, particularly in the designation of specific units for particular types of medicines, if deemed necessary;
- nominate trained substitutes or deputies for key management and specialized scientific personnel;
- ensure adequate supervision of staff, including trainees, by senior staff familiar with the testing or calibration, validation and verification of methods and procedures, as well as their purpose and the assessment of the results;
- have management that has the overall responsibility for the technical operations and the provision of resources needed in order to ensure the required quality of laboratory operations;
- designate a member of staff as quality manager, who, irrespective of other duties the staff member may have, will ensure compliance with the QMS. The nominated quality manager should have direct access to the highest level of management;

- ensure adequate information flow and communication between staff at all levels; staff are to be made aware of the relevance and importance of their activities, as well as having a good understanding of the mission, the strategic direction and operational priorities;
- ensure the traceability of the sample from receipt, throughout the stages of testing, to the completion of the analytical test report; a registry should be in place for receiving, distributing and supervising the consignment of the samples to the specific units. The records on all incoming samples and all accompanying documents should be maintained;
- maintain an up-to-date collection of all specifications and related documents (paper or electronic) used in the laboratory;
- have appropriate safety procedures (section 7).

3.2 Quality management system

3.4 The quality manager should ensure the establishment, implementation and maintenance of a QMS appropriate to the scope of activities in the laboratory.

3.5 The QMS should be communicated and understood by the appropriate personnel prior to its implementation. The elements of this system should be documented (for example, electronically or on paper).

3.6 The quality manual, or equivalent document, should contain, as a minimum:

- a quality policy statement, including at least the following:
  - a statement of the laboratory management's intentions with respect to the standard of service it will provide, including policies and objectives that address the competence, impartiality and consistent operation of the laboratory;
  - a commitment to developing, implementing, and maintaining an effective QMS and continuously improving its effectiveness;
  - the laboratory management's commitment to compliance with the content of these guidelines;
  - a requirement that all personnel concerned have access to the management system documentation and related information applicable to their responsibilities and are aware of the requirements for implementation of the policies and procedures in their work;
- the structure of the laboratory (organizational chart or equivalent document);

- the operational and functional activities pertaining to quality so that the extent and the limits of the responsibilities are clearly defined;
- an outline of the structure of documentation used in the laboratory QMS;
- the general internal quality management procedures and standard operating procedures;
- the requirements of qualification, experience and competencies of personnel and the policy for initial and in-service training of staff;
- policies for:
  - internal and external audits;
  - implementing and verifying corrective and preventive actions;
  - dealing with complaints;
  - performing management reviews of the QMS;
  - selecting, establishing and approving analytical procedures;
  - handling atypical and out-of-specification results;
  - data governance;
  - the employment, handling and storage conditions of appropriate reference substances and reference materials;
  - participation in proficiency testing schemes and collaborative studies, as appropriate, for the assessment of performance (this requirement is optional for the QCL of a pharmaceutical manufacturer);
  - addressing risks and opportunities;
  - evaluation, selection, monitoring of performance and re-evaluation of select service providers and suppliers.

3.7 The quality manager should ensure the establishment, implementation and maintenance of standard operating procedures for all administrative and technical operations, including the following (numbers in parentheses refer to relevant subsections):

- personnel matters, including qualifications and training (5.1);
- control of documents, records and data integrity (3.3, 3.5 and 3.6);
- change control (3.4);
- corrective and preventive actions (3.7);
- internal audits (3.8);
- complaints (3.9);

- purchase and receipt of consignments of supplies (for example, reagents and materials) (4.1 and 5.4);
- procurement, preparation and control of reference substances and reference materials (5.5);
- qualification of equipment, including calibration (5.3);
- preventive maintenance and verification of instruments and equipment (5.3);
- internal labelling and storage of materials and solutions (5.4);
- sampling, if performed by the laboratory (6.1);
- testing of samples with descriptions of the methods and equipment used (6.5);
- validation and verification of analytical procedures (6.3);
- validity of test results (6.8);
- atypical and out-of-specification results (6.9);
- nonconforming work (6.11);
- risks and opportunities (4.4);
- cleaning of laboratory facilities, including bench tops, equipment, workstations, clean rooms (aseptic suites) and glassware (5.2);
- monitoring of environmental conditions (for example, temperature and humidity) (5.2);
- monitoring of storage conditions (5.2);
- disposal of reagents, standards and samples (5.2, 5.4, 6.2, 6.12 and 7).

3.8 The key elements of a qualification and validation programme of the laboratory should be clearly defined and documented in a validation master plan.

3.9 The activities of the laboratory should be systematically and periodically audited to verify compliance with the requirements of the QMS through internal (see subsection 3.8) and external audits.

3.3 Control of documentation

3.10 A master list identifying the current version and the distribution of documents should be established and be readily available, either electronically or on paper.

3.11 The procedures to control and review all documents (both internally generated and from external sources) should ensure that:

- each document, whether a technical or a quality document, has a unique identifier, version number and date of implementation;
- authorized standard operating procedures are readily accessible at the relevant locations, either electronically or physically;
- the documents are reviewed regularly and updated if required;
- any invalid document is removed and replaced with the authorized, revised document with immediate effect (either electronic or paper-based);
- a revised document includes references to the previous document;
- previous versions and invalid documents are retained in the archives (either electronic or paper-based) to ensure traceability of the content and the evolution of the procedures; any other existing copies are destroyed;
- all involved staff are trained on the new and revised standard operating procedures;
- all documentation, including records (either electronic or paper-based), is retained according to national legislation but for not less than five years.

3.12 Staff should be informed when new and revised procedures enter into force. The quality management system in place (see subsection 3.2) should ensure that:

- revised documents are prepared by the initiator (or a person who performs the same function), reviewed, and approved at the same level as the original document and subsequently released by the quality manager (or their team);
- staff acknowledge that they are aware of applicable changes and their implementation date by a signature (electronic or manual) or by an alternative mechanism.

3.13 Detailed recommendations are provided in the WHO guideline on data integrity (*4*) and should be implemented.

3.4 Change control

3.14 The laboratory should have a standard operating procedure to manage changes. Steps in the procedure should include the assessment of impact, gaps, risks and opportunities. Requests for changes should be reviewed and implemented only after approval by management. Records should be kept.

3.15 When changes are required, necessitated by, for example, improvement to current procedures or introduction of a new method or relevant procedure, or increase or decrease in workload, range of laboratory activities, or staffing levels, these should be approved and monitored by senior management.

3.16 If relevant, change processes should also be addressed as part of management review (see subsection 3.10), enabling monitoring by senior management.

3.17 The quality manager should ensure that changes are documented, assessed for impact, approved, planned, implemented and reviewed.

3.18 Staff should acknowledge by signature that they are aware of applicable changes and their date of implementation.

3.5 Control of records

3.19 Identification, collection, indexing, retrieval, storage, backup, access, maintenance and disposal of all quality and technical or scientific records (paper, electronic or hybrid) should be described in the applicable standard operating procedure.

3.20 All original observations, including calculations and derived data, calibration, validation, verification records and final results, should be retained according to national legislation or contractual agreements, but for not less than five years.

3.21 The records should include the data recorded in the analytical worksheet by the technician or analyst on consecutively numbered pages with references to the appendices containing the relevant recordings either on paper (for example, balance weighing records) or electronically (for example, chromatograms and spectra).

3.22 For the data recorded in forms or templates, a procedure should be in place to control the issuance of blank paper templates (or forms) for data recording with reconciliation and authenticity controls where required (*4*).

3.23 The records for each test should contain sufficient information to permit the tests to be repeated or the results to be recalculated, if necessary. The records should include the identity of the personnel involved in the sampling, preparation and testing of the samples.

3.24 The records of samples to be used in legal proceedings should be kept according to the applicable legal requirements.

3.25 A data and information management system ensuring traceability of operations, which is either paper based or software based – for example, a laboratory information management system (LIMS) – should be applied. Access to stored electronic data should be restricted to authorized personnel.

3.26 Samples tested in the laboratory should be retained for a shelf-life plus one year for a pharmaceutical product on the market and 15 years for an investigational product, unless national regulations are more stringent or contractual arrangements require otherwise.

3.27 All quality and technical or scientific records (including analytical test reports, certificates of analysis and analytical worksheets) should be legible, readily retrievable, stored and retained within a secure and suitable environment preventing damage, deterioration or loss.

3.28 The conditions under which all original records are stored should be such so as to ensure their security and confidentiality, and access to them should be restricted to authorized personnel. Electronic storage and signatures are employed but with restricted access and in conformance with requirements for electronic records (*4–12*).

3.29 Quality management records should include reports from internal and external audits, inspections and management reviews, risk assessment, and records of all complaints and their investigations and corrective and preventive actions.

3.6 Control of data

3.30 A master plan should be prepared for the validation of any information system used for the collection, processing, recording, reporting, storage or retrieval of data. Any validation report to demonstrate suitability for use should be prepared and verified by the quality manager or designated person for the task and available to the staff concerned after approval of the laboratory director or designated person. A standard operating procedure should be available that describes the use of a LIMS or a paper or electronic recording system, access rules, and the periodicity and type of backup, either cloud-based or on another server, including the restoration of data.

3.31 Commercial off-the-shelf software in general use within its designed application range can be considered to be sufficiently validated. When applicable, validation documentation should be available and readily retrievable, as for any analytical system.

3.32 The laboratory should authorize, document and validate any changes before implementation, which includes laboratory software configuration or modifications to commercial off-the-shelf software. Where applicable, a validation report should be available.

3.33 The information systems should be:

- protected from unauthorized access to ensure data integrity (that is, using individual access login and password);
- safeguarded against tampering and loss;
- operated in an environment that complies with provider or laboratory specifications;
- capable of recording system failures and the appropriate immediate and corrective actions.

3.34 The quality manager should ensure that for test data in computerized systems:

- electronic data are protected from unauthorized access, and an audit trail is enabled, maintained and periodically checked;
- computer software developed by the user is documented in sufficient detail and appropriately validated or verified as being suitable for use;
- computers and automated equipment are maintained so as to function properly and are provided with the environmental and operating conditions necessary to ensure the integrity of test data;
- electronic data are backed up at appropriate regular intervals, are retrievable and are stored suitably to prevent data loss.

3.35 Electronic forms, prepared from modifications to commercial off-the-shelf software (such as Microsoft Excel), should be duly validated and their validation should be described in a validation report (*12*).

3.36 When a LIMS is managed and maintained off site or through an external host, it should be ascertained that the host of the system complies with all applicable requirements of this document.

3.37 Further information (*4*) can be consulted. Further guidance on the validation of data-processing equipment can be found in other sources (*7*, *9*–*12*).

3.7 Corrective and preventive actions

3.38 Any deviation or nonconformity reported by any member of the staff or otherwise found should be investigated by conducting a root cause analysis with the analyst to identify the problem found and take appropriate action to rectify the nonconformity.

3.39 The laboratory should:

- identify the responsible persons for any action deemed necessary and establish timelines for implementation;
- review the effectiveness of any corrective action taken to eliminate the problem;
- evaluate any risks and opportunities that were identified;
- prepare a report to include evidence of the nature of the deviations, determined causes, any subsequent actions taken, and the results of any corrective action implemented, which should be recorded and retained.

3.40 A critical analysis of the deviations and nonconformities detected by the laboratory and their impact on the management system and the risks and opportunities identified by the laboratory should be performed on a regular basis (see subsection 3.10).

3.41 Any situation that may lead to a potential deviation or nonconformity should be adequately addressed, leading to preventive action. Preventive actions can be treated as a risk or as an opportunity, depending on the type of potential impact of the action (see subsection 4.4).

3.8 Internal audits

3.42 The quality manager is responsible for organizing internal audits addressing all relevant elements of the QMS, comprising the following actions: plan, establish, implement and maintain an audit programme including the frequency, methods and responsibilities, which also takes into consideration the importance of the laboratory activities concerned, changes affecting the laboratory and the results of previous audits.

3.43 A standard operating procedure should be established, incorporating a detailed procedure for the planning and performance of the audits, which will:

- ensure that internal audits are planned and scheduled periodically by the quality manager (at least once a year) to enable systematic assessments;

- define the scope of each audit and use risk-based criteria to determine the most critical activities to be audited, including the implementation of corrective and preventive actions after the last audit, if relevant;
- ensure that audits are carried out by trained personnel who are independent of the activity to be audited;
- ensure that the results of the audits (audit conclusion) are reported to relevant management, discussed during management review (see subsection 3.10), and communicated to staff;
- implement appropriate corrections and corrective actions without delay should any nonconformity be identified;
- monitor the effectiveness of the implemented corrective actions;
- retain records as evidence of the implementation of the audit programme and the audit results.

3.44 Laboratories may also be subject to audits by external auditors to assess their procedures and systems (for example, medicine inspectorate for manufacturers, peer review or ISO accreditation for NQCLs and other types of QCLs).

3.9 Complaints

3.45 The laboratory director should be aware of complaints received and ensure that the process for handling complaints is coordinated and comprises, as a minimum, the following:

- a description of the process for receiving, verifying, investigating and tracking a submitted complaint, and deciding what actions are to be taken in response;
- assurance that the appropriate action is taken within previously defined timelines to resolve the complaint, if needed;
- verification that the whole process is documented and fully traceable;
- informing the complainant of the outcome of the investigation performed, where possible and if requested.

3.46 Where possible, the process should include a member of the staff not directly related to the matter of the complaint. The quality manager should ensure that all the necessary information is collected, verified and recorded and inform the complainant of the outcome of the process, if the complainant's identity is available.

3.10 Management review

3.47 Laboratory management reviews should be convened at planned intervals (at least annually) to monitor the effectiveness of the management system.

3.48 Senior management consisting of, as a minimum, the responsible management board director, the laboratory director (or equivalent job title) and the quality manager should ensure that the decisions taken previously have had the expected impact on the laboratory's activities and resources. Additionally, planning for the following period should be undertaken to enable the continued suitability, adequacy and effectiveness of the laboratory QMS.

3.49 The outcomes of management reviews should be recorded, documenting all decisions and actions related to the effectiveness of the QMS, improvement of the laboratory activities, required resources and necessary improvements.

3.50 The records of the management review should also include information related to the following specific activities or items:

- suitability of policies and procedures;
- performance management (see subsection 4.3);
- status of actions from previous management reviews;
- changes in internal and external factors that have an impact on the laboratory;
- outcome of internal and external audits or inspections and any follow-up required to correct any deficiencies;
- changes in the laboratory activities (type, volume, range);
- adequacy of resources (human, financial, material);
- training programme;
- feedback from customers and staff;
- the outcome of complaints received;
- corrective and preventive actions;
- effectiveness of any implemented improvements;
- follow-up and monitoring of identified risks and opportunities;
- the results of external quality control (collaborative studies or proficiency tests) and any investigations carried out when doubtful or unsatisfactory results are obtained;
- results of trend analysis;
- atypical and out-of-specification results.

3.11 Improvement

3.51 The laboratory should identify and select opportunities for improvement and implement any necessary actions. These opportunities can be identified through a review of policies, procedures and objectives, audit and inspection results, corrective and preventive actions, risk assessment, management review, staff suggestions, and analysis of data, trends, and proficiency testing results.

3.52 The laboratory should request feedback from its customers, for instance, using customer satisfaction surveys, communication records and review of reports. This information should be used as an improvement tool.

4. Planning and strategic management

4.1 Externally provided services and supplies

4.1 The process for the selection and purchase of products (supplies) and services that the laboratory requires should be described, for example, measurement materials (including reference materials and certified reference materials), chemical and biological reference substances, equipment, reagents and services (for example, calibration, qualification, sampling, testing, maintenance, proficiency testing schemes, and assessment and auditing).

4.2 The laboratory should record:

- the review and approval of the laboratory's requirements for externally provided products and services;
- the definition of the criteria for evaluation, selection, and monitoring of performance and re-evaluation of the external providers;
- the evaluation of suppliers of critical products and services that affect the quality of testing, and listing of approved suppliers that have been demonstrated to be of suitable quality with respect to the requirements of the laboratory;
- any actions taken arising from evaluation, monitoring of performance and re evaluation of the external providers.

4.3 The laboratory should communicate its requirements to external providers for:

- the products and services to be provided and their acceptance criteria;

- competence (if applicable), including any required qualification of personnel;
- activities that the laboratory or its customer intends to perform at the external provider's premises.

4.4 The laboratory should prepare a master list of suitable external suppliers for the products and services considered to be essential.

4.2 Review of tenders and contracts

4.5 The procedure established by the laboratory (customer) for the review of requests, tenders and contracts should ensure that:

- the requirements are adequately defined and documented;
- the contract laboratory or a contracted organization has the capability and resources to meet the requirements;
- appropriate methods or procedures are selected, which are capable of meeting the requirements of the laboratory and suitable for the samples to be tested;
- the contracted laboratory informs the laboratory when the method requested is considered to be inappropriate or out of date and provides any clarification to the customer's request.

4.6 There should be a written contract that clearly establishes the duties and responsibilities of each party and defines the contracted work and any technical arrangements made in connection with it, which may include monitoring the contract laboratory's performance in relation to the work performed.

4.7 Any differences between the request or tender and the contract should be resolved before laboratory activities commence, and each contract should be acceptable to both the contracted laboratory and the customer. Deviations requested by the customer should not compromise the integrity of the contract laboratory or the validity of the results.

4.8 The customer should be informed of and agree to any deviation from the contract.

4.9 If there is a need for an amendment to the contract after the commencement of the work, the contract should be reviewed, and the affected personnel of the contract laboratory should be informed. Records of reviews should be retained.

4.10 Records of relevant discussions with a customer relating to the customer's requirements or the results of the contract laboratory activities should be retained.

4.11 When subcontracting is required:

- only organizations approved for the type of activity required should be addressed;
- the contract should allow the laboratory to audit the facilities and competencies of the contracted organization and ensure access by the laboratory to records and retained samples;
- the contracted laboratory should inform and gain approval from the customer about the specific activities to be performed;
- the contracted organization should not pass any work entrusted to it under contract to a third party without the laboratory's prior evaluation and approval of the arrangements.

4.12 The laboratory is responsible for periodically assessing the competence of any contracted organization.

4.13 The laboratory should maintain a register of all subcontractors used, with records of the assessment of their competences.

4.14 The laboratory takes responsibility for all results reported, including those supplied by the subcontracting organization.

4.3 Performance management

4.15 The laboratory management review should set objectives, performance indicators and measurable targets for its activities for a specific time frame, which should be monitored regularly and, if necessary, appropriate actions taken. The objectives should be SMART: specific, measurable, achievable, relevant, and time bound. Some examples of performance indicators are the number of products tested versus the number of products planned to be tested, the percentage of complaints resolved within the given time frame, or the percentage of analytical test reports issued within a specific time frame.

4.16 If the laboratory is part of an organization, such as an NMRA, the objectives and targets should be fully aligned with the mission, vision and strategic goals of the organization and should be translated into operational plans and individual staff objectives, which should be monitored.

4.17 The laboratory should monitor the technical performance regularly with regard to the following:

- the competence of personnel (see subsection 5.1);
- the validity of test results (see subsection 6.8), in particular, the regular assessment of performance related to participation in a proficiency test scheme;
- nonconforming work (see subsection 6.11) and its impact in terms of risk management.

4.4 Quality risk management

4.18 The laboratory should have a formal, well established approach to risk management involving the identification, assessment, treatment, prioritization, continuous monitoring and review of risks. It should consider the potential impact of all types of risks associated with processes, activities, stakeholders, products and services, and should define procedures and methodologies to minimize, monitor and control the probability or impact of unfortunate and undesired events and potential failures (*13*).

4.19 Two primary principles of quality risk management are:

- the evaluation of the risk to quality should be based on scientific knowledge and, ultimately, link to the protection of the patient;
- the level of effort, formality and documentation of the quality risk management process should be commensurate with the level of risk.

4.20 The laboratory should establish, whenever possible and if applicable, an interdisciplinary team led by the quality manager, including experts from different areas, to coordinate, facilitate and improve science-based decision-making with respect to risks – whether they be general risks for the laboratory or risks related to analytical testing. Possible steps to initiate and plan a quality risk management process may include:

- defining the risk (or opportunity), including the potential cause of the event identified;
- assembling background information on the potential impact (positive or negative, or opportunity);
- specifying a timeline, deliverables and an appropriate level of decision-making for the risk management process.

4.21 The laboratory should plan:

- actions to address the risks and opportunities identified, which should be appropriate to the potential impact on the validity of laboratory results or any laboratory activities (this can include

identifying and avoiding threats, eliminating the risk source, changing the likelihood of losses or consequences, adopting new practices, or using new technologies);

- how to integrate and implement these actions into its management system;
- how to evaluate the effectiveness of these actions.

4.22 The process of identification and treatment of risks and opportunities should be recorded, monitored and duly reviewed on a regular basis by senior management during management review (see subsection 3.10).

4.23 The risks and opportunities identified and monitored should be sufficiently communicated to staff.

4.5 Crisis management

4.24 Specific concerns relate to ensuring the correct and efficient functioning of the laboratory at all times, which depends on suitable planning and budgeting to obtain the necessary resources (maintenance of infrastructure and energy supply, as well as securing the continuity of laboratory activities). Business continuity planning allows the laboratory to take effective measures when issues or incidents arise, enabling management of those issues and providing continuity of business. Thus, key functions of the business, in particular key public health functions, can be fully recovered in the shortest possible time at acceptable costs.

4.25 The laboratory should establish and document a system of prevention and recovery in the event of an unplanned disruption to service, which guarantees employees' security and allows the continuation of work.

4.26 The established system or plan should be preventive and defined in advance, so that business processes, assets, and personnel are protected and able to regain functional competency quickly in the event of a significant disruption, such as a natural disaster (fire, flood or weather-related events), a cyberattack or a pandemic. The documented recovery plan should include the following:

- inputs from key stakeholders and personnel;
- the definition of critical activities, which will determine key resources, such as information technology (IT), infrastructure and key personnel;
- the performance of a risk analysis to establish any risk that can affect the laboratory's activities and the impact of those risks;

- implementation of measures to mitigate risks and recover activities that are identified as critical to the organization, which should be tested for efficacy and reviewed periodically to ensure that the risk analysis is up to date;
- where possible, the definition of a continuity team of adequately trained members, responsible for establishing and implementing appropriate planning and recovery strategies, and, when necessary, adapting these strategies to changing circumstances.

4.27 Recovery strategies for IT should be developed, such as implementing manual workflows so that the activities will continue while computer systems are being restored. An IT disaster recovery plan should be defined.

4.28 The laboratory should test the business continuity plan established, for example by simulation, to confirm its suitability for the intended purpose. Evidence of the testing of the business continuity plan should be maintained.

4.29 Other departments within the organization (if applicable) and stakeholders should be informed whenever a situation capable of presenting a risk to public health occurs, and should be apprised of the remedial actions taken.

4.6 Communication management

4.30 The laboratory should ensure that staff and stakeholders are informed and aware of the results of performance monitoring, either from management review (see subsection 3.10) or from other monitoring tools (see subsection 4.3).

4.31 A laboratory that is part of an organization, such as an NMRA or manufacturing company, should have communication channels with other parts of the organization that are defined and established to facilitate decision-making processes and other relevant processes.

5. Resources

5.1 Personnel

5.1 Personnel with the necessary education, training, technical knowledge and experience for their assigned functions should be employed either permanently or under contract. The competence requirements for personnel for each function should be documented. The laboratory should have procedures and criteria for selecting and assessing the competence of the personnel in accordance with the QMS.

5.2 Job descriptions should be in place for all personnel involved in tests and other laboratory activities, for example, calibration, validation, verification, qualification and maintenance. The laboratory should maintain records of the competencies of the personnel, including their education, qualification, training and experience.

5.3 The laboratory should have the following managerial and technical personnel:

- A laboratory director (or manager or head of the laboratory, or an appropriate job title) with appropriate qualifications (university degree in an appropriate discipline) for the position, with experience in a supervisory role in pharmaceutical analysis in a quality control laboratory, in the regulatory sector or in industry, who assumes full responsibility for all operations, including analytical, organizational, administrative and educational. This person is also responsible for ensuring that:
  - members of the laboratory staff have the competencies and qualifications appropriate to their required functions and their grades reflect their responsibilities;
  - the adequacy of existing training procedures for staff is reviewed periodically;
  - the technical management is adequately supervised;
  - the certificates of analysis, analytical test reports and other important reports and protocols are approved.

  The laboratory director should preferably be supported and complemented by one or more technical managers (or senior analysts) with extensive experience in pharmaceutical analysis in a quality control laboratory, who have been designated responsibility for the analytical operations and for direct management and supervision of the team of analysts and technicians.
- A quality manager who shall have the responsibility and authority to implement and ensure compliance with the QMS and quality control activities. The quality manager should remain independent of routine laboratory analytical activities, depending on the size of the laboratory. The quality manager organizes internal audits of various laboratory activities, with the participation, preferably, of another member of staff from another section, according to a schedule approved during the management review. The quality manager, with the support of technical managers whenever necessary, ensures that:

- personnel operating specific equipment, instruments or other devices are competent for the tasks they are performing;
- personnel involved in tests or calibrations, validations or verifications are competent for the tasks they are performing;
- regular in-service training programmes are arranged to update and extend the skills of both analysts and technicians;
- the laboratory participates regularly in suitable proficiency testing schemes and, whenever possible, collaborative studies (as applicable);
- due arrangements are made for the safekeeping and control of substances that are subject to poison regulation or to the controls applied to narcotic, psychotropic and radioactive substances, and which should be stored under lock and key, and handled and used in designated places under the supervision of an authorized person.

- Qualified analysts, who normally should be graduates in pharmacy, analytical chemistry or other relevant subject, with the requisite knowledge, skills and ability to adequately perform the tasks assigned to them by managers or supervisors. Appropriately qualified and experienced analysts with a thorough understanding of the management system, including the review, interpretation and reporting of test results, the maintenance of an internal chain of custody, and proper implementation of corrective and preventive actions in response to analytical problems, should also be available to serve as laboratory supervisors.
- Technicians should hold diplomas in their subjects awarded by technical or vocational schools or have the requisite hands-on experience to perform the assigned activities.

5.4 Staff undergoing training should be appropriately supervised and assessed upon completion of the training. This assessment should be fully documented.

5.5 The laboratory director or designated person should authorize personnel to perform specific laboratory activities. Only sufficiently qualified and trained personnel should be allowed to perform specific laboratory activities.

5.6 The laboratory should have procedures and criteria for the continuous assessment of personnel competence, which should be documented.

5.7 The laboratory should provide training or requalification of personnel, as appropriate.

5.8 The laboratory should maintain a list or matrix of the competencies of each staff member, documented procedures, and criteria for the continuous assessment of personnel competencies, which may include:

- performance of specific tests (such as pH, density and dissolution);
- verification and review of results;
- performance of analytical equipment qualification;
- preparation and management of laboratory solutions;
- preparation of standard operating procedures (at the request of the quality manager).

5.9 The laboratory director, or designated person, is responsible for:

- the consignment of samples to specific units;
- approval of analytical test reports and certificates of analysis.

5.10 Any designated qualified personnel are responsible for:

- review of all analytical data to ensure the validity of the test results by checking the work performed and results obtained by the technician or analyst;
- general technical activities that, by definition, are performed by the technical management, such as the review of technical documents (for example, analytical test reports and certificates of analysis), as long as this activity is delegated;
- the implementation and execution of specific tests or analytical techniques requiring advanced technical training and knowledge, including verifying and reviewing raw data and analytical worksheets.

5.11 The laboratory should have an appropriate training schedule for staff, particularly for those staff who respond to the technical and managerial needs of the laboratory. Inputs to the training plan can be gathered from internal audits, management reviews, risk and opportunity assessments, or other available options. On successful completion of training, the results of evaluation should be recorded and made available, and the information should be added to the competency matrix or master list.

5.2 Premises

5.12 The requirements for facilities intended for laboratory activities should be documented and should be of a suitable size, construction and location.

5.13 Premises should adequately accommodate the features required of a pharmaceutical testing laboratory and should minimize the risk to the health of staff and the quality of the analytical results. Emergency exits should be available.

5.14 Appropriate entrance and sample reception areas must be provided for staff, visitors and samples.

5.15 Rest and refreshment rooms and toilets should be separate from laboratory areas.

5.16 Changing areas should be easily accessible and appropriate for the number of users.

5.17 The laboratory storage facilities should be organized for the correct storage of samples, reagents and equipment. Separate storage facilities should be maintained for the secure storage of samples, retained samples, reagents, laboratory accessories, and reference substances or materials. In general, storage facilities should ensure the following criteria are met.

- Storage facilities should be appropriate to store samples and reagents at the appropriate temperature and humidity conditions to maintain stability, if necessary, under refrigeration (2–8 °C) and frozen (–20 °C) conditions, or other necessary storage conditions, and be securely locked.
- Reagents, reference substances and samples subject to poison regulations or to the controls applied to narcotic and psychotropic substances should be clearly marked and be kept separately in locked cabinets in accordance with national legislation. A designated responsible member of staff should have responsibility for their safekeeping, maintaining a register of these substances, and controlling their use.
- The head of each unit should accept personal responsibility for the safekeeping of any of these controlled reagents or other controlled substances kept in the workplace. All specified storage conditions should be controlled and monitored, and records maintained. Access should be restricted to designated personnel.
- The appropriate safety procedures should be rigorously implemented wherever toxic or flammable reagents are stored or used.

- The laboratory should provide appropriate separate storage rooms for storing flammable substances, fuming and concentrated acids and bases, volatile amines, peroxide-forming reagents, and self-igniting materials, such as metallic sodium and potassium.
- Small stocks of acids, bases and solvents may be kept in the laboratory.
- Gases can come from installed generators or external gas tanks stored outdoors in a well ventilated area, preferably isolated from the main building. Wherever possible, gas bottles are to be avoided in the laboratory. If gas bottles are present in the laboratory, they should be firmly and safely secured. However, it is recommended that gas generators be installed.

5.18 The laboratory should be equipped with adequate instruments and equipment, including workbenches, workstations and fume hoods. Separate instrument rooms for different measurement techniques should be available as required for method performance or to avoid contamination. There should be adequate safety equipment appropriately located, and measures should be in place to ensure good housekeeping and cleaning routines.

5.19 Weighing areas should be located where adequate environmental conditions of temperature and humidity are controlled.

5.20 Where necessary, the preparation and analysis of cytotoxic and genotoxic substances should be performed in a room equipped with, for example, an isolator and laminar flow workbench to handle, weigh, and manipulate cytotoxic and genotoxic (and highly toxic) substances. Appropriate procedures should be in place to avoid exposure and contamination of the staff, such as the use of gowns, suitable particle masks, goggles and protective gloves.

5.21 Archive facilities should be provided to ensure the secure storage and retrieval of all documents. The design and condition of the archives should be such as to protect the contents from deterioration.

- Records should be kept in a secure room with access restricted to authorized personnel.
- Electronic records should be retained, and duplicate copies should be retained in an external facility, for example, saved to an external server or cloud.

5.22 The environmental conditions, including lighting, energy sources, temperature, humidity and air pressure, should be appropriate to the

functions and operations to be performed in the various locations. The specific conditions requiring control and monitoring should be based on the needs of the activity. The laboratory should ensure that the relevant environmental conditions are monitored, controlled and documented.

5.23 Procedures should be in place for the safe removal of types of waste, conforming to the local environmental standards, including toxic waste (chemical and biological), reagents, samples, solvents and air filters.

5.3 Equipment, instruments and other devices

5.24 The laboratory should have the required apparatus, equipment, instruments or instrument system used in pharmacopoeial analyses (analytical equipment) for the correct performance of the tests and related activities.

5.25 A list of equipment considered by the Expert Committee to be adequate, for either a first-stage or medium-sized pharmaceutical quality control laboratory, is provided in Appendix 1.

5.26 All equipment and their modules and accessories must be uniquely identified, including:

- the manufacturer's name, instrument name, model and serial number;
- any identifying number allocated by the laboratory;
- the location, where appropriate;
- the equipment manufacturer's instructions, if available, or an indication of their location;
- the version and due date for requalification of any computer hardware, firmware and software.

5.27 All analytical equipment should be fit for its intended purpose, which is demonstrated by equipment qualification (EQ), which encompasses design qualification (DQ), installation qualification (IQ), operational qualification (OQ), and performance qualification (PQ).

5.28 All four stages will apply to the purchase of new equipment. Aspects of DQ and IQ may need to be repeated following major changes (see subsection 3.4). PQ aspects of OQ should be carried out throughout the entire life cycle of the equipment.

5.29 EQ must comply primarily with pharmacopoeial requirements and should address the intended purpose, and should follow the manufacturer's recommendations.

5.30 The laboratory is ultimately responsible for EQ. For complex equipment, the laboratory may use a specialized service.

5.31 The laboratory should ensure that the EQ process meets compliance requirements and that qualification processes are being followed and supported by complete, valid and documented data.

5.32 In the equipment purchasing phase, the laboratory should compile a user requirement specification document for each piece of equipment and specify in it that the supplier of the equipment provides documents, tools and services to support EQ – in particular, to provide clear instructions and details of tests required to demonstrate satisfactory performance, either performed by the laboratory or by the supplier or other external service provider. The laboratory should maintain oversight of such testing, ensuring that the qualification protocols are followed and supported by data, fully complete and documented. The laboratory should also ensure that the supplier or an external service provider delivers the necessary training, maintenance, repair and installation support.

5.33 The laboratory should establish a policy for when equipment should be serviced (that is, subject to maintenance, calibration and qualification). The following must be clearly described for each type of analytical equipment in use:

- the regularity of any service
- the events after which service is necessary.

5.34 An EQ plan or matrix should be available to allow a clear overview of which equipment undergoes any intervention, when the intervention will take place, and whether or not it is performed by staff or by an external service provider. The laboratory should keep track of the interventions that were performed and when they were performed in case there is a significant deviation from the established schedule (see subsection 3.7).

5.35 A preventive maintenance schedule should be established in an equipment qualification and maintenance plan. Activities under the plan can be performed by the laboratory or entrusted to a competent organization and should be followed by appropriate EQ tests.

5.36 All analytical equipment requiring qualification, calibration or maintenance should be labelled, coded or otherwise identified to indicate the status and the date when the applicable action is scheduled.

5.37 All calibrations or equipment qualifications should be (where relevant and possible) traceable to an appropriate reference, for example, certified reference materials, or to the relevant national or international standards, such as the International System of Units (SI).

5.38 The laboratory should ensure a change control process to guide the assessment, execution, documentation and approval of any changes to the analytical equipment. Designated qualified personnel should assess the effects of any changes to determine if any requalification activities are required.

5.39 Typical changes, after which analytical equipment should undergo the appropriate requalification, are:

- movement or relocation of the equipment;
- interruption to services or utilities;
- repair or maintenance (including preventive);
- modifications;
- change of purpose or use;
- suspect analytical results that, after a suitable investigation, indicate that an analytical instrument employed does not meet EQ requirements.

5.40 Analytical equipment shown to be defective or out of the specified limits should be taken out of service and clearly labelled or marked. It should not be used until it has been repaired and requalified.

5.41 Each stage of the qualification process involves:

- the preparation of a qualification plan defining the scope of qualification (for example, the tests to be performed with their acceptance criteria, which can be combined with the qualification protocol);
- the implementation of the plan to ensure that the results of the tests are recorded as the tests are performed;
- the issuance of a report (and, if required, a certificate) in which the results of EQ are documented.

5.42 Specific standard operating procedures for the maintenance and qualification of analytical equipment performed regularly should be established. The personnel responsible for each operation with analytical equipment (authorized) must be clearly defined.

5.43 Documentation covering EQ should satisfy at least the following requirements:

- define clearly the responsible persons to perform the required tests for maintenance, calibration and EQ;
- provide details of each check and test to be performed, the specification and acceptance criteria;
- provide sufficient information on the procedures and materials required to perform each check and test;
- state the date on which the EQ test was performed and the result of qualification for each check or test;
- state the reason for performing qualification (for example, following the installation of new equipment, following routine service, or following equipment malfunction);
- provide clear information about the action to be taken in the event of test or qualification failure;
- state the circumstances that may or will necessitate requalification of the equipment (for example, following repair, service or recalibration);
- provide the name and signature of the person (or persons) who actually performed the tests, and the name and signature of the quality manager or designated qualified personnel authorizing the completion of a qualification.

5.44 Equipment logbooks should be maintained to:

- identify the individual modules and accessories that constitute the equipment;
- record the overall history of the equipment (including the initial qualification and entry into service);
- include dates of when subsequent maintenance, calibration and qualification have been performed and when these are next scheduled.

5.45 The software used by the laboratory must be appropriately validated, preferably at the time of development; otherwise, if the laboratory is unable to control the development of the software, a software validation certificate from the manufacturer, ensuring compliance with the requirements of the pharmaceutical sector, should be acceptable.

5.46 The level of software validation is determined by its function. It is customary to distinguish between firmware levels (lack of user access) and software used for equipment control, data acquisition and processing.

- Further guidance on qualification of equipment is available in the literature (*6*, *14–17*).

5.4 Reagents and materials

5.47 Reagents and chemicals, including solvents and materials used in tests and assays, should be of appropriate quality and suitable for the intended use.

5.48 Commercial reagents should be obtained from verified and approved qualified providers.

5.49 Reagents from external providers should be accompanied by the certificate of analysis and the safety data sheet, if required.

5.50 Management of the reagents must cover the entire life cycle of the reagents from purchasing and preparation (in the case of preparations) to use and disposal, and should be covered by a standard operating procedure.

5.51 The following major points should be considered in the life cycle of reagents:

- type of reagents and the quality, depending on their use;
- selection of the supplier;
- verification of reagents upon receipt;
- labelling of the reagent (avoiding misuse or misidentification);
- storage conditions;
- ensuring that the reagent is not compromised in any way before being used;
- checking the expiry dates of reagents before use (it is not necessary to document this verification);
- documenting the use of reagents used in analyses, ensuring traceability at least to batch number and expiry date;
- disposal of the reagent.

5.52 The verification should comprise an administrative part (a documented check of the invoice, delivery note, and the integrity of the container, including storage temperature) and a scientific part (a documented check of the actual quality of the reagent given on the label or certificate against the requested quality). Specific in house testing may be required for some reagents.

5.53 For reagents purchased in their original container and purchased reagents that have been transferred into another container, the verification on receipt should be made.

5.54 The level of detail of the verification should be determined by the laboratory, unless otherwise stated.

5.55 The labelling information for all types of reagents should be stated on the container or in a leaflet, register or LIMS (or equivalent), which should include the following:

- name of the substance or reagent;
- date of receipt and date of opening of the container (or preparation date);
- expiry date (or retest date, as justified);
- storage conditions and, if applicable, any specific protection measures (such as protection from heat, light or atmosphere);
- concentration or purity of the reagent, if applicable;
- hazard and precaution codes.

5.56 For purchased reagents in their original container, the following additional information is expected on the label:

- manufacturer, supplier, brand and reference of the substance;
- batch number;
- identification: where the same batch is supplied in several containers, appropriate identification (for example, vial 1, 2, 3) can be indicated in the labels;
- name or initials of the person who opened it.

5.57 For purchased reagents that have been transferred into another container, the following additional information is expected on the label:

- name or initials of the person who transferred the reagent;
- batch number;
- transfer date;
- identification – in cases of transfer to several vials (aliquoted), appropriate identification (for example, vial 1, 2, 3) should be indicated in the labels.

5.58 In-house reagents (preparation of reagent solutions in the laboratory) should have the following labelling:

- name or initials of the person who prepared the reagent;
- date of preparation and validity period;
- name, reference, batch number and quantity of the reagents in the preparation (can be replaced by a reference, for example a project number);
- titre (or concentration or standardization factor);
- date of the determination of the titre and validity period, based on risk management and sound scientific principles;
- name or initials of the person who determined the titre.

5.59 For water manufactured by the laboratory, the following labelling is expected:

- name or initials of the person who dispensed the water and date of dispensing;
- if more than one production apparatus is available, the identity of the apparatus used must be documented.

5.60 For volumetric solutions, the following labelling is expected:

- name or initials of the person who prepared the reagent;
- date of preparation and validity period;
- name of the reagents in the preparation;
- titre (or concentration or standardization factor);
- date of the determination of the titre and validity period, based on risk management and sound scientific principles;
- name or initials of the person who determined the titre.

5.61 For the preparation of reagent solutions in the laboratory:

- responsibility for this task should be clearly stated in the qualification matrix or in the job description of the assigned staff member;
- standard operating procedures should be used that cover the entire life cycle of the use of reagents in the laboratory and are in accordance with published pharmacopoeial or other appropriate standards (*18*);
- records should be kept of the preparation of reagent solutions and standardization of volumetric solutions.

5.62 For the transportation and subdivision of reagents:

- whenever possible, they should be transported in the original containers;
- when subdivision is necessary, suitable clean containers should be used and appropriately labelled.

5.63 All reagent containers should be visually inspected to ensure that the seals are intact, both when they are delivered to the store and when they are distributed to the units. Containers that appear to have been tampered with should be rejected.

5.64 The appropriate grade of water for a specific test should be used as described by the pharmacopoeias or in an approved test.

5.65 The quality of the water should be verified regularly to ensure that the required grade of water complies with the appropriate specification.

5.66 Reagents should be stored under the appropriate storage conditions (temperature, ventilation, fire hazard) and appropriately maintained (organized, tidy, segregated).

5.67 A designated staff member trained in safe handling of chemicals should be responsible for the storage facilities and their inventory, and for noting the expiry date of chemicals and reagents (*18*).

5.68 The expiry period policy must be documented by the laboratory (as part of standard operating procedures).

5.69 The expiry date (before opening) given by the manufacturer must be considered valid. In the following cases, the laboratory shall determine a suitable expiry date, and a justification for assigning a new expiry date shall be documented:

- no expiry data is provided by the supplier;
- when, after opening or transfer, environmental conditions (such as air or humidity) or further operations (such as dissolving a lyophilized material) affect the quality of the reagent.

5.70 The expiry date can be prolonged by providing scientifically sound and documented justifications, for example in cases where expired reagents can be used for a special purpose. In this case, the container must be relabelled appropriately.

5.71 Reagents should be disposed of appropriately when the expiry date is exceeded or when they are no longer required.

5.72 Disposal may be done at defined intervals or when the expiry date is checked prior to potential use, as applicable.

5.73 Reagents must be disposed of appropriately, safely and in compliance with legal requirements.

5.5 Reference substances and reference materials

5.74 Reference substances are necessary to ensure adequate quality control of pharmaceutical products.

5.75 Pharmacopoeial reference substances should be employed when available and appropriate for the analysis. Otherwise:

- An NQCL should use reference substances from a reputable commercial source or supplied by the manufacturer of the pharmaceutical product approved by the national medicines licensing authority (19) and used for the testing of a sample. The use of secondary reference substances by an NQCL is discouraged when primary reference substances are available and suitable for the intended use.
- The manufacturer's laboratory should establish primary reference substances. It can establish secondary (working) reference substances traceable to primary reference substances for use in routine analyses, provided that metrological traceability is ensured for the property value concerned. Pharmacopoeial reference substances are considered primary reference substances against which secondary (working) reference substances can be calibrated.

5.76 A nominated staff member should be responsible for the control of reference substances and reference materials.

5.77 An identification number should be assigned to all reference substances and reference materials. The laboratory may exclude pharmacopoeial reference substances from this identification system, as they are fully traceable by their pharmacopoeial reference number and batch or lot number.

- A new identification number should be assigned to each new batch.
- This number should be marked on each vial of the reference substance.
- The identification number, along with the validity statement, should be quoted in the analytical worksheet each time the reference substance is used.

5.78 A register for all reference substances and reference materials should be maintained and contain the following information:

- the identification number of the substance or material;
- a precise description of the substance or material;
- the source;
- the date of receipt;
- the batch designation or other identification code;
- the intended use of the reference substance or reference material;
- the location of storage in the laboratory and any special storage conditions;
- any further necessary information (such as the results of visual inspections);
- expiry date or retest date (if applicable), and valid use-by date;
- a certificate or leaflet of a pharmacopoeial reference substance and a certified reference material that indicates the use, the assigned content, if applicable, and its status (validity);
- in the case of secondary reference substances or certified reference material, the certificate of calibration or analysis;
- a file (paper-based or electronic) should be kept in which all information on the properties of each reference substance is entered, including the safety data sheets.

5.79 The intended use, expiry date or retest date of reference substances and reference materials used in the laboratory should be confirmed before use, and the corresponding information should be included in the test report. The use of the pharmacopoeial reference substance for purposes other than those specified in the pharmacopoeia is discouraged and is at the user's discretion, based on a risk assessment.

5.80 Reference substances prepared and stored in the laboratory should be retested at regular intervals to ensure that deterioration has not occurred. The interval for retesting depends on a number of factors, including the stability of the substance, storage conditions, type of container (for single or multiple uses) and the frequency of opening the container. If a non-compliant result is obtained on retesting a reference substance, a retrospective check of the tests performed using that reference substance should be carried out. For the evaluation of outcomes of retrospective checks and consideration of possible corrective actions, a risk analysis should be applied.

5.81 More detailed information on the handling, storage and retesting of reference substances established by the laboratory is given in the WHO *General guidelines for the establishment, maintenance and distribution of chemical reference substances* (*19*).

6. Technical activities

6.1 Sampling

6.1 If the laboratory is responsible for the sampling of pharmaceutical products for subsequent testing, a standard operating procedure should be established to include both a recognized sampling plan to ensure that a representative sample is obtained and measures to ensure that the chain of custody is effective.

6.2 The laboratory should have a sampling plan when it carries out sampling of substances, materials or products for subsequent testing or calibration. The sampling method should address the factors to be controlled to ensure the validity of subsequent testing or calibration results. The sampling plan and method shall be available at the site where sampling is undertaken. Sampling plans should, whenever reasonable, be based on appropriate statistical methods.

6.3 The laboratory shall retain records of sampling data that form part of the testing that is undertaken. These records shall include, where relevant:

- reference to the sampling method used;
- date and time of sampling;
- data to identify and describe the sample (for example, amount, name, number, and correspondence to container from which it was taken, when applicable);
- identification of the personnel performing sampling;
- identification of the tools used for sampling;
- environmental or transport conditions;
- diagrams or other equivalent means to identify the sampling location, when appropriate;
- deviations from, additions to or exclusions from the sampling method and sampling plan.

6.4 Further information is provided in *WHO guidelines for sampling of pharmaceutical products and related materials* (*20*) and *WHO guidance on testing of "suspect" falsified medicines* (*21*).

6.2 Incoming samples

6.5 Paragraphs 6.6 and 6.7 are applicable to NQCLs. The principle of the four W's (who, what, when and where) should be applied. The chain of custody of each sample should be recorded.

6.6 Samples received by a laboratory may be for compliance testing or investigative testing.

- Samples for compliance testing include routine samples for control or samples submitted in connection with a marketing authorization process. Close collaboration with the providers of the samples is important. In particular, the quantity or amount of a sample should be sufficient to enable, if required, a number of replicate tests to be carried out and for part of the sample to be retained.
- Samples for investigative testing comprise suspicious, illegal, falsified or suspected substandard pharmaceutical products (*21*). Well documented screening procedures should be in place, as well as confirmatory analytical procedures to verify the identity of the substance or the ingredients. If an estimation of the content of an identified ingredient is required, then an appropriate quantitative analytical procedure should be applied. The value obtained may be reported with an indication of the uncertainty of measurement, if required, especially in the case of borderline test results.

6.7 It is common for a sample to be divided into three approximately equal portions for submission to the laboratory: one for immediate testing, the second for confirmation of testing, and the third for retention in case of dispute. It is important to ensure that the sample is large enough to enable, if required, a number of replicate tests to be carried out, and to ensure that, if there is a need for microbiological testing, a separate container for testing is provided.

6.8 A standard test request form should be completed for each sample submitted to the laboratory. In the case of a pharmaceutical manufacturer's laboratory, the requirements may be given in the master production instructions.

6.9 The test request form should contain the following information:

- the name of the person or institution that provided the sample and the date of receipt;
- the source of the material;
- a full description of the sample, including stated composition, international nonproprietary name and brand names (if available and whenever relevant);

- the package and container;
- dosage form and concentration or strength, the manufacturer's name, and the batch or lot number (if available);
- the size of the sample;
- the reason for requesting the analysis;
- the date of sampling;
- the size of the consignment from which it was taken (if appropriate);
- the expiry date or retest date, if known;
- reference documents and the specifications to be used for testing;
- a record of any further comments (for example, discrepancies found or associated hazard);
- the required storage conditions.

6.10 The laboratory should review the test request to ensure that:

- the sample amount is sufficient for the tests requested;
- the laboratory has the required capability and resources to perform the appropriate analytical tests, as previously defined;
- the appropriate tests or methods available are capable of meeting customers' requirements.

6.11 Any issue should be resolved with the originator of the request for analysis before testing starts, and a record of the review should be retained. If the laboratory is responsible for deciding which samples are to be tested, the test request form should be adapted accordingly.

6.12 Each sample and accompanying documentation (for example, the test request) should be assigned a unique registration number. Separate numbers should be assigned to requests referring to two or more medicines, different dosage forms, different batches of the same medicine, or different sources of the same batch.

6.13 A label bearing the unique registration number should be affixed to each container of the sample. Care should be taken to avoid masking any other markings or inscriptions.

6.14 A register should be kept in which the following information is recorded:

- the registration number of the sample;
- the date of receipt;
- the specific unit or units to which the sample is to be forwarded for analysis.

6.15 The sample received should be visually inspected by laboratory staff to ensure that the labelling conforms with the information contained in the test request. The findings should be recorded, dated and signed. If discrepancies are found, or if the sample is obviously damaged, this should be recorded without delay on the test request form. Any queries should be immediately referred back to the provider of the sample.

6.16 The sample prior to testing, the retained sample and any portions of the sample remaining after the performance of all the required tests should be retained and stored appropriately.

6.17 The specific unit to which the sample is sent for testing is determined by the laboratory director (or designated person).

6.18 A request for analysis may be accepted verbally only in emergencies. All details should immediately be placed on record pending the receipt of written confirmation.

6.19 Unless a computerized system is used, copies or duplicates of all documentation should accompany each numbered sample when sent to the specific unit in order to verify the identification, origin and purpose of the sample for receipt and testing activities, as well as any relevant additional information.

6.20 Testing should be performed as described in subsection 6.5.

6.3 Selection, validation and verification of analytical procedures

6.21 The analytical procedures to be used for testing – either compliance testing or investigative testing – should be selected by the laboratory prior to the start of the analysis.

6.22 All analytical procedures employed for testing should be suitable for the intended use. When a non-pharmacopeial substance or product is to be analysed, it is preferable to apply the approved methods of the manufacturer; otherwise, validation of the method to be employed should be undertaken (*6*), which also serves to establish acceptance criteria for the system suitability tests that are subsequently employed for the verification of the analytical procedure before analysis.

6.23 For investigative testing, well documented screening procedures should be in place, as well as confirmatory analytical procedures to verify the identity of the substance or the ingredients. If an estimation of the content of an identified ingredient is required, then an appropriate quantitative analytical procedure should be applied. The value obtained should be reported with

an indication of the uncertainty of measurement, if required, especially in the case of borderline test results.

6.24 Validation should be performed according to an approved validation protocol, which includes analytical performance characteristics to be verified for various types of analytical procedures. Typical characteristics that should be considered are listed in Table A4.1 (in the development phase of an analytical procedure, robustness, such as the ability of the procedure to provide results of acceptable accuracy and precision under a variety of conditions, should also be considered). The results are to be documented in the validation report. Some large-scale pharmaceutical manufacturers control the production of products by applying real-time release testing on the production site, using process analytical technology. Such technology must be validated to ensure that the product meets the specification throughout the production cycle and has been approved by the relevant licensing authority.

Table A4.1
Characteristics to be considered during validation of analytical procedures

Type of analytical procedure	Identification	Testing for impurities		Assay
Characteristics		Quantitative tests	Limit tests	dissolution (measurement only) content/potency
Accuracy	–	+	–	+
Precision				+
Repeatability	–	+	–	+
Intermediate	–	+[a]	–	+
Precision				+
Specificity	+	+	+	+
Detection limit	–	–[b]	+	–
Quantitation limit	–	+	–	–
Linearity	–	+	–	+
Range	–	+	–	+

– Characteristic is normally not evaluated; + characteristic should normally be evaluated.

[a] In cases where a reproducibility study has been performed, intermediate precision is not needed.

[b] May be needed in some cases.

6.25 Pharmacopoeial procedures and those approved by the licensing authority can be considered as validated for the use described in the monograph. If validation is not required, method verification should be performed according to an approved protocol or procedure to demonstrate that the laboratory can successfully execute the method and that the pharmacopoeial procedure used is suitable for the sample being tested. The laboratory should, in particular, confirm that:

- for a finished pharmaceutical product, no interferences arise from the excipients present;
- for an active pharmaceutical ingredient (API), impurities coming from the route of synthesis are adequately differentiated;
- the system suitability requirements are fulfilled;
- the reporting threshold for related substances is met;
- the accuracy and the precision of the procedure are within predefined limits.

6.26 If the pharmacopoeial method is adapted for a new purpose other than the purpose described in the pharmacopoeia, it should be validated for such a use. Similarly, the sample preparation process must be critically assessed for the need for validation.

6.27 System suitability tests should be performed prior to and throughout the analysis of samples to ensure that the complete analytical system (including instrument, reagents, columns and analysts) is continuously suitable for the intended application.

6.28 Verification is not required for basic pharmacopoeial methods, such as colour of solution, pH determination and wet chemical methods. However, requirements given in the respective general chapters must be fulfilled at all times to ensure suitability for the intended use.

6.29 If method verification is required, but the results obtained do not comply with the analytical acceptance criteria, then they should be considered as nonconforming work (see subsection 6.11).

6.30 A major change to the analytical procedure, or in the composition of the product tested or in the synthesis of the API, should require revalidation (or reverification) of the compendial procedure or the analytical procedure approved by the licensing authority.

6.31 The performance of analytical procedures should be monitored throughout their life cycle.

6.32 Further guidance on the validation of analytical procedures is available in *WHO good manufacturing practices: guidelines on validation* (*6*).

6.4 Technical records

6.33 The analytical worksheet, or any suitable alternative document, is an internal document to be used by the analyst for recording information about the sample, the test procedure, reagents, standards, materials, calculations and the results of testing. It includes all raw data obtained in the analysis. An electronic system, such as LIMS, can also be used.

6.34 The analytical worksheet contains documentary evidence either to confirm that the sample being examined is in accordance with the requirements or to support an out-of-specification result.

6.35 A unique analytical worksheet should be used for each numbered sample or group of samples.

6.36 Completed analytical worksheets from different units relating to the same sample should be combined.

6.37 The analytical worksheet should provide the following information:

- registration number of the sample;
- page numbering, including the total number of pages (including annexes);
- date of the test request;
- dates on which the analysis was started and completed;
- name and signature of the analyst;
- a description of the sample received;
- references to the specifications and a full description of test methods by which the sample was tested, including the limits, if applicable; as an alternative, a traceable reference to the test method is acceptable;
- identification of the test equipment used;
- reference substances used (including the provider, lot number, potency or content);
- results of the system suitability test, if applicable, as well as any analytical acceptance criteria;
- identification of reagents, solvents and columns (if applicable) employed;
- results obtained, including those obtained from another internal analytical section or external laboratory, if applicable;

- interpretation of the results and the final conclusions (whether or not the sample was found to comply with the specifications), approved and signed by designated qualified personnel;
- further comments, for example, any deviation from a prescribed procedure, which should be approved and reported or treated as nonconforming work (see subsection 6.11), or whether the sample had been forwarded to another unit or contract laboratory for a specific analysis, and the dates on which it was transferred and the result was received.

6.38 All values obtained from each test, including blank results, should immediately be entered on the analytical worksheet, and all graphical data, whether obtained from recording instruments or plotted by hand, should be attached or be traceable to an electronic record file or document.

6.39 The completed analytical worksheet should be signed by the responsible analyst and reviewed and approved by designated qualified personnel (either in paper format or electronically). Calculations and data transfers should be checked in an appropriate and systematic manner or controlled by a validated electronic system.

6.40 Any changes made to original records, either in paper or electronic format, should be traceable to what was changed, who was responsible, when it was performed, and why. The deletion of data is not acceptable.

6.41 When a mistake is made in an analytical worksheet or when data or text need to be amended, the correction must be traceable.

6.42 The analytical worksheet and any attachments, including calculations and recordings of instrumental analyses, should be archived together with the specification (*4*).

6.43 Detailed recommendations are provided in the WHO *Guideline on data integrity* (*4*) and should be implemented.

6.5 Testing

6.44 Testing of production samples from pharmaceutical manufacturers may be conducted entirely in the laboratory or, for some with high output, as a combination of in-process controls (as for real-time release testing), using process analytical technology, and laboratory testing. Samples for laboratory testing are taken and analysed throughout the production process and tested as soon as possible. Samples received by an NQCL are stored appropriately before being included in the laboratory workplan.

6.45 Pharmaceutical manufacturers apply testing methods that have been approved by the medicine licensing authority, whereas NQCLs apply, whenever available, the monograph of the appropriate pharmacopoeia when testing for compliance with the specification. Otherwise, the approved testing methods of the manufacturer are applied.

6.46 The sample should be stored appropriately in a dedicated sample storage facility within a controlled environment until testing can be performed according to the workplan of the laboratory.

6.47 When a test method included in the specification is not within the scope of the laboratory, the sample may be outsourced to a contract laboratory having the test method within its scope (see subsection 4.2). The responsible analyst prepares the request and arranges to transfer the required number of units (bottles, vials or tablets). Each of these units should bear the correct registration number. When the analytical test report contains the results of the tests performed by the contract laboratory, these results should be identified as such in the final report.

6.48 Detailed guidance on pharmacopoeial requirements is usually given in the general notices and specific monographs of the pharmacopoeia. Test procedures should be described in detail and should provide sufficient information to allow trained analysts to perform the analysis in a reliable and reproducible manner. System suitability criteria defined in the method should be fulfilled. The implementation of any deviation from the test procedure should be approved and documented and, where applicable, addressed as nonconforming work (see subsection 6.11).

6.49 Compliance with internal quality control criteria should be ensured (see subsection 6.11).

6.50 Detailed recommendations on chromatographic testing and processing are provided in the WHO guidance on *Good chromatography practices* (*22*) and should be followed.

6.6 Evaluation of test results

6.51 Quantitative test results, particularly those obtained in the manufacture of a finished dosage form of a pharmaceutical product, should be recorded in such a way that trends are detectable and, where practical, should be reviewed and evaluated statistically after completion of the tests. The evaluation should take into consideration established action and rejection limits to decide if the product meets the acceptance requirement.

6.52 For compliance testing, the product should meet all the acceptance requirements of the analytical tests included in the approved specification. Test results are compared with the specification limits to ascertain if the sample meets the requirements, and a conclusion is prepared as to the conformance of the test result with the specification.

6.53 Any test result should be traceable to a suitable primary reference substance, either of a pharmacopoeia or of a manufacturer or, if appropriate, to a certified reference material.

6.54 Atypical results should be investigated.

6.55 Neither pharmacopoeias nor NMRAs require the assay value found to be expressed with its associated uncertainty, as the upper and lower limits set already take into account the uncertainty of the measurement and, hence, no further tolerances are to be applied to the limits specified. However, for investigative testing in an unknown sample, it may also be necessary to report the content with its associated uncertainty.

6.56 Test results should be reviewed and approved or rejected by designated qualified personnel according to the competency master list or matrix (see subsection 5.1).

6.7 Measurement uncertainty

6.57 The uncertainty of measurement results is an essential component of the overall assessment and interpretation of analytical data. Understanding and appropriately addressing the measurement uncertainty is fundamental to ensuring the accuracy, reliability and reproducibility of the analytical results.

6.58 The requirements for measurement uncertainty apply to all quantitative tests performed by NQCLs.

6.59 When compliance testing is conducted using pharmacopoeial analytical procedures and analytical procedures described in the marketing authorization documentation, the requirements for evaluation of measurement uncertainty are considered to be met if all critical sources of uncertainty are controlled. In such cases, there is no obligation to report the measurement uncertainty. The decision on whether to estimate and take account of the measurement uncertainty in the statement of conformity with a specification limit rests with the laboratory. The decision is made on a case-by-case basis, and should be documented in advance.

6.60 When compliance testing is performed by internally developed analytical procedures that have undergone appropriate validation for their intended use, the specification limits, which must account for estimated measurement uncertainty, must be such that an unquestionable decision on compliance can be reached.

6.61 A thorough assessment of the measurement uncertainty may be required, for instance, when:

- employing ad hoc methods such as screening, analysis of unknown products or trace analysis;
- using methods with limited uncertainty information;
- confirming out-of-specification results, particularly if the test cannot be repeated;
- establishing limits for performance tests of measurement apparatus and critical parameters of methods.

6.62 If an analytical procedure is frequently employed in a laboratory and its measurement uncertainty has already been established and verified, there is no requirement to evaluate the measurement uncertainty for each individual result. However, the laboratory must be able to demonstrate that the critical factors that affect the measurement uncertainty have been properly managed and controlled. By ensuring that these influential factors are under control, the laboratory can have confidence in the previously established measurement uncertainty and its applicability to subsequent results obtained using the same analytical procedure.

6.63 Applying the concept of measurement uncertainty to compliance testing enables managing the risk of making the wrong acceptance or rejection decisions, provided the following elements of the concept of uncertainty are implemented:

- the decision rule on compliance of pharmaceutical products with specifications is defined;
- the laboratory evaluates the uncertainty of the analysis results.

6.64 The laboratory has the discretion to conduct an assessment of the measurement uncertainty as an internal quality control measure, when deemed appropriate.

6.65 The pharmacopoeial decision rule should be applied to all specification limits stated in the pharmacopoeial monographs and marketing authorization documentation.

6.66 The pharmacopoeial decision rule is based on the following principles:

- analytical variation typical of normal (routine) analytical practice is taken into account in the specified limits;
- the decision on compliance is made only on the basis of whether the result of the analysis meets the specified limits. No further tolerances (for example, obtained by evaluation of measurement uncertainty or setting the acceptance and rejection zones) should be applied to the specified limits.

6.67 The pharmacopoeial decision rule is simple: accept or reject, with a guard bandwidth equal to the analytical variation typical of normal analytical practice. The analyte concentration must be within a range narrower than the specification width (by analytical variation accounted for in the specification), ensuring a low probability of rejecting a product (low manufacturer risk). The pharmacopoeial decision rule works correctly only if the actual value of the uncertainty (in practice – estimated uncertainty) is fixed – that is, does not exceed the critical value, which is the target uncertainty set for the test. A decision on compliance is considered conclusive if the estimated uncertainty is less than or equal to the target uncertainty of a reportable result (pass). If the estimated uncertainty is greater than the target uncertainty, then a decision is considered inconclusive, and an investigation is required to establish the reasons for the unacceptably high uncertainty. The laboratory should ensure that the estimated uncertainty does not exceed the target uncertainty when performing the analysis.

6.68 For an NQCL to correctly reproduce an analytical procedure described in the pharmacopoeial monograph or marketing authorization documentation, the actual analytical variability should not exceed the variability characteristic of normal analytical practice.

6.69 Target uncertainty and the maximum permissible uncertainty for standard analytical operations (for normal analytical practice) are provided in Appendix 2.

6.70 The application of the concept of standard analytical practice for the evaluation of measurement uncertainty is provided in Appendix 3.

6.8 Validity of test results

6.71 The laboratory should have a procedure for ensuring the validity of results by reviewing the following activities, as appropriate:

- reference substances or reference materials;
- verification of measuring and testing equipment;
- appropriate quality control checks;
- data analysis that does not require additional experiments (use of control charts, trend analysis and different kinds of correlation of results of the sample being tested);
- replicate tests or calibrations using the same or different methods;
- retesting of retained samples;
- review of all raw data and reported results;
- review of measurement uncertainty results, if required.

6.72 Apart from the QCL of a pharmaceutical manufacturer, the performance of the laboratory should be assessed regularly by participation in:

- proficiency testing schemes, organized both internally and externally;
- interlaboratory comparisons, such as collaborative studies.

6.73 Data from monitoring activities should be subject to management review, at least annually, to ensure that necessary actions to control and, if applicable, to improve the laboratory's activities are effective.

6.74 If the results of the analysis of data from monitoring activities are found to be outside predefined criteria, appropriate action should be taken to prevent the reporting of incorrect results.

6.9 Out-of-specification results

6.75 An out-of-specification result is a result that does not comply with the acceptance criteria of any test in the specification, found in drug master files, company documentation, approved marketing submissions, or official compendia (*6*, *23*).

6.76 When a suspected out-of-specification result has been identified, a review of the different procedures applied during the testing process should be undertaken by the supervisor with the analyst or technician by using a checklist and before any retesting is performed. The investigation should ensure that:

- if stable, original sample preparations are not discarded until the investigation is complete;
- the appropriate procedures were applied and followed correctly, including requirements for validation and verification, and internal quality control tools;

- examination of the raw data is undertaken to identify possible discrepancies;
- all calculations are checked;
- the equipment used was qualified and calibrated, and system suitability tests were performed and were acceptable;
- the appropriate reagents, solvents and reference substances were used;
- the correct glassware was used.

6.77 The identification of an error that caused an aberrant result invalidates the result, and a retest of the sample will be necessary, which should be conducted by the same technician or analyst.

6.78 Suspected out-of-specification results can be rejected only if they are clearly due to an identified error. When an investigation is inconclusive, a confirmatory determination is to be performed by another trained analyst. A similar result would indicate a confirmed out-of-specification result. If comparable results are not obtained by the second analyst, the lack of consistency should be investigated. Further confirmation using another validated method, if available, may be advised and, if performed, should be fully documented.

6.79 If available, hypothesis testing should be considered in order to better define the root cause.

6.80 A standard operating procedure should be in place for the conduct of an investigation into a suspected out-of-specification test result. All investigations and their conclusions should be recorded. In the event of an error, root cause analysis should be performed, and any corrective actions should be documented, implemented, and recognized as risks and as opportunities for improvement.

6.81 All test data should be recorded and retained. If no error was identified, all test results should be reported. The standard operating procedure defined above should also consider the general rules to report this type of result.

6.82 All conclusions should be recorded (either on the analytical worksheet or in another support) by the analyst and reviewed and approved by the supervisor.

6.83 A critical review of the nature, number and root cause of out-of-specification results obtained within a given period, either confirmed or not confirmed, should be conducted during the management review (see subsection 3.10).

6.10 Reporting of results

6.84 The analytical test report (hard copies or by electronic means) is a compilation, by the study supervisor, of the analytical test results obtained for approval by the quality manager, laboratory director or designated person. Subsequently, the dossier containing all the information pertaining to the sample, including the origin, chain of custody and analytical data, is archived.

6.85 Any amendments or changes to the original analytical test report will require the issue of a new corrected document, where:

- any change of information should be clearly identified and dated;
- the reason for the change should be included in the new corrected document;
- the new report should be uniquely identified and contain a reference to the original document it will replace.

6.86 When using pharmacopoeial methods and manufacturer's approved methods for compliance testing, it is not required that the expanded uncertainty be reported.

6.87 The laboratory decides when to report the uncertainty of a result and how conformance to specifications was evaluated (see recommendations in subsection 6.7).

6.88 The analytical test report should provide the following information:

- a title (for example, "test report", "analytical test report", or another suitable title);
- the laboratory registration number of the sample;
- the laboratory test report number;
- the name and address of the laboratory testing the sample;
- the name and address of the originator of the request for analysis;
- the name, description and batch number of the sample, where appropriate;
- an introduction giving the background to and the purpose of the investigation, if applicable;
- a reference to the specifications used for testing the sample or a detailed description of the procedures employed (sample for investigative testing), including the limits;

- the results of all the tests performed or the numerical results, with the standard deviation of all the tests performed (if applicable);
- when applicable, the expanded measurement uncertainty of the reportable result with reference to its assessment and an explanation of how it was used in making the compliance decision;
- a discussion of the results obtained, where appropriate;
- a conclusion as to whether or not the samples were found to be within the limits of the specifications used, or, for a sample for investigative testing, the substances or ingredients identified;
- a statement to the effect that the results relate only to the items tested, calibrated or sampled;
- a clear identification when results are from external providers;
- the date on which the tests were completed;
- the signature of the laboratory director or other authorized person reviewing and authorizing the report;
- the name and address of the original manufacturer and, if applicable, those of the repacker or trader;
- whether or not the samples comply with the requirements;
- if applicable, opinions and interpretations, adequately supported by evidence and issued by authorized personnel;
- the date on which the sample was received;
- the expiry date or retest date, if applicable;
- a statement indicating that the analytical test report, or any portion thereof, cannot be reproduced without the authorization of the laboratory.

6.89 A certificate of analysis is prepared for each batch of a substance or product. The certificate of analysis contains the same information as the analytical test report.

6.90 For NQCLs, the issuance of a certificate of analysis is not obligatory as long as the analytical test report is adequately issued and remains at the laboratory as an internal document.

6.91 The laboratory is responsible for all the information provided in the report, except when the customer provides the information.

- Data provided by the customer should be clearly identified.
- In addition, a disclaimer should be included in the report when the information is supplied by the customer, which could compromise the validity of the results.

- Where the laboratory has not been responsible for the sampling stage (for example, the sample has been provided by the customer), the report should state that the results apply to the sample as received.

6.11 Nonconforming work

6.92 The term "nonconforming work" refers to any instance where analytical activities deviate from established procedures, internal requirements, or the analytical specifications that have been agreed upon with the customer. Such deviations encompass a range of issues, including equipment, environment conditions, internal quality control criteria and system suitability criteria. All instances of nonconforming work must be duly recorded, addressed and managed. Essentially, nonconforming work represents a technical or analytical deviation from the specified limits.

6.93 Managing nonconforming work follows the same rationale as described in subsection 3.7 and can be treated under the same system, ensuring that:

- actions (including the halting or repeating of work and withholding of reports, as necessary) are based upon the risk levels established for the affected activity;
- an evaluation is made of the significance of the nonconforming work, including an analysis of the impact on previous results;
- a decision is taken on the acceptability of the nonconforming work;
- where necessary, the customer is notified, and work is recalled;
- the responsibility for authorizing the resumption of work is defined.

6.94 Records of the nonconforming work are retained, as well as all defined actions.

6.95 Corrective actions (see subsection 3.7) should be implemented if the evaluation indicates that there is a possibility that the nonconforming work could recur or there is a doubt about the conformity with the QMS.

6.96 Analysis of the data obtained from nonconforming work should be performed, addressing specifically those issues for which a trend is observed throughout time (for example a systematic nonconforming work obtained for the same testing method, which may indicate a possible cause when trend analysis is performed). The results from this analysis and possible impacts on the identified risks and opportunities should be reviewed periodically (see subsection 3.10), and an assessment should be made of the impact of the nonconforming work on the reported results.

6.12 Retained samples

6.97 Samples should be retained (see subsection 6.2) as required by legislation or by the originator of the request for analysis (*24*).

6.98 The minimum amount of sample to be delivered for testing to the laboratory should be communicated to the authority, the manufacturer or the person responsible for sampling. There should be a sufficient amount of retained sample to allow at least two reanalyses.

6.99 The retained sample should be contained in its original packaging.

6.100 Sample disposal criteria should be established, according to national legislation or applicable international recommendations, or, if required, by the originator of the request for analysis.

7. Safety rules

7.1 Environmental health and safety policies should be followed to protect the staff, the public and the environment. A documented laboratory safety policy, which should include general and specific safety instructions reflecting identified risk, should be available to and applied by each member of staff. A staff member should be given the responsibility of overseeing the policy and ensuring compliance by all staff.

7.2 A waste management system conforming to local legislation should be in place to ensure the safe disposal of chemicals, solvents and other relevant materials.

7.3 General and specific safety procedures reflecting identified risk should be made available to each staff member. Seminars on safety-related issues should be held at predefined intervals, as specified in QMS documentation.

7.4 General rules for safe working should be included in standard operating procedures in accordance with national regulations and normally include the following requirements.

- Safety data sheets should be available to staff before testing is carried out.
- Smoking, eating and drinking in the laboratory should be prohibited.
- Staff should be familiar with the use of firefighting equipment, including fire extinguishers, fire blankets and gas masks.

- Staff should wear laboratory coats or other suitable protective clothing, as required, including eye protection.
- Special care should be taken, as appropriate, in handling highly potent, infectious or volatile substances.
- Highly toxic or genotoxic samples should be handled in a specially designed facility to avoid the risk of contamination.
- All containers of chemicals should be appropriately labelled and include prominent warnings (for example, "poison", "flammable", "radioactive"), whenever appropriate.
- Adequate insulation and spark-proofing should be provided for electrical wiring and equipment, including refrigerators.
- Rules on the safe handling of cylinders of compressed gases should be observed and staff should be familiar with the relevant colour identification codes.
- Staff should not work alone in the laboratory.
- First-aid materials should be provided, and staff instructed in first-aid techniques, emergency care and the use of antidotes.

7.5 Protective clothing should be available, including eye protection, masks and gloves, and should be fit for purpose. Safety showers (eyes and full body) should be installed at a suitable location and should be fit for purpose. Rubber suction bulbs should be used on manual pipettes and siphons. Staff should be instructed in the safe handling of glassware, corrosive reagents and solvents, including the use of safety containers or baskets to avoid spillage from containers. Warnings, precautions and instructions should be incorporated, when appropriate, in standard operating procedures for work with violent, uncontrollable or dangerous reactions when handling specific reagents (for example, mixing water and acids or acetone–chloroform and ammonia), flammable products, and oxidizing or radioactive agents. Peroxide-free solvents should be used. Staff should be aware of methods for the safe disposal of unwanted corrosive or dangerous products by neutralization or deactivation and of the need for safe and complete disposal of mercury and its salts.

7.6 A standard operating procedure for the storage and handling of controlled substances complying with applicable national legislation should be available and enforced.

7.7 Poisonous or hazardous products should be identified, labelled appropriately and kept separately from other products.

7.8 Unnecessary contact with reagents, especially solvents and their vapours, should be avoided. The use of known carcinogens and mutagens as reagents should be limited or totally excluded.

7.9 Replacement of toxic solvents and reagents with less toxic materials or reduction of their use should always be the aim, particularly when new techniques are developed and validated.

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Appendix 1

Equipment for a first-stage and medium-sized pharmaceutical quality control laboratory

A list of equipment considered by the Expert Committee to be adequate, either for a first-stage or medium-sized pharmaceutical quality control laboratory, is given in Table 1.

This list does not represent any requirements that should be fulfilled to comply with these guidelines. National medicines regulatory authorities (NMRAs) or laboratories wishing to perform pharmaceutical analyses may consider the following list in the establishment or upgrading of their testing facilities. For budgetary reasons it is necessary, besides the cost of equipment, to take into consideration the cost of reference materials, reagents, solvents, glassware, other laboratory commodities and personnel. Experience has shown that, for sustainability, a laboratory should allow a margin of 10–15% per year of the purchasing expenditure on equipment to cover the cost of maintenance.

Table 1
Equipment for a first-stage and medium-sized pharmaceutical quality control laboratory

First-stage laboratory	
Equipment and major instruments	**Quantity**
Top-loading balance	1
Analytical balance (5 digits)	1 or 2
Melting-point apparatus	1
pH meter (with assorted electrodes)	1
Microscope	1
Polarimeter	1
High-performance liquid chromatograph with ultraviolet detector	2
Ultraviolet/visible spectrophotometer	1
Infrared spectrophotometer with pellet press	1
Karl Fischer titrator (semi-micro determination of water)	1

First-stage laboratory *(continued)*	
Equipment and major instruments	**Quantity**
Agate mortar with pestle	1
Equipment for thin-layer chromatography	1
Temperature and humidity probe	1
Thin-layer chromatography spotter	1
Developing chambers	6 + 1[a]
Atomizers	6
Ultraviolet viewing lamp	1
Disintegration test equipment (1 basket for 6 tablets)	1
Dissolution apparatus	1
Soxhlet extraction apparatus (60 mL)	3 + 1[a]
Micrometer calipers	1
Pycnometers	2
Burettes/pipettes (10 mL and 25 mL/1, 2, 5, 10, 20, 25, 50 mL)	3 of each
Desiccator	1 + 1[a]
Centrifuge (table-top model, 4-place swing rotor)	1
Water bath (20 litres)	1
Hot plates with magnetic stirrers	3
Vacuum pump (rotary, oil)	1
Drying oven (60 litres)	1
Vacuum oven (17 litres)	1
Muffle furnace	1
Refrigerator (explosion-proof)	1
Water distilling apparatus (8 litres/hour)	1
Water deionizer (10 litres/hour)	1
Dehumidifier (where needed)	1
Fume hood	1

First-stage laboratory *(continued)*	
Optional items	**Quantity**
Analytical microbalance	1
Flame photometer (including air compressor)	1
Refractometer	1
Viscometer	1
Vortex mixer	1
Shaker (wrist-action)	1
Pipette rinser	1
Constant temperature water bath	1
Ultrasonic cleaner (5 litres)	1
Medium-sized laboratory	
Equipment and major instruments	
Top-loading balance	1 or 2
Analytical balance (5 digits)	2
Analytical microbalance	1
Microscope	1 or 2
Equipment for thin-layer chromatography	1
Thin-layer chromatography multispotter	1
Developing chambers	6
Atomizers	6
Ultraviolet viewing lamp	1
Temperature and humidity probe	2
Potentiometric titrimeter	1
Micro Kjeldahl equipment (including fume flasks)	1
Soxhlet extraction apparatus (60 mL)	3
Densimeter, combined with viscometer	1
Burettes/pipettes (10 mL and 25 mL/1, 2, 5, 10, 20, 25, 50 mL)	6 of each
Micrometer calipers	1

Medium-sized laboratory *(continued)*	
Equipment and major instruments	**Quantity**
Heating mantles for flasks (assorted sizes: 50, 200 and 2000 mL)	6
Sieves (assorted sizes)	1 set
Centrifuge (floor model)	1
Shaker (wrist-action)	1
Vortex mixers	2
Water bath (electrical, 20 litres)	2 or 3
Hot plates with magnetic stirrers	3 or 4
Vacuum pump (rotary, oil)	2
Vacuum rotary evaporator	1
Drying oven (60 litres)	2 or 3
Muffle furnace (23 litres)	1
Vacuum oven (17 litres)	1
Desiccators	2
Refrigerator (explosion-proof)	2
Freezer	1
Ultrasonic cleaners (5 litres)	2
Laboratory glassware washing machine	1
Water distilling apparatus (8 litres/hour)	1
Water deionizing equipment (10 litres/hour)	1
Fume hoods	2
Melting-point apparatus	1
Polarimeter	1
pH meters (with assorted electrodes)	2
High-performance liquid chromatograph with variable wavelength:	
Ultraviolet/visible detector	2 or 3
Ultraviolet/visible spectrophotometer, double-beam	1
Diode array	1 or 2

Medium-sized laboratory *(continued)*	
Equipment and major instruments	**Quantity**
Infrared spectrophotometer (MIR, NIR) with pellet press	1
Agate mortar with pestle	1
Gas chromatograph (flame ionization, direct and static head space injection)	1
Karl Fischer titrators (1 semi-micro and 1 coulometric for microdetermination of water)	2
Disintegration test equipment (1 basket for 6 tablets)	1
Dissolution test equipment (for 6 tablets/capsules)	1
Oxygen flask combustion apparatus	1
Optional items	
Refractometer	1
Atomic absorption spectrophotometer (flame, furnace)	1
Spectrofluorometer	1
High-performance liquid chromatograph detectors:	1
Fluorescence	1
Mass spectrometric (MS)	1
Evaporative light scattering (ELSD)	1
Charged aerosol (CAD)	1
Refractive index	1
Gas chromatograph detectors:	1
Electron capture detector (ECD)	1
Nitrogen/phosphorous (NPD)	1
Mass spectrometric (MS)	1
Capillary electrophoresis equipment	1
Thin-layer chromatography scanner	1
Hardness tester	1
Friability tester	1

Medium-sized laboratory *(continued)*	
Optional items	**Quantity**
Ice machine	1
Solvent recovery apparatus	1
Equipment for microbiology unit	
pH meter	1
Ultraviolet/visible spectrophotometer, single-beam	1
Microscopes (for bacteriology)	1
Membrane filter assembly for sterility tests	2
Colony counter with magnifier	1
Laminar air flow unit	1
Hot-air sterilizer	1
Incubators, 60 litres	1
Anaerobic jar	2 or 3
Zone reader	1
Centrifuge	1
Water bath (thermostatically controlled)	1
Autoclaves (100 litres, top-loading)	2
Refrigerators (340 litres)	2
Deep freeze	2
Laboratory glassware washing machine	1
Equipment for pharmacognosy/phytochemistry unit	
Grinder/mill (for preparation of sample of herbal materials)	1
Top-loading balance	1
Sieves	1
Microscope[b]	1 set
Soxhlet extraction apparatus	1
Water bath	2 or 3
Heating mantles for flasks	1

Equipment for pharmacognosy/phytochemistry unit *(continued)*	
	Quantity
Hot plates with magnetic stirrers	1 or 2
Equipment for thin-layer chromatography	2
Developing chambers	1 or 2
Desiccators	3 or 4
Rotary vacuum apparatus	2
Distillation equipment	1
Conical percolators	1
Apparatus for determination of water content by azeotropic method[b]	2 or 3
Apparatus for determination of volatile oils[b]	1
Apparatus for determination of arsenic limit test[c]	1

[a] Needed in the case that herbal medicines are also tested.

[b] Quality control methods for herbal materials. Geneva: World Health Organization; 2011 (https://apps.who.int/iris/bitstream/handle/10665/44479/9789241500739_eng.pdf?sequence=1, accessed 19 January 2024).

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Appendix 2

Recommendations for the target uncertainty and the maximum permissible uncertainty for normal analytical practice

To effectively apply the concept of uncertainty to compliance testing in the pharmaceutical sector, the following key recommendations should be formulated (see subsection 6.7):

- recommendations for the target uncertainty for pharmacopoeial tests;
- recommendations for the maximum permissible uncertainty for standard analytical operations (recommendations for normal analytical practice).

Recommendations for the target uncertainty for pharmacopoeial tests

To assess the risk of making an incorrect decision on compliance, the estimated uncertainty (U^{est}) should be compared with the target uncertainty (U^{tg}).

For the assay of an API or excipient, the minimum value of measurement uncertainty usually comprises (*1–3*):

- 1.0% for volumetric titration of the conjugate acids, non-aqueous and acid–base titrations;
- 1.5% for redox and argentometric titrations;
- 2.0% for complexometric titrations;
- 2.0% and 3.0% for ultraviolet spectrophotometry assays, using the reference substance and specific absorbance, respectively;
- 2.0% for liquid chromatographic assays.

U^{tg} is an expanded uncertainty, expressed as a 90% two-sided confidence interval, which is equivalent to a 95% one-sided confidence interval.

The minimum value of U^{tg} corresponds to the minimum width of content limits for assay. Therefore, the minimum value of U^{tg} = 2.0% means that the metrologically correct content limits should not be narrower than 98–102%.

For finished pharmaceutical products, the following requirements for U^{tg} can usually be applied (*4*).

- For assay, the target uncertainty should be insignificant compared to the half-width of the symmetrical two-sided content limits, U^{tg} = (UCL – LCL)/2 × 0.32, where UCL and LCL are upper and lower content limits, respectively.
- For assay with a one-sided content limit (known as "not less than …"), U^{tg} = 6.4%. This requirement can also be applied to APIs and excipients with a one-sided content limit.
- For tests for dissolution and uniformity of dosage units, U^{tg} = 3.0%.
- For related impurities and residual solvents, U^{tg} = 16.0% (the found quantity of impurity is used only for comparison with the specification limit). This requirement can also be applied to APIs or excipients.

Recommendations for the maximum permissible uncertainty for normal analytical practice

The approach of normal (routine) analytical practice (NAP) establishes the maximum permissible level of uncertainty from standard analytical operations (U_i^{tg}) U^{tg} and reflects the minimum pharmacopoeial requirements that should be met by all laboratories performing compliance testing (see subsection 6.7). Adherence to NAP is assumed when performing analytical procedures outlined in monographs (*5*–*7*) and marketing authorization documentation (*8*).

Currently, most of the analytical procedures described in pharmacopoeias and marketing authorization documentation have been validated without the use of the concept of uncertainty; hence, without considering that when the procedures are reproduced in another laboratory, the actual uncertainty of the analytical result (in practice, the estimated uncertainty, or U^{est}) can be as large as the maximum permissible value (NAP recommendations), which can be greater than that achieved during the analytical procedure development or validation. Therefore, some sources of variation, which may become significant when reproducing the analytical procedure in another laboratory, may not be accounted for, since they were insignificant in the developer's laboratory (and in the interlaboratory trials for pharmacopoeial analytical procedures).

Thus, the classic approach to quality assurance does not consider the "worst case", that is, when the laboratory meets the NAP recommendations minimally, which may result in approving metrologically incorrect analytical procedures for which reproducibility problems may occur with an unacceptably high risk.

To control the risk of obtaining an unacceptably large value of U^{est}, it is reasonable to carry out the bottom-up evaluation of measurement uncertainty during the development of a procedure based on the NAP recommendations (that

is, perform an uncertainty estimation for the "worst case"). If the uncertainty estimated for the worst case (U^{NAP}) exceeds U^{tg}, then there is a high risk that U^{est} will also exceed U^{tg} when reproducing the procedure, and the laboratory will not be able to make a conclusive decision on compliance. In such a case the analytical procedure needs optimization of measurements and sample preparation steps.

Here and below, measurement uncertainty is an expanded uncertainty, expressed as a 90% two-sided confidence interval, which is equivalent to a 95% one-sided confidence interval.

Typically, variability sources can be divided into measurement related (for example, random variability of an analytical signal) and associated with sample preparation operations (weighing, dilution).

The requirements for the maximum permissible uncertainty (target uncertainty) for standardized analytical operations (NAP recommendations – U_i^{tg}) may be specified directly in the analytical procedure (as a requirement for the suitability of the analytical system) or other regulations (for example, as a requirement for the qualification of analytical equipment in the pharmacopoeias).

The example of a variability source for which U_i^{tg} is harmonized between pharmacopoeias is the random variability of the analytical signal for assay by separation technique of an API (or excipient) where the value is 100% for a pure substance (*2*, *9*, *10*). This approach assumes that random variability from the analytical signal is the main component of uncertainty associated with measurements. Requirements for the maximum permitted relative standard deviation ($\%RSD_{max}$) for the given assay upper content limits are set so that a 90% two-sided confidence interval (equal to a 95% one-sided interval), calculated for the uncertainty component of the analysis result related to the precision of measurements, does not exceed 0.5 of U^{tg}.

The recommendations for $\%RSD_{max}$ for assay by separation technique for finished pharmaceutical products with symmetrical assay content limits are shown in Table 1 (*11*). These requirements are set so that a 95% one-sided confidence interval calculated for the uncertainty component of the analysis result related to the precision of measurements does not exceed U^{tg}. It is recommended that U^{tg} for finished pharmaceutical preparations should comprise not more than 0.32 of the half-width of symmetrical content limits.

Table 1
Requirements for maximum permitted relative standard deviation (%RSD_{max}) of the analytical signal for assay by separation technique for finished pharmaceutical products with symmetrical assay content limits

	Number of individual injections *n*[a]						
	2	3	4	5	6	7	8
(UCL – LCL)/2[b]	%RSD_{max}						
5	0.25	0.67	0.96	1.19	1.38	1.54	1.69
7.5	0.38	1.01	1.44	1.78	2.06	2.31	2.53
10	0.51	1.34	1.92	2.37	2.75	3.08	3.38
15	0.76	2.01	2.88	3.56	4.13	4.62	5.07
20	1.01	2.68	3.85	4.75	5.50	6.16	6.76

[a] Assuming that the same number of repetitive injections is made for the test and reference solutions.
[b] UCL and LCL are upper and lower content limits, respectively, expressed in per cent in relation to the nominal content value.

For spectrophotometric assays the next recommendations can be used as NAP recommendations (*12*):

- for a series of measurements of the absorbance with cuvette withdrawal RSD ≤ 0.52%;
- not less than three measurements for the test and reference solutions.

NAP recommendations for individual operations with volumetric glassware ISO class A are shown in Tables 2–4 (*1*, *4*). It should be noted that these estimates of uncertainty exceed the maximum permissible deviation from the nominal volume under the requirements for ISO class A volumetric glassware, as the NAP recommendations additionally account for the random variability introduced by the analyst in routine analysis.

Table 2
Target uncertainties typical of NAP due to the use of volumetric flasks ISO class A of different volumes

Volumetric flask volume, mL	Target uncertainty, mL	Target uncertainty, %
10	0.05	0.50
20	0.057	0.28

Table 2 *continued*

Volumetric flask volume, mL	Target uncertainty, mL	Target uncertainty, %
25	0.0575	0.23
50	0.085	0.17
100	0.12	0.12
200	0.20	0.10
250	0.20	0.08
500	0.35	0.07
1000	0.50	0.05

Table 3
Target uncertainties typical of NAP due to the use of transfer pipettes ISO class A of various volumes

Transfer pipette volume, mL	Target uncertainty, mL	Target uncertainty, %
1.0	0.010	0.98
2.0	0.012	0.61
5.0	0.018	0.37
10.0	0.025	0.25
20.0	0.037	0.18
25.0	0.037	0.15
50.0	0.061	0.12

Table 4
Target uncertainties typical of NAP due to the use of graduated pipettes ISO class A of different volumes

Graduated pipette volume, mL	Target uncertainty, mL	Target uncertainty, %[a]
0.5	0.0061	1.23
1.0	0.0074	0.74
2.0	0.012	0.62
5.0	0.037	0.74

Table 4 *continued*

Graduated pipette volume, mL	Target uncertainty, mL	Target uncertainty, %[a]
10.0	0.062	0.62
25.0	0.123	0.49

[a] Indicated in relation to the total volume of the pipette.

For weighing operations, it is recommended to use U^{tg} = 0.2 mg as the NAP recommendation (*1*, *4*). This recommendation reflects typical minimum requirements for balances in NQCLs.

If the NQCL has a balance of a higher class, then to estimate uncertainty in line with NAP recommendations when reproducing the analytical procedure, it becomes essential to employ a criterion for the balance qualification (maximum permissible uncertainty).

For the initial reproduction of the analytical procedure in an NQCL, it is advisable to use the bottom-up approach for the uncertainty estimation as per the NAP recommendations. The text of the procedure and a priori knowledge of the analytical technique indicate the significant sources of variability.

Often the risk of obtaining an unacceptably large U^{est} can be mitigated by increasing the accuracy of the concentration of the test and reference solutions. This can be achieved by increasing the test portions or volumes of the volumetric glassware used, without changing the final concentration of the test and reference solutions. Such an adjustment of the approved analytical procedure is allowed by pharmacopoeial practice (*13*).

However, the actual uncertainty in a particular NQCL may be greater than the NAP recommendations. Therefore, it is necessary to confirm experimentally that actual uncertainties from variability sources regulated by NAP do not exceed the recommended value of U_i^{tg} during the real analysis. That is, the uncertainty estimation for the "worst case" (NAP recommendation) does not override the estimation of uncertainty in the laboratory, as described, for example, in (*8*).

An example of the uncertainty estimation based on NAP recommendations for chromatographic assays of an API is provided in Appendix 3.

References

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Appendix 3

Examples of the uncertainty estimation for compliance with normal analytical practice (the "worst case") for assay of pharmaceutical substances by chromatography

The pharmacopoeias state that the normal (routine) analytical practice (NAP) or (routine) analytical errors are considered in pharmacopoeial acceptance criteria (*1*–*3*). This means that the laboratory can reproduce a pharmacopoeial analytical procedure only if the actual uncertainty for the standard analytical operations (NAP operations) does not exceed that accounted for in the specifications. The same statement is correct regarding analytical procedures from marketing authorization because, here, the same decision rule is used (hence, the same approach to the construction of criteria) (*4*).

The recommendations for the permissible uncertainty associated with standard analytical operations can be found in the *European Pharmacopoeia* (*5*), Table 1, and the *State Pharmacopoeia of Ukraine* (*6*). The recommendations for maximum permissible uncertainty for standard analytical operations in a routine analysis (sample preparation – weighing and dilution using volumetric glassware ISO class A, and measurements) are given in Appendix 2.

The uncertainty estimation for the case of minimum compliance with NAP (the "worst case") is based on the text of the analytical procedure without the use of any experimental data. This allows the developer to optimize the text of the analytical procedure before its approval or the reproduction of an already approved procedure in the laboratory (to reduce the uncertainty of the preparation of solutions or measurements). This enables mitigation of the risk of obtaining an unacceptably large actual value of uncertainty, which could lead to inconclusive decisions on compliance during the reproduction of an analytical procedure.

It is important to highlight that when estimating uncertainty for NAP compliance (for the "worst case" scenario), the resulting uncertainty estimation applies universally to any laboratory required to meet pharmacopoeial requirements. Conversely, the general procedure for estimating uncertainty aims to provide a real estimation of uncertainty within a specific laboratory environment, which may vary for different laboratories performing the same analytical procedure. The uncertainty estimation for NAP compliance should not be considered a substitute for the generally accepted practice of individual uncertainty estimation in each laboratory to determine the actual uncertainty.

The uncertainty estimation for NAP compliance is based on the premise that:

- the significant sources of variation are usually identified in the text of the analytical procedure (primarily, they follow from the calculation formula). Such sources of variation are present in any laboratory and, therefore, need to be standardized and controlled;
- "unexpected" and non-standardized sources of variation (such as incomplete analyte extraction during sample preparation, or interference of excipients with measurements) are absent or insignificant. This should be ensured at the development and validation stages of the analytical procedure.

The purpose of uncertainty estimation for the case of NAP compliance is to calculate the expanded uncertainty for a reportable result (combined uncertainty) based on the maximum permissible uncertainties (according to the NAP) for standard analytical operations (given in Appendix 2). The rules for combined uncertainty estimation are determined by how the parameters that are sources of variation are included in the calculation formula for the reportable result (X). It is supposed that all sources of variability are independent, and there is no correlation between them.

Here and below, measurement uncertainty is an expanded uncertainty expressed as a 90% two-sided confidence interval, which is equivalent to a 95% one-sided confidence interval.

Sources of uncertainty for the assay can be grouped as follows: (group 1) measurement uncertainty (U_{Meas}); (group 2) sample preparation uncertainty (U_{SP}), which is subdivided into (group 2.1) weighing uncertainty ($U_{m,i}$) and (group 2.2) dilutions uncertainty ($U_{V,i}$); and (group 3) uncertainty of the value assigned to a reference substance (U_{RS}).

The typical formula for the assay is:

$$X = \frac{r}{r_0} \times \frac{m}{m_0} \times \frac{V_{01} \times V_{02} \times V_{03} \ldots V_{0n}}{V_1 \times V_2 \times V_3 \ldots V_n} \times \frac{P_{RS}\%}{100\%} \times K$$

1	2		3	4
	2.1	2.2		

Where:

r and r_0 are analytical signals (peak area, peak height, or their ratio) for the test solution and the reference solution;

m and m_0 are the test portions of the test sample and reference substance;

V is the nominal volume for volumetric flasks and pipettes used for making dilutions;

P_{RS} is the analyte content in the reference substance, expressed as a percentage;

K is the coefficient for converting the concentration into a reportable result (in most cases for assay of API, $K = 1$).

All sources of variation from the calculation formula, except for U_{MEAS}, are expressed as intervals (not as standard deviations). Therefore, for uncertainty estimation, it is reasonable to directly combine uncertainties from individual sources of variability as intervals without converting them to standard deviations and then back to intervals (*6*). This approach leads to the same uncertainty estimates as the classical approach (*4*).

For the assay by chromatographic methods, for a typical case, all sources of variability are reflected in the calculation formula as a product or quotient. Therefore, the combined uncertainty for X can be estimated as the square root of the sum of the squares of the partial components of the uncertainty (in this case, expressed as a percentage).

The typical sources of variability arising from measurements (group 1) and sample preparation (group 2) are standardized (Appendix 2); they are the primary focus for the uncertainty estimation for NAP compliance.

For the uncertainty estimation, it is acceptable to assume that for pharmacopoeial reference substances, U_{RS} is insignificant compared to the U^{tg} and may not be considered in the uncertainty estimation. The U_{RS} is insignificant for any pharmacopoeial applications if it does not exceed 0.5% (*7*).

1. An example of uncertainty estimation for NAP compliance for a chromatographic assay of API

For metrologically correct analytical procedures for a chromatographic assay of API, the upper content limit is not less than 102.0%; therefore, $U^{tg} = 2.0\%$ (Appendix 2).

Uncertainty for the analytical signal. Following the harmonized approach (*8*), the uncertainty for the analytical signal (U^{tg}_{Meas}) is (Appendix 2):

$$U^{tg}_{Meas} = 0.5 \times U^{tg} = 0.5 \times 2.0\% = 1.0\%.$$

Sample preparation uncertainty. It is rational to make requirements that the combined uncertainty of sample preparation (U^{tg}_{SP}) also be not more than 0.5 of U^{tg}:

$$U^{tg}_{SP} = 0.5 \times U^{tg} = 0.5 \times 2.0\% = 1.0\%.$$

2. An example of the analytical procedure for which an uncertainty estimation for NAP compliance is made

An amount of 50.0 mg of the substance being tested (m) or reference substance (m_0) is dissolved in the diluent and diluted to 50.0 mL (V_1 and V_{01}). Then, 1.0 mL of this solution (V_2 and V_{02}) is diluted to 10.0 mL (V_3 and V_{03}).

The calculation formula for the substance content in % w/w (without calculation to dry/volatile solvent-free substance) is as follows:

$$X = \frac{r}{r_0} \times \frac{m}{m_0} \times \frac{V_{01} \times V_{02}}{V_1 \times V_2} \times \frac{P_{RS}\%}{100\%}.$$

Uncertainty related to the sources of variation during sample preparation (group 2) is estimated as in Table 1.

Table 1
Uncertainty related to the sources of variation during sample preparation

Variability sources	Associated expanded uncertainty (%)
Test solution	
1. Taking a test portion of 50.0 mg of the substance being tested	= 0.2 mg[a]/50mg × 100% = 0.4%
2. Dilution to 50.0 mL (V_1)	0.17%[b]
3. Taking an aliquot of 1.0 mL (V_2)	0.74%[c]
4. Dilution to 10.0 mL (V_3)	0.50%[b]
Reference solution	
5. Taking a test portion of 50.0 mg of reference substance	= 0.2 mg[a]/50 mg × 100% = 0.4%
6. Dilution to 50.0 mL (V_{01})	0.17%[b]
7. Taking an aliquot of 1.0 mL (V_{02})	0.74%[c]
8. Dilution to 10.0 mL (V_{03})	0.50%[b]

[a] 0.2 mg is the recommended target uncertainty for the weighing operation (normal analytical practice recommendation, Appendix 2).

[b] Appendix 2, Table 2.

[c] Appendix 2, Table 4.

In this case, it is better to use a graduated pipette of 1.0 mL because formally it assures lower uncertainty than a transfer pipette of 1.0 mL.

The uncertainty for sample preparation according to NAP recommendations (U_{SP}^{tg}) can be estimated as follows:

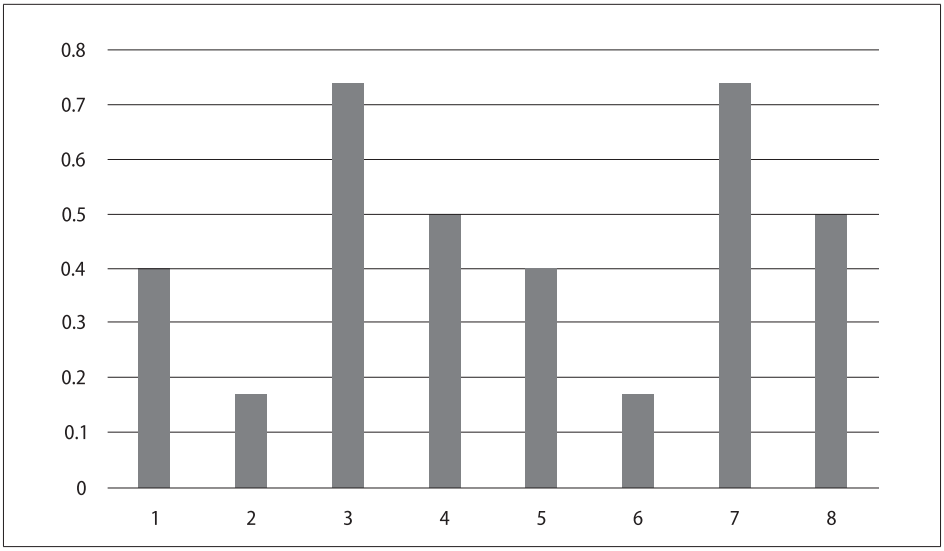
$$U_{SP}^{tg} = \sqrt{(0.4^2 + 0.17^2 + 0.74^2 + 0.5^2) \times 2} = 1.40\%.$$

U_{SP}^{tg} exceeds critical value $U_{SP}^{tg} = 1.0\%$; therefore, this analytical procedure creates an unacceptably high risk of obtaining too high uncertainty of X at reproduction of this analytical procedure in a laboratory, which complies with pharmacopoeial requirements at the minimum level (NAP recommendations).

It is recommended to optimize the accuracy of the test and reference solutions preparation.

The efficacy of sample preparation can be visualized as in Fig. 1: the x-axis shows the number of the sample preparation operation (numbers 1–8); the y-axis shows associated uncertainty (%).

Fig. 1
Relative contribution of the uncertainty of sample preparation operations (1)



The uncertainty estimates tend to decrease and converge with the optimization of the sources of variation.

Operations of the second dilution, numbers 3 and 7 (taking an aliquot of 1.0 mL) need optimization first, and then operations numbers 4 and 8 (dilution to 10.0 mL).

Using glassware of standard volumes, the modification of the second dilution without changing the final concentration can be proposed as follows: 5.0 mL of solution (V_2 and V_{02}) is diluted to 50.0 mL (V_3 and V_{03}).

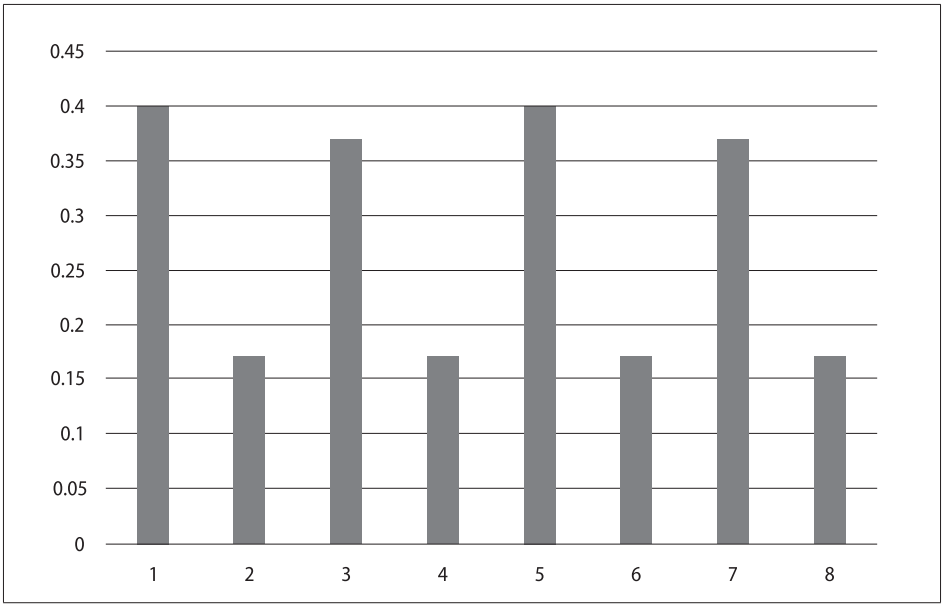
Then, the uncertainty of sample preparation operations is estimated as in Table 2.

Table 2
Uncertainty related to the sources of variation during sample preparation: second dilution

Variability sources	Associated expanded uncertainty (%)
Test solution	
3. Taking an aliquot of 5.0 mL (V_2)	0.37%
4. Dilution to 50.0 mL (V_3)	0. 17%
Reference solution	
7. Taking an aliquot of 5.0 mL (V_{02})	0. 37%
8. Dilution to 50.0 mL (V_{03})	0. 17%

The ratio for estimated uncertainties is shown in Fig. 2.

Fig. 2
Relative contribution of the uncertainty of sample preparation operations (2)



The estimated uncertainty for sample preparation (U_{SP}^{tg}) can be calculated as follows:

$$U_{SP}^{tg} = \sqrt{(0.4^2 + 0.17^2 + 0.37^2 + 0.17^2) \times 2} = 0.84\%.$$

As can be seen, after optimizing the accuracy of the preparation of solutions, U_{SP}^{tg} does not exceed the critical value U_{SP}^{tg} = 1.0%. Therefore, this analytical procedure does not lead to an unacceptably high risk of obtaining too high uncertainty of X and can be approved by the developer or used by NQCLs.

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