World Health Organization

DRAFT WORKING DOCUMENT FOR COMMENTS:

WHO good practices for pharmaceutical quality control laboratories

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SCHEDULE FOR DRAFT WORKING DOCUMENT QAS/21.882:

WHO good practices for pharmaceutical quality control laboratories

Description of Activity	Date
Preparation of first draft working document by HQ/LNS Laboratory Networks and Services and external experts.	January 2021
Discussion at the Consultation on Screening Technologies, Laboratory Tools, and Specifications for Medicines. Establishment of an expert working group to further develop the document.	10 – 13 May 2021
Internal discussion on the scope and addressees of the document with colleagues from the Regulation and Prequalification Department	June 2021
Discussion of the document in a series of virtual meetings with the expert working group. Preparation of revision 1.	November 2021 – May 2023
Discuss at the Consultation on Good Practices for Health Products Manufacture and Inspection	27-29 June 2023
Preparation of second draft working document for public consultation	July – August 2023
Mailing of revision 2 of the working document inviting comments and posting it on the WHO website for public consultation.	August – October 2023
Any other follow-up action as required.	TBD

WHO good practices for pharmaceutical quality control laboratories

World Health Organization

1 General considerations

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 guidelines which were published as Annex 3 of the WHO Technical Report Series, No. 902, 2002. These guidelines were subsequently revised and published as Annex 1 of the WHO Technical Report Series, No 957, 2010 and was renamed as "WHO good practices for pharmaceutical quality control laboratories".

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

The present document provides advice on the quality management system (QMS) within which the analysis of pharmaceutical products by quality control laboratories (QCL) 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 laboratory practices for pharmaceutical quality control laboratories and facilitate mutual recognition of test results.

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

The good practice outlined below is to be considered as a general guide and it may be adapted to meet individual needs provided that an equivalent level of assurance is achieved. For items 4.3, 4.4, 4.5, 4.6 and 6.7 (Performance evaluation, Risk management, Crisis management, Communication management and Measurement Uncertainty, where applicable), from the new section 4 on “Planning and strategic management”, a period of adaptation from the publication of this document will be given to allow laboratories to properly implement these new requirements.

This guideline is applicable to any pharmaceutical quality control laboratory, be it a national quality control laboratory (NQCL), a commercial quality control laboratory, a third-party

contract quality control laboratory or a quality control laboratory of a pharmaceutical manufacturer. However, it does not include guidance for those laboratories involved in the testing of biological products (e.g., vaccines and blood products), nor for microbiology laboratories. Separate guidance for such laboratories is available, e.g., WHO good practices for pharmaceutical microbiology laboratories *(3)*. It should be noted that specifications and quality assurance objectives may be different for NQCLs and quality control laboratories of a pharmaceutical manufacturer. The laboratories which comply with these guidelines should be organized in operating to meet the requirements set out in this document.

Pharmaceutical quality control testing

In a QCL of a pharmaceutical manufacturer testing usually comprises of the repetitive analysis of pharmaceutical products. However, an NQCL has to be able to test and to 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.

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; and
- the analysis should be correctly planned and executed.

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

National Quality Control Laboratories (NQCLs)

A government, normally through the national medicines regulatory authority (NRA), may establish and maintain a NQCL. Large countries may require several NQCLs to conform to 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 NRA.

A NQCL should provide effective support to and collaborate with the NRA. 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 NRA and, where necessary, the

appropriate legal action should be instituted.

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; and

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

It is also expected that NQCLs perform compliance testing in accordance to 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.

2 Glossary

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

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

active pharmaceutical ingredient (API). 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 test report. An analytical test report usually includes a brief description of the test procedure(s) employed, results of the analysis, discussion (if applicable) and conclusions and/or recommendations for one or more samples submitted for testing (6.10).

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 (6.4).

analytical acceptance criteria. Performance criteria applied to results obtained from the analysis

performed. These criteria are pre-defined 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.

acceptance criterion for an analytical result. Predefined and documented criteria by which a result is considered to be within the limit(s) or to exceed the limit(s) indicated in the specification.

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 which 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 and/or letters which 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 (i.e., a certificate) that provides the value of the specified property, its associated uncertainty and a statement of metrological traceability.

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

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 the organization to manage 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 cyber-attack or a pandemic.

design qualification (DQ). 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.

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.

equipment qualification (EQ). Action of proving and documenting that any analytical equipment complies with the required specifications and performs suitably for its intended purpose (5.3).

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. It is calculated from a combined standard uncertainty and a coverage factor k. Estimation of uncertainty from a certain source of variation can be indicated already as an expanded uncertainty (for example, the maximum admissible deviation from the nominal volume for volumetric apparatus).

good manufacturing practice(s) (GMP). That part of quality assurance which 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 (IQ). The performance of tests to ensure that the analytical equipment used in a laboratory is correctly installed and operates in accordance with established

specifications.

level of confidence. A number expressing the degree of confidence in a quoted result, e.g., 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 (QMS) performed by senior management on a regular basis.

manufacturer. A company that carries out operations such as the production, packaging, testing, repackaging, labelling and/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 characterises 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 (OQ). Documented verification that the analytical equipment performs as intended over all anticipated operating ranges.

out-of-specification (OOS) result. All test results that fall outside the specifications or acceptance criteria established in product dossiers, drug master files, pharmacopoeias or by the manufacturer.

out-of-trend (OOT) result. A result, from a series of analytical results obtained during a certain period of time, which 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 that trend analysis is performed for test results during stability testing, environmental controls and yields, where applicable.

performance qualification (PQ). 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 (API), which 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 and/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.

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 (QMS). An appropriate infrastructure, 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

(3.2).

quality manager (QM). 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 (3.1.4. m.).

quality manual. A handbook that describes the various elements of the quality management system (QMS) for assuring the quality of the test results generated by a laboratory (3.2.3).

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

quality unit(s). An organizational unit, independent of production, which 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, which 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. (Source: WHO Guideline on risk management)

secondary reference substance (or standard). A substance whose characteristics are assigned and/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, full handwritten signature, personal seal or 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 (SOP). An authorized written procedure giving instructions for performing operations, both general and specific.

standard uncertainty. 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.

system suitability test. A test which is performed to ensure that the analytical procedure fulfils the acceptance criteria which 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 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 which 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 lab demonstrate it has the ability to adequately operate the pharmacopoeial method or official method approved by regulatory authorities

verification of performance. A test procedure regularly applied to a system (e.g., liquid chromatographic system) to demonstrate consistency of response.

3 Organization and management system

3.1 Structural and general requirements

3.1.1 The laboratory, or the organization of which it is part, should be an entity that is legally authorized to function and can be held responsible for the test results, certificates of analysis and other types of work that they perform.

3.1.2 The laboratory should be organized and operate so as to meet the requirements laid down in these guidelines.

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

3.1.4 The laboratory should:

a. have managerial and technical personnel with the authority and resources (i.e. financial, human and infrastructure) needed to carry out their duties;
b. 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;
c. 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; evaluate, review and document continuously the declarations of interest with respect to the ongoing work;
d. 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, but not limited to information contained in marketing authorizations, analytical methods, the transfer of results or reports, etc.;
e. be responsible, through legally enforceable commitments, for the management of all information obtained or created during the performance of laboratory activities;
f. 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 and act impartially, be competent and work in accordance with the laboratory's QMS;
g. 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 NRA in the case of a NQCL), and the relationships between management, technical

operations, support services and the QMS;

h. specify the responsibility, authority and inter-relationships of all personnel who manage, perform, verify, review or approve work which affects the results of laboratory activities;

i. ensure the precise allocation of responsibilities, particularly in the designation of specific units for particular types of medicines, if deemed necessary;

j. nominate trained substitutes/deputies for key management and specialized scientific personnel;

k. provide adequate supervision of staff, including trainees, by persons familiar with the test and/or calibration, validation and verification of methods and procedures, as well as their purpose and the assessment of the results;

l. have management, which has the overall responsibility for the technical operations and the provision of resources needed in order to ensure the required quality of laboratory operations;

m. designate a member of staff as quality manager who, irrespective of other duties he/she may have, will ensure compliance with the QMS. The nominated quality manager should have direct access to the highest level of management at which decisions are taken on laboratory policies or resources;

n. 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;

o. ensure the traceability of the sample from receipt, throughout the stages of testing, to the completion of the analytical test report; a registry 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;

p. maintain an up-to-date collection of all specifications and related documents (paper or electronic) used in the laboratory; and

q. have appropriate safety procedures (section 7).

3.2 Quality management system

3.2.1 The Quality Manager should ensure the establishment, implementation and maintenance of a QMS appropriate to the scope of activities in the laboratory.

3.2.2 The QMS should be communicated and understood by the appropriate personnel. The elements of this system should be documented (e.g., electronically or paper).

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

a. a quality policy statement, including at least the following:

i. a statement of the laboratory management's intentions with respect to the standard of service it will provide, including policies and objectives which address the competence, impartiality and consistent operation of the laboratory,
ii. a commitment to developing, implementing and maintaining an effective QMS and continuously improving its effectiveness,
iii. the laboratory management's commitment to compliance with the content of these guidelines, and
iv. 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;

b. the structure of the laboratory (organizational chart or equivalent document);
c. the operational and functional activities pertaining to quality so that the extent and the limits of the responsibilities are clearly defined;
d. an outline of the structure of documentation used in the laboratory QMS;
e. the general internal quality management procedures;
f. the requirements of qualification, experience and competencies of personnel and the policy for initial and in-service training of staff;
g. The following policies should be applied:-
h. internal and external audits;
i. implementing and verifying corrective and preventive actions;
j. dealing with complaints;
k. for performing management reviews of the QMS;
l. selecting, establishing and approving analytical procedures;
m. handling of atypical and OOS results;
n. data governance;
o. the employment, handling and storage conditions of appropriate reference substances and reference materials;
p. participation in proficiency testing schemes and collaborative studies, as appropriate, for the assessment of performance;

[**Note from the Secretariat.** In the previous version of the guideline, the requirement for having "a policy for participation in appropriate proficiency testing schemes and collaborative studies and the evaluation of the performance" was "applicable to national pharmaceutical quality control laboratories but may be applied by other laboratories". With the revision of the guideline, this requirement shall become applicable to any pharmaceutical quality control laboratory, be it a quality control laboratory of a pharmaceutical manufacturer, a commercial

laboratory, a third-party contract laboratory or a national quality control laboratory (see Chapter 1, General Considerations). **Comments are sought on this proposal.]**

q. addressing risks and opportunities; and

r. evaluation, selection, monitoring of performance and re-evaluation of select service providers and suppliers".

3.2.4 The Quality Manager should ensure the establishment, implementation and maintenance of Standard Operating Procedures (SOPs) for all administrative and technical operations, such as:

a. personnel matters, including qualifications, training, clothing and hygiene (5.1);
b. control of documents, records and data integrity (3.3, 3.5 and 3.6);
c. change control (3.4);
d. implementation and verification of corrective and preventive actions (3.7);
e. internal audits (3.8);
f. dealing with complaints (3.9);
g. the purchase and receipt of consignments of supplies (e.g., reagents, materials) (4.1 and 5.4);
h. the procurement, preparation and control of reference substances and reference materials (5.5);
i. the qualification of equipment, including calibration (5.3);
j. preventive maintenance and verification of instruments and equipment (5.3);
k. the internal labelling, quarantine and storage of materials and solutions (5.4);
l. sampling, if performed by the laboratory (6.1);
m. the testing of samples with descriptions of the methods and equipment used (6.5);
n. validation and verification of analytical procedures (6.3);
o. validity of test results (6.8);
p. atypical and OOS results (6.9);
q. nonconforming work (6.11);
r. risks and opportunities (4.4);
s. the cleaning of laboratory facilities, including bench tops, equipment, workstations, clean rooms (aseptic suites) and glassware (5.2);
t. the monitoring of environmental conditions (e.g., temperature and humidity) (5.2);
u. the monitoring of storage conditions (5.2); and
v. the disposal of reagents, standards and samples (5.2, 6.2, 6.12 and 7).

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

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

3.3 Control of documentation

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

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

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

3.3.3 Staff should be informed when new and revised procedures enter into force. The change control system in place (3.4.1) should ensure that:

a. 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 (quality unit); and
b. staff acknowledge that they are aware of applicable changes and their date of implementation by a signature (electronic or manual) or by an alternative mechanism.

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

3.4 Change control

3.4.1 The laboratory should have an SOP to manage changes. Steps in the procedure should include the assessment of impact, gaps, risk and opportunities. Request for changes should be reviewed and implemented only after approval by the responsible persons. Records should be kept.

3.4.2 When changes are required, necessitated by, for example, improvement to or introduction of new method or relevant procedure, increase or decrease in work-load, range of laboratory activities, staffing levels, these should be approved and monitored by senior management.

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

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

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

3.5 Control of records

3.5.1 Identification, collection, indexing, retrieval, storage, access, maintenance and disposal of all quality and technical/scientific records should be described in the applicable procedure.

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

3.5.3 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 (e.g., chromatograms and spectra, if applicable, either in paper or electronic mode).

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

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

3.5.6 A data and information management system, which is either paper-based, or software-based (e.g., a Laboratory Information Management System, LIMS) that ensures traceability of operations, should be in place. Access to stored electronic data should be restricted to authorized personnel.

3.5.7 Samples tested in the laboratory shall 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 do not require otherwise.

3.5.8 All quality and technical/scientific records (including analytical test reports, certificates of analysis and analytical worksheets) should be legible, readily retrievable, stored and retained within a secure depository with controlled access which provides a suitable environment preventing damage or deterioration and/or loss.

3.5.9 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)*.

3.5.10 Quality management records should include reports from internal (and external, if performed) audits, inspections and management reviews, risk assessment, as well as records of all complaints and their investigations and records of possible corrective and preventive actions.

3.5.11 Detailed recommendations are provided in the *WHO guideline on data integrity (4)* and should be implemented. Additional guidance on implementation can be found in the GEON guideline on *Management of documents and records (5)*.

3.6 Control of data

3.6.1 A master plan should be prepared for the validation of any information system used for collection, processing, recording, reporting, storage or retrieval of data. Any validation report, to demonstrate suitability for use, should be prepared, approved by the Quality manager and available to the staff concerned. A Standard Operating Procedure (SOP) should be available which describes the use of a LIMS and/ or paper/electronic based recording system, access rules and the periodicity and type of backup, either cloud-based or on another server, including the restoration of data, should be implemented.

3.6.2 Commercial off-the-shelf software in general use within its designed application range can be considered to be sufficiently validated.

3.6.3 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.

3.6.4 The information systems should be:

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

3.6.5 The Quality Manager should ensure that for test data in computerized systems:

a. electronic data is protected from unauthorized access and an audit trail is maintained;
b. computer software developed by the user is documented in sufficient detail and appropriately validated or verified as being suitable for use;
c. 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; and
d. electronic data is backed up at appropriate regular intervals, is retrievable and stored suitably to prevent data loss.

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

3.6.7 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.

3.6.8 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

3.7.1 The laboratory should investigate any deviation or non-conformity reported by an analyst, or otherwise found, conduct a root cause analysis with the analyst to identify the problem(s) found and take the appropriate action to rectify the non-conformity.

3.7.2 The Quality Manager should:

a. define the responsible person(s) for any action deemed necessary and establish timelines for implementation,
b. review the effectiveness of any corrective action taken to eliminate the problem,
c. evaluate any risks and opportunities which were identified, and.

d. prepare a report to include evidence of the nature of the deviations, determined cause(s), any subsequent actions taken, and the results of any corrective action implemented, recorded and retained.

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

3.7.4 Any situation which may lead to a potential deviation/nonconformity should be adequately addressed, similar to 3.7.3, leading to a preventive action. Preventive actions can be treated as a risk or as an opportunity, depending on the type of potential impact of the action (4.4).

3.7.5 Any actions arising from handling nonconforming work (6.11) are to be addressed as described in 3.7.1 to 3.7.4.

3.8 Internal audits

3.8.1 The quality manager is responsible for organizing internal audits addressing all relevant elements of the QMS which comprises 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.

3.8.2 An SOP should be established and incorporate a detailed procedure for the planning and performance of the audits:

a. ensure that internal audits are planned and scheduled periodically by the Quality Manager (at least once a year) to allow for systematic audits;
b. define the scope for 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;
c. ensure that audits are carried out by the Quality Manager assisted by trained personnel who are independent from the activity to be audited
d. ensure that the results of the audits (audit conclusion) are reported to relevant management and communicated to staff;
e. Implement appropriate corrective and preventive actions without undue delay should non-compliance(s) have been identified; and
f. retain records as evidence of the implementation of the audit programme and the audit results. Laboratories may also be subject to audits to assess their procedures and systems

by external auditors (e.g., medicine inspectorate for manufacturers, peer review and/ or ISO accreditation for NQCLs.) Participation in an appropriate externally organised QAS for NQCLs should, also, be undertaken (e.g., WHO EQAAS). Audit reports should be reported and discussed at the Management Review.

3.9 Complaints

3.9.1 The handling process for complaints should be co-ordinated by the Quality Manager and comprise, as a minimum, the following:

a. a description of the process for receiving, verifying, investigating, tracking and deciding what actions are to be taken in response to a submitted complaint;
b. assurance that the appropriate action is taken to resolve the complaint, if needed;
c. verification that the whole process is documented and fully traceable; and
d. the complainant should be informed of the outcome of the investigation performed.

3.9.2 Where possible, the process should include a member of the staff not directly related with 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.

3.10 Management review

3.10.1 Laboratory management review(s) should be convened at planned intervals (at least annually) to monitor the effectiveness of the management system.

3.10.2 Senior management consisting, as a minimum, of the responsible management board director, the Laboratory Director 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 allow for its continuing suitability, adequacy, and effectiveness of the laboratory

3.10.3 The minutes of the management review record all decisions and actions related, at least, to the effectiveness of the QMS, improvement of the laboratory activities, required resources and necessary improvements.

3.10.4 The minutes of the management review should include information related, at least, to the following:

a. suitability of policies and procedures;
b. fulfilment of objectives;

c. status of actions from previous management reviews;
d. changes in internal and external factors that have impact in the laboratory;
e. outcome of internal and external audits or inspections and any follow-up required to correct any deficiencies;
f. changes in the laboratory activities (type, volume, range);
g. adequacy of resources (human, financial, material);
h. training programme;
i. feedback from customers and staff;
j. outcome of complaints received;
k. corrective and preventive actions;
l. effectiveness of any implemented improvements;
m. follow-up and monitoring of identified risks and opportunities;
n. outcomes of the assurance of the validity of results, such as the results of external quality control (collaborative studies and/or proficiency tests) and any investigations carried out as doubtful or unsatisfactory results obtained;
o. results of trend analysis; and
p. atypical and OOS results.

3.11 Improvement

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

3.11.2 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

4.1.1 The process for the selection and purchase of products and services which are required by the laboratory should be described. Products, for example, measurement materials (CRM/RM), chemical and biological reference substances (CRS and BRS), equipment, reagents, and services, for example, calibration, qualification, sampling, testing, maintenance, proficiency testing schemes and assessment and auditing should be included.

4.1.2 The laboratory should record:

a. the review and approval of the laboratory's requirements for externally provided supplies and services;
b. the definition of the criteria for evaluation, selection, monitoring of performance and re-evaluation of the external providers;
c. the evaluation of suppliers of critical supplies and services which affect quality of testing, and list approved suppliers whenever applicable, which have been demonstrated to be of a suitable quality with respect to the requirements of the laboratory; and
d. any actions taken arising from evaluations, monitoring of performance and re-evaluations of the external providers.

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

a. the products and services to be provided and their acceptance criteria;
b. competence (if applicable), including any required qualification of personnel; and
c. activities that the laboratory, or its customer, intend to perform at the external provider's premises.

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

4.2 Review of tenders and contracts

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

a. the requirements are adequately defined and documented;
b. the contract laboratory or a contracted organization has the capability and resources to meet the requirements;
c. the appropriate methods or procedures are selected which are capable of meeting the requirements of the laboratory and suitable for the samples to be tested; and
d. the contract 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.

4.2.2 There should be a written contract which clearly establishes the duties and responsibilities of each party, 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.

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

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

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

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

4.2.7 When subcontracting is performed:

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

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

4.2.9 The laboratory should maintain a register of all subcontractors that it uses and a record of the assessment of the competence of subcontractors.

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

4.3 Performance management

4.3.1 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 are taken. The objectives should be SMART: Specific, Measurable, Achievable, Relevant and Time-based. 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 timeframe or the percentage of analytical test reports issued within a specific time frame.

4.3.2 If the laboratory is part of an organization, such as a National Regulatory Authority, the objectives and targets should be fully aligned with the mission, vision and strategic goals of the organization, and are expected to be translated into operational plans and individual staff objectives (3).

4.3.3 The laboratory should monitor the technical performance regularly with regards to:

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

4.4 Quality Risk management

4.4.1 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 define tasks to minimize, monitor and control the probability and/or impact of unfortunate and undesired events and of potential failures *(13)*.

Two primary principles of quality risk management are:

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

4.4.2 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 risk, whether they are general risks for the laboratory or risks related with analytical testing. Possible steps to initiate and plan a quality risk management process may include:

a. defining the risk (or opportunity), including the potential cause for the event identified;
b. assembling background information on the potential impact (either positive, opportunity or negative risk); and

c. specifying a time-line, deliverables and an appropriate level of decision-making for the risk management process.

4.4.3 The laboratory should plan:

a. actions to address the risks and opportunities identified (4.4.1) 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 loss or consequences, adopting new practices, using new technologies, among many other options);
b. how to integrate and implement these actions into its management system; and
c. how to evaluate the effectiveness of these actions.

4.4.4 The process of identification and treatment of risks and opportunities should be recorded, monitored and duly reviewed on a regularly basis by senior management during management review (3.9).

4.4.5 The risks and opportunities identified and monitored should be communicated to staff in an adequate manner.

4.5 Crisis management

4.5.1 There are specific concerns about ensuring the correct and efficient functioning of the laboratory at all times, which are dependent 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 an incident 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.

4.5.2 The laboratory should establish and document system of prevention and recovery in the event of an unplanned disruption in service which should guarantees an employee's security and allows them to continue performing their work.

4.5.3 The established system or plan is preventive, hence defined in advance, potentially allowing for business processes, assets and personnel to be protected and able to function quickly in the event of a significant disruption, such as a natural disaster (fire, flood, weather-related events), a cyber-attack or a pandemic. The documented recovery plan should include:

a. inputs from key stakeholders and personnel;

b. the definition of critical activities, which will determine key resources, such as IT, infrastructure, key personnel, among others;

c. the performance of a risk analysis to establish any risk which can affect the laboratory's activities, and the impact of those risks. The implementation of measures to mitigate the risks and recover activities which are identified as critical to the organization, which should be tested for efficacy and reviewed periodically to ensure that it is up-to-date; and

d. where possible establishing, a continuity team of adequately trained members (see section 6.5), responsible to establish and implement appropriate planning and recovery strategies and to adopt and when necessary, adapt them.

4.5.4 Recovery strategies for information technology should be developed, such as keeping or implemented manual workflows so that the activities will continue while computer systems are being restored. An IT disaster recovery plan should be defined.

4.5.5 The laboratory should test the business continuity plan established, e.g., by simulation, to confirm its suitability for the intended purpose.

4.5.6 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 the remedial actions taken.

4.6 Communication management

4.6.1 The laboratory should ensure that staff and stakeholders are informed and are aware of the results of performance monitoring (4.3), either from management review (3.9 and 4.3.1), or from other monitoring tools (4.3.2).

4.6.2 A laboratory that is part of an organization, such as a National Regulatory Authority 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 (4.5.6).

5 Resources

5.1 Personnel

5.1.1 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.

5.1.2 The job descriptions should be in place for all personnel involved in tests and other laboratory activities, for example, calibrations, validations, verifications, qualifications and maintenance. The laboratory should maintain records of the competencies of the personnel, including their education, qualification, training, and experience.

5.1.3 The laboratory should have the following managerial and technical personnel.

a. A laboratory manager (or director or head of the laboratory) who should have appropriate qualifications to the position, with extensive experience in a supervisory role in medicines analysis in a pharmaceutical quality control laboratory, in the regulatory sector or in industry. Its experience should enable it to assume full responsibility for all operations, including analytical, organisational, administrative and educational. This person is also responsible for ensuring that:
   i. key members of the laboratory staff have the requisite competencies appropriate for their required functions and their grades reflect their responsibilities;
   ii. the adequacy of existing training procedures for staffing, is reviewed periodically
   iii. the technical management is adequately supervised; and
   iv. the certificates of analysis, analytical test reports and other important reports and protocols are approved.

b. The laboratory director could be supported and complemented by one or more technical managers, with extensive experience in medicines analysis in a pharmaceutical quality control laboratory (for instance, in microbiological testing), which would have the full responsibility for the analytical operations and for direct management and supervision of the team of analysts.

c. The laboratory should have a Quality Manager who shall have responsibility and authority to implement and ensure compliance with the Quality Management System and quality control activities. Preferably, the Quality Manager should remain independent from routine laboratory analytical activities, depending on the size of the laboratory. The QM

organizes internal audits of various laboratory activities, with the participation, preferably, of another member of staff, according to a schedule approved during the Management Review. The QM ensures that:

i. personnel operating specific equipment, instruments or other devices are competent for the tasks they are performing;
ii. personnel involved in tests and/or calibrations, validations or verifications are competent for the tasks they are performing;
iii. regular in-service training programmes to update and extend the skills of both analysts and technicians are arranged;
iv. the laboratory participates regularly in suitable proficiency testing schemes and, whenever possible, collaborative studies;
v. SOPs are prepared, approved and are available for all activities of the laboratory; and
vi. the safekeeping and control of substances 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 place under the supervision of an authorized person.

d. Qualified analysts, which normally should be graduates in pharmacy, analytical chemistry, or other relevant subjects, with the requisite knowledge, skills and ability to adequately perform the tasks assigned to them by managers. 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.

e. Technical staff should hold diplomas in their subjects awarded by technical or vocational schools.

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

5.1.5 The laboratory should authorize personnel to perform specific laboratory activities. Only sufficiently qualified/trained personnel should be allowed to perform specific laboratory activities.

5.1.6 The laboratory should have documented procedures and criteria for the continuous assessment of competence of personnel.

5.1.7 The laboratory should provide training/requalification of personnel.

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

a. performance of specific tests (i.e., pH, density, dissolution);
b. verification and review of results;
c. performance of analytical equipment qualification;
d. preparation and management of laboratory solutions; and
e. preparation of SOPs (at the request of the QM). :

5.1.9 The Laboratory Director is responsible for:

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

5.1.10 Supervisor analyst is responsible for:

a. review of all analytical data to ensure the validity of the test result(s) to check the work performed and results obtained by the technician or analyst;
b. general technical activities which, by definition, are performed by the technical management, such as the review of technical documents (e.g., analytical test reports and certificates of analysis), as long as this activity is delegated; and
c. 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.

5.1.11 The laboratory should have an appropriate training schedule for staff, in particular to the ones responding to the technical and managerial needs of the laboratory. Inputs to the training plan can be gathered from internal audits, management review, from risks and opportunities, as well as other options available. On successful completion of training, the result(s) of evaluation should be recorded and available, and the name of the staff member be added to the competency matrix /master list.

5.2 Premises

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

5.2.2 Premises should adequately accommodate the features required of a medicine testing laboratory and such as to minimise the risk to the health of staff and the quality of the analytical results.

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

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

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

5.2.6 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 and laboratory accessories, reference substances and reference materials.

a. Storage facilities should be equipped to store material at the appropriate temperature and humidity conditions to maintain stability, if necessary, under refrigeration (2–8 °C) and frozen (-20 °C) and securely locked.
b. 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 the responsibility for the safekeeping of any of these reagents when in the workplace, to maintain a register of these substances and to control their use.
c. The head of each unit should accept personal responsibility for the safekeeping of any of these reagents kept in the workplace. All specified storage conditions should be controlled, monitored and records maintained. Access should be restricted to designated personnel.
d. The appropriate safety procedures should be drawn up and rigorously implemented wherever toxic or flammable reagents are stored or used.
e. The laboratory should provide appropriate separate storage rooms for storing flammable substances, fuming and concentrated acids and bases, volatile amines, self-igniting materials, such as metallic sodium and potassium.
f. Small stocks of acids, bases and solvents may be kept in the laboratory.
g. Gases can come from installed generators, external gas tanks stored outdoors, in a well-ventilated area, preferably isolated from the main building. Wherever possible, gas bottles in the laboratory are to be avoided but if gas bottles are present in the laboratory, they should be safely secured. However, it is recommended to install gas generators.

5.2.7 The laboratory should be equipped with adequate instruments and equipment, including work

benches, work stations and fume hoods. Separate instrument rooms for different measurement techniques should be available. There should be adequate safety equipment appropriately located and measures should be in place to ensure good housekeeping and cleaning routines.

5.2.8 Weighing areas should have adequate environmental conditions of which temperature and humidity are controlled.

5.2.9 Where necessary, cytotoxic substances preparation room should be equipped with, for example, isolator, laminar flow work bench, to handle, weigh, and manipulate genotoxic (and highly toxic) substances. Appropriate procedures should be in place to avoid exposure and contamination of the staff.

5.2.10 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 so as to protect the contents from deterioration.

a. Records should be kept in a secure room with access restricted to senior personnel.
b. Electronic records should be retained, and duplicate copies saved to an external server/cloud.

5.2.11 The environmental conditions, including lighting, energy sources, temperature, humidity and air pressure, should be appropriate to the functions and operations to be performed. The laboratory should ensure that the environmental conditions are monitored, controlled and documented.

5.2.12 Procedures should be in place for the safe removal of types of waste including toxic waste (chemical and biological), reagents, samples, solvents and air filters.

5.3 Equipment, instruments and other devices

5.3.1 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.

5.3.2 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 provided in Appendix 1.

5.3.3 All analytical equipment should be fit-for-its intended purpose. To demonstrate this, the EQ approach is recommended.

5.3.4 The EQ process can be described in terms of the following stages: Design Qualification (DQ), Installation Qualification (IQ), Operational Qualification (OQ), and Performance Qualification

(PQ).

5.3.5 The applicability of each stage of EQ will vary during the lifetime of the equipment; it depends on its role in the measurement process. All four stages will apply to the purchase of a new equipment. Aspects of DQ and IQ may need to be repeated following major changes (see Change Control in points 5.3.16 – 5.3.19). PQ, and many aspects of OQ, should be carried out throughout the entire lifecycle of the equipment.

5.3.6 The level of EQ must comply primarily with pharmacopoeia requirements and should address the intended purpose, as well as follow the manufacturers' recommendations.

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

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

5.3.9 The laboratory should ensure that the supplier of the equipment provides documents, tools, and services to assist EQ and, in particular, to provide clear instructions and details of tests required to demonstrate satisfactory performance, either they are performed by the laboratory or by the supplier or other external service provider. Such testing should remain under the control of the laboratory. The laboratory should also ensure that the supplier or an external service provider delivers necessary training, maintenance, repair and installation support.

5.3.10 The laboratory should establish a policy for when equipment should be serviced (i.e., subject to maintenance, calibration, and EQ testing). It must be clearly described for each type of analytical equipment in use:

a. the regularity of any kind of service; and
b. the events after which any kind of service is necessary.

5.3.11 An EQ plan / matrix should be available, to allow a clear overview of which are the equipment which undergo any type of intervention, if it is performed by staff or by an external service provider and when this intervention will take place. The laboratory should keep track of the interventions which were performed and when they were performed and in case there is a significant deviation from the established schedule, it should be addressed under 3.7.

5.3.12 A preventive maintenance schedule should be included in a specific plan, or in an equipment qualification and maintenance plan. These activities can be performed by the laboratory or

entrusted to a competent organization and must be followed by appropriate EQ tests.

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

5.3.14 Direct evidence of traceability is less important for parameters for which stability during analysis is critical rather than accuracy (e.g., mobile phase flow rates, for which stability is controlled by a system suitability test).

5.3.15 For qualification or calibration of analytical equipment, suitable reference substances or reference materials should be used.

5.3.16 A change control process should be assured by the laboratory to guide the assessment, execution, documentation, and approval of any changes to the analytical equipment. Senior analysts should assess the effects of changes to determine what, if any, requalification activities are required.

5.3.17 The typical changes, after which analytical equipment should undergo the appropriate requalification are:

a. movement or relocation of the equipment;
b. interruption to services or utilities;
c. repair or maintenance (including preventive);
d. modifications;
e. change of purpose/use; and
f. analytical results which, after a suitable investigation, indicate that the EQ is no longer valid.

5.3.18 Analytical equipment, shown to be defective, or outside specified limits, should be taken out of service and clearly labeled or marked. It should not be used until they have been repaired and requalified.

5.3.19 Each stage of the qualification process involves the same general approach to the EQ documentation: the preparation of a qualification plan (can be combined with protocol) defining the scope of qualification (e.g. the tests to be performed and the acceptance criteria); the execution of the plan (during which the results of the tests are recorded on a work-sheet by a competent analyst as the tests are performed); and the production of a report (and, if required, a certificate) in which the results of EQ are documented.

5.3.20 Specific SOPs 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.

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

a. all equipment and their modules and accessories must be uniquely identified, including:
   i. the manufacturer's name, instrument name, model, and serial number; any identifying number allocated by the Laboratory;
   ii. the location, where appropriate
   iii. the equipment manufacturer's instructions, if available, or an indication of their location; and
   iv. the version and due date of requalification of any computer hardware, firmware and software.
b. All analytical equipment requiring calibration should be labeled, coded, or otherwise identified to indicate the status of calibration and the date when re-calibration is scheduled.
c. define clearly the responsibility level of the senior analyst required to perform maintenance, calibration and EQ;
d. provide details of each check and test to be performed, the specification and acceptance criteria;
e. provide sufficient information on the procedures and materials required to perform each check and test;
f. state the date on which EQ test(s) was performed and the result of qualification and each check or test;
g. state the reason for performing qualification (e.g. following the installation of a new equipment, following routine service, or following equipment malfunction);
h. provide clear information on the action to be taken in the event of test or qualification failure;
i. state the circumstances which may or will necessitate re-qualification of the equipment (e.g., following service or re-calibration); and
j. a history of any damage, malfunction, modification or repair; the name(s) and signatures of the person who actually performed the test(s), and the name and signature of the QM authorizing the completion of a qualification.

5.3.22 Equipment log-books should be maintained to identify the individual modules and accessories that constitute the equipment and be used to record the overall history of the equipment (e.g. the date of purchase, the initial qualification, and entry into service; the dates of when subsequent maintenance, calibration, and qualification have been performed and when these are next

scheduled.

5.3.23 The software that the laboratory uses must be appropriately validated, preferably at the same time as the software is developed. If the laboratory is not able to control the development of the software, it is an accepted practice to provide a software validation certificate from the manufacturer, to ensure compliance with the requirements of the pharmaceutical sector.

5.3.24 The level of software validation is determined by its function. It is customary to distinguish between firmware levels (lack of user access), and software that is used for Equipment Control, Data Acquisition, and Processing.

5.3.25 For further guidance on qualification of equipment, please refer to *(6, 14-17)*.

5.4 Reagents and materials

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

5.4.2 Commercial reagents should come from verified and approved external providers, preferably certified suppliers.

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

5.4.4 Management of the reagents must cover the entire life cycle of the reagents from purchasing/preparation (in the case of preparations) to use and disposal.

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

a. type of reagents and the quality, depending on their use,
b. selection of the supplier based on the suppliers' qualifications,
c. verification of reagents upon receipt,
d. labelling of the reagent (avoiding misuse/misidentification),
e. storage conditions,
f. ensuring that the reagent is not compromised in any way before being used,
g. checking the expiry dates of reagents before use (it is not necessary to document this verification),
h. documenting the use of reagents used in analyses ensuring traceability at least to batch number and expiry date, and
i. disposal of the reagent.

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

5.4.7 The verification should be made as 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.

5.4.8 The level of verification should be decided by the laboratory.

5.4.9 The labelling information for all types of reagents should be recorded on the container or may be recorded in a leaflet, register, or LIMS system (or equivalent) and should include the following information:

a. name of the substance/reagent,
b. date of receipt and date of opening the container (or preparation date),
c. expiry date (or retest date, as justified),
d. storage conditions, if applicable, any specific protection measures (e.g., protect from heat/light/atmosphere),
e. concentration and/or purity of the reagent, if applicable, and
f. hazard and precaution codes.

5.4.10 For purchased reagents in their original container additionally is expected the following labelling:

a. manufacturer or supplier of the substance,
b. batch number, and
c. identification: where the same batch is supplied in several containers, appropriate identification (e.g., vials 1, 2, 3) can be indicated in the labels.

5.4.11 For purchased reagents which have been transferred into another container, additionally is expected the following labelling:

a. name/Initials of the person who transferred the reagent,
b. batch number,
c. transfer date, and
d. identification (in cases of transfer to several vials (aliquoted), appropriate identification (e.g., vial 1, 2, 3) should be indicated in the labels).

5.4.12 For in-house reagents (preparation of reagent solutions in the laboratory), additionally is expected the following labelling:

a. name/Initials of the person who prepared the reagent.
b. name and quantity of the reagents in the preparation (can be replaced by a reference, e.g., project number).
c. titre (or concentration or standardization factor).
d. date of the determination of the titre, and
e. name/Initials of the person who determined the titre.

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

a. name/Initials of the person who dispensed the water, and
b. if more than one production apparatus is available, the identity of the apparatus used must be documented.

5.4.14 For volumetric solutions, additionally is expected the following labelling:

a. name/Initials of the person who prepared the reagent,
b. name and quantity of the reagents in the preparation (can be replaced by a reference, e.g., project number),
c. titre,
d. date of the determination of the titre, and
e. name/Initials of the person who determined the titre.

5.4.15 For the preparation of reagent solutions in the laboratory:

a. responsibility for this task should be clearly specified in the job description of the assigned staff member,
b. SOP(s) should be used which cover the entire life cycle of the use of reagents in the laboratory and are in accordance with published pharmacopoeial or other appropriate standards (19).
c. records should be kept of the preparation of reagent solutions and standardization of volumetric solutions.

5.4.16 For the transportation and subdivision of reagents:

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

5.4.17 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. Reagents that appear to

have been tampered with should be rejected.

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

5.4.19 The quality of the water should be verified regularly to ensure that the various grades of water meet the appropriate specifications.

5.4.20 Reagents should be stored under the appropriate storage conditions (e.g., temperature, ventilation, fire hazard) and appropriately maintained (e.g., organised, tidy, segregated).

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

5.4.22 The expiry period policy must be documented by the laboratory (e.g., SOP).

5.4.23 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:

a. no expiry data is provided by the supplier, and
b. when after opening/transfer, environmental conditions (e.g., air, humidity) or further operations (e.g., dissolving a lyophilised material) affect the quality of the reagent.

5.4.24 The expiry date can be prolonged by providing scientifically sound and documented justifications, e.g., in cases where expired reagents can be used for a special purpose. In this case, the container must be re-labelled appropriately.

5.4.25 Reagents must be disposed of when the expiry date is exceeded or when they are no longer required.

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

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

5.5 Reference substances and reference materials

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

5.5.2 Reference materials are usually necessary for the calibration and/or qualification of equipment,

instruments, or other devices.

5.5.3 Pharmacopoeial reference substances should be employed when available and appropriate for the analysis. Otherwise,

- 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 (20) and used for the testing of a sample. The use of secondary reference substances by NQCL is discouraged.

- 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. Pharmacopoeial reference substances are considered primary reference substances against which secondary (working) reference substances can be calibrated.

5.5.4 A nominated staff member should be responsible for reference substances and reference materials.

5.5.5 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/lot number.

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

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

a. the identification number of the substance or material;
b. a precise description of the substance or material;
c. the source;
d. the date of receipt;
e. the batch designation or other identification code;
f. the intended use of the reference substance or reference material;
g. the location of storage in the laboratory, and any special storage conditions;
h. any further necessary information (e.g., the results of visual inspections);
i. expiry date or retest date (if applicable), otherwise – the valid use-by date;
j. a certificate or leaflet of a pharmacopoeial reference substance and a certified reference

material which indicates the use, the assigned content, if applicable, and its status (validity);

k. in the case of secondary reference substances or certified reference material, the certificate of calibration or analysis; and

l. 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.

5.5.7 The validity of reference substances and reference materials used in the laboratory should be checked before use and the corresponding information should be included in the test report (intended use, expiry date or retest date). The use of the pharmacopoeial reference substance for purposes other than those specified in the pharmacopoeia is at the user's risk, which should be properly assessed.

5.5.8 Reference substances prepared and stored in the laboratory should be re-tested 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.

5.5.9 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

6.1.1 If the laboratory is responsible for the sampling of pharmaceutical products for subsequent testing, a standard operating procedure, including a sampling plan, and a chain-of-custody procedure, should be established.

6.1.2 Samples should be representative of the batches of material from which they are taken and sampling should be carried out to avoid contamination, mix-ups or other adverse effects on the quality of the material being sampled.

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

a. reference to the sampling method used;
b. date and time of sampling;
c. data to identify and describe the sample (e.g. number, amount, name);
d. identification of the personnel performing sampling;
e. identification of the tools used for sampling ;
f. environmental or transport conditions;
g. diagrams or other equivalent means to identify the sampling location, when appropriate; and
h. deviations, additions to or exclusions from the sampling method and sampling plan.

6.1.4 Further information is provided in WHO guidance on sampling *(20)* and guidance on testing of "suspect" falsified medicines *(21)*.

6.2 Incoming samples

Sections 6.2.1 – 6.2.2 are applicable to NQCLs. The principle of the four W's (Who, What, When & Where) should be applied. Chain of Custody of each sample should be recorded.

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

a. 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, it is important that the quantity or amount of sample is sufficient to enable, if required, a number of replicate tests to be carried out and for part of the sample to be retained.

b. 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 ingredient(s). 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 case of borderline test results.

6.2.2 A sample should 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.

6.2.3 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.

6.2.4 The test request form should contain the following information:

a. the name of the person or institution that provided the sample and date of receipt
b. the source of the material;
c. a full description of the sample, including its composition, international non-proprietary name (INN) and brand name(s), (if available);
d. the package and container
e. dosage form and concentration or strength, the manufacturer name and the batch/lot number (if available);
f. the size of the sample;
g. the reason for requesting the analysis;
h. the date on which the sample was collected;
i. the size of the consignment from which it was taken, (if appropriate);
j. the expiry date or re-test date, if known;
k. reference documents and the specifications to be used for testing;
l. a record of any further comments (e.g. discrepancies found or associated hazard); and
m. the required storage conditions.

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

a. the sample amount is sufficient for the tests requested
b. the requirements for analytical testing are adequately defined and the laboratory has the required capability and resources to meet them; and

c. the appropriate tests and/or methods available are capable of meeting customers' requirements.

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.

6.2.6 Each sample and accompanying document (e.g., 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, or different batches of the same medicine or different sources of the same batch.

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

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

a. the registration number of the sample;
b. the date of receipt; and
c. the specific unit to which the sample is to be forwarded for analysis.

6.2.9 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.

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

6.2.11 The specific unit to which the sample is sent for testing is determined by the Laboratory Director (or designee).

6.2.12 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.

6.2.13 Unless a computerized system is used, copies or duplicates of all documentation should accompany each numbered sample when sent to the specific unit.

6.2.14 Testing should be performed as described under 6.5.

6.3 Selection, Validation, and verification of analytical procedures

6.3.1 The analytical procedures to be used for testing, either compliance testing or investigative testing, should be selected prior to the start of the analysis by the Laboratory.

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

6.3.3 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 which should be considered are listed in Table 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 (RTRT) on the production site by applying Process Analytical Technology (PAT). 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 1 - Characteristics to be consider 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 Precision	–	+[a]	–	+
				+
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.

6.3.4 Pharmacopoeial and official procedures can be considered as validated for the use described in the monograph(s), provided the pharmacopoeia does not explicitly require the validation of the

procedure. If validation is not required, method verification should be performed according to an approved protocol or a procedure to demonstrate that the laboratory can successfully execute the method and the pharmacopoeial procedure used is suitable for the sample being tested. The laboratory should in particular confirm that,

a. for a finished pharmaceutical product no interferences arise from the excipients present
b. for an API, impurities coming from the route of synthesis are adequately differentiated.
c. the system suitability requirements are appropriately fulfilled.
d. the reporting threshold for related substances are met,
e. the recovery and the precision of the procedure are within predefined limits.

If the pharmacopoeial method is adapted for a new purpose, other than the purpose described in the pharmacopoeia, then it should be validated for such a use.

6.3.5 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.

6.3.6 Verification is not required for basic pharmacopoeial methods such as (but not limited to), 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.

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

6.3.8 A major change to the analytical procedure, or in the composition of the product tested or in the synthesis of the API, might require re-validation of the compendial or official analytical procedure.

6.3.9 The performance of analytical procedures should be monitored over time throughout their life cycle.

6.3.10 Further guidance on validation of analytical procedures is available in WHO guideline on validation *(6)*.

6.4 Technical records

6.4.1 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, calculations and the results of testing. It includes all raw data obtained in the analysis.

6.4.2 The analytical worksheet contains documentary evidence either to confirm that the sample being examined is in accordance with the requirements or to support an OOS result.

6.4.3 A separate analytical worksheet should be used for each numbered sample or group of samples.

6.4.4 Analytical worksheets from different units relating to the same sample should be assembled together after all testing times have been finished/or after the whole analysis for the sample has been finished.

6.4.5 The analytical worksheet should provide the following information:

a. registration number of the sample;
b. page numbering, including the total number of pages (and including annexes);
c. date of the test request;
d. date(s) on which the analysis was started and completed;
e. name and signature of the analyst;
f. a description of the sample received;
g. references to the specifications and a full description of test methods by which the sample was tested, including the limits, if applicable;
h. identification of the test equipment used;
i. reference substance(s) used (including the provider, lot number, potency/content);
j. results of the system suitability test if, applicable;
k. identification of reagents, solvents, and columns (if applicable) employed;
l. results obtained, including those obtained from another internal analytical section, or external laboratory if applicable;
m. interpretation of the results and the final conclusions (whether or not the sample was found to comply with the specifications), approved and signed by a senior analyst/ supervisor; and
n. further comments, for example any deviation from a prescribed procedure which should be approved and reported or/and treated as nonconforming work (6.11), or when a part of the sample had been forwarded to another unit or contract laboratory for special tests and the date on which the results were received.

6.4.6 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.

6.4.7 The completed analytical worksheet should be signed by the responsible analyst(s) and reviewed and approved by the supervising senior analyst (either in paper format or electronically).

Calculations and data transfers should be checked in an appropriate and systematic manner.

6.4.8 Any changes made to original records, either in paper or electronic format, should be traceable: old and new information should be visible (or possible to visualize); who was responsible; when was it performed; and why. The deletion of data is not acceptable.

6.4.9 When a mistake is made in an analytical worksheet or when data or text need to be amended, the correction must be traceable (as directed in 3.5.9).

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

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

6.5 Testing

Testing of production samples from pharmaceutical manufacturers may be conducted entirely in the laboratory or for some, with high output, as a combination in-process controls, as of RTRT, using PAT, 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 work-plan.

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

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

6.5.2 When an unusual test is included in the specification requirements, the sample may need to be analysed by another unit or by a contract laboratory (4.2). The responsible analyst prepares the request and arranges for the transfer of the required number of units (bottles, vials or tablets) from the sample. Each of these units should bear the correct registration number. When the analytical test report contains the result (s) of the test(s) performed by a contract laboratory, these results should be identified as such in the final report.

6.5.3 Detailed guidance on pharmacopoeial requirements is usually given in the general notices and

specific monographs of the pharmacopeia. 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. Where system suitability criteria are defined in the method, they should be fulfilled. Any deviation from the test procedure should be approved and documented and, where applicable, addressed as nonconforming work (6.11).

6.5.4 Compliance with internal quality control criteria should be ensured (6.11).

6.5.5 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

6.6.1 Quantitative test results, particularly those obtained in the manufacture of an FPP, 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.

6.6.2 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 and a conclusion is prepared as to the conformance of the test result towards the specification.

6.6.3 Any test result should be traceable, when appropriate, to a suitable primary reference substance or material or, if appropriate, to a certified reference material.

6.6.4 Doubtful (atypical) results should be investigated.

6.6.5 Neither pharmacopoeias nor NRAs 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 while expressing result of investigative sample tested by the method which are not described in a pharmacopoeia or manufacturer's approved documentation. However, for investigative testing to identify the active ingredient in an unknown sample, it may also be required to report the content with its associated uncertainty

6.6.6 Test results should be reviewed and approved or rejected by a senior analyst/supervisor, according to the competency master list/matrix (5.1.7).

6.7 Measurement uncertainty

6.7.1 The uncertainty of measurement results is an essential component in 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.

6.7.2 The application of the concept of measurement uncertainty is necessary to comply with the requirements of ISO 17025. These requirements apply to all quantitative tests performed by NQCLs. The evaluation of measurement uncertainty for NQCLs can be found in the OMCL Quality Assurance Documents (24).

6.7.3 When compliance testing is conducted using pharmacopoeial analytical procedures and analytical procedures described in the marketing authorization documentation, the ISO 17025 requirements for evaluation of measurement uncertainty are considered to be met if all 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 to a specification limit rest with the laboratory and is made on a case-by-case basis.

6.7.4 Compliance testing may be performed by internally developed analytical procedures as long as these procedures have undergone appropriate validation for their intended use and allow for an unquestionable decision on compliance with the specification limits, taking account of the estimated measurement uncertainty.

6.7.5 A more thorough assessment of the measurement uncertainty should be performed, for instance, when:

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

6.7.6 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.

6.7.7 Applying the concept of measurement uncertainty to compliance testing allows for managing the risk of making the wrong accept/reject decisions, provided the following elements of the concept of uncertainty are implemented:

a. the decision rule on compliance of pharmaceutical products with specifications is defined; and
b. the uncertainty of the analysis results is evaluated by the laboratory.

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

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

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

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

6.7.11 The pharmacopoeial decision rule is simple “accept/reject”, with a guard bandwidth equal to the analytic variation typical of normal analytic practice. For a quality product, the analyte concentration must be within a range narrower than the specification width (by analytical variation accounted for in the specification). This provides a low probability of rejecting a quality product (low manufacturer risk). The pharmacopoeial decision rule works correctly only if the actual value of the uncertainty (in practice – estimated uncertainty) is fixed, i.e., does not exceed the critical value, which is the target uncertainty set for the certain 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 reason(s) for the unacceptably high uncertainty. The laboratory should ensure that the estimated uncertainty does not exceed the target uncertainty when performing analysis.

6.7.12 Compliance with normal analytical practice is required due to the specifics of the construction of acceptance criteria in pharmacopoeial monographs and marketing authorization documentation.

Therefore, for 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.

6.7.13 The recommendations for the target uncertainty and the maximum admissible uncertainty for standard analytical operations (for normal analytical practice) are provided in Annex 2.

6.7.14 The application of the concept of normal analytical practice to the evaluation of measurement uncertainty is provided in Annex 3.

6.8 Validity of test results

6.8.1 The laboratory should have a procedure for ensuring the validity of results by reviewing the following activities, as appropriate by a senior staff member or QA manager:

a. reference substances and/or reference materials;
b. verifications of measuring and testing equipment;
c. appropriate quality control checks;
d. the data analysis, that does not require additional experiments (use of control charts and different kinds of correlation of results of the sample being tested).
e. replicate tests or calibrations using the same or different methods;
f. retesting of retained samples; and
g. a review of all raw data and reported results.

6.8.2 The performance of the laboratory should be assessed regularly by participation in:

a. proficiency testing schemes, organised both internally and externally; and/or
b. inter-laboratory comparisons such as collaborative studies.

6.8.3 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.

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

6.9 Out-of-specification results

6.9.1 An out-of-specification (OOS) result is a result which 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)*.

6.9.2 When a doubtful result (suspected OOS result) has been identified, a review of the different procedures applied during the testing process is to be undertaken by the supervisor with the analyst or technician before re-testing is performed by using a checklist. The investigation should ensure that:

a. original sample preparations are not discarded until the investigation is complete;
b. the appropriate procedure(s) was (were) applied and followed correctly;
c. examination of the raw data recorded on the analytical worksheet is undertaken to identify

possible discrepancies;

d. all calculations are checked;

e. the equipment used was qualified and calibrated and that system suitability tests were performed and were acceptable;

f. the appropriate reagents, solvents and reference substances were used; and

g. confirm that the correct glassware was used.

6.9.3 The identification of an error which caused an aberrant result will invalidate the result and a re-test of the sample will be necessary which should be conducted by the same technician /analyst.

6.9.4 Doubtful 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 an OOS result. However, further confirmation using another validated method, if available, may be advised and, if performed, should be fully documented.

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

6.9.6 An SOP should be in place for the conduct of an investigation of an OOS test result. All investigations and their conclusions should be recorded. In the event of an error, any corrective action taken, and any preventive action introduced should be recorded, implemented and treated as risks/opportunities.

6.9.7 If required, all individual results (all test data) with acceptance criteria should be reported. The SOP defined in 6.9.6 should also consider the general rules to report this type of results.

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

6.9.9 Critical review of the nature, number, and root cause of OOS, obtained within a given period, either confirmed or not confirmed, should be conducted during the Management review.

6.10 Reporting of results

6.10.1 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 QM and / or the Laboratory Director and/or designee. Subsequently, the dossier containing all the information pertaining to the sample including the origin, chain of custody, analytical data is archived.

6.10.2 Any amendments or changes to the original analytical test report will require the issue of a new

corrected document, where:

a. any change of information should be clearly identified and dated;
b. where appropriate, the reason for the change should be included in the new corrected document;
c. the new report should be uniquely identified and contain a reference to the original document it will replace; and
d. the new corrected document meets all the requirements.

6.10.3 When using pharmacopoeia methods and manufacturer's approved methods for compliance testing, it is not required to report the expanded uncertainty.

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

6.10.5 The analytical test report should provide the following information:

a. a title (e.g., "Test Report", "Analytical Test Report" or other suitable title);
b. the laboratory registration number of the sample;
c. the laboratory test report number;
d. the name and address of the laboratory testing the sample;
e. the name and address of the originator of the request for analysis;
f. the name, description and batch number of the sample, where appropriate;
g. an introduction giving the background to and the purpose of the investigation, if applicable;
h. 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;
i. the results of all the tests performed or the numerical results with the standard deviation of all the tests performed (if applicable);
j. where applicable, the expanded measurement uncertainty of the reportable result with a reference to its assessment and an explanation of how it was used in making the compliance decision;
k. a discussion of the results obtained, where appropriate;
l. a conclusion as to whether or not the sample(s) was (were) found to be within the limits of the specifications used, or for a sample for investigative testing, the substance(s) or ingredient(s) identified;
m. a statement to the effect that the results relate only to the items tested, calibrated or sampled;
n. a clear identification when results are from external providers;
o. the date on which the test(s) was (were) completed;
p. the signature of the head of the laboratory and/or other authorized person, reviewing and

authorizing the report;

q. the name and address of the original manufacturer and, if applicable, those of the re-packer and/or trader;
r. whether or not the sample(s) complies (comply) with the requirements;
s. if applicable, opinions and interpretations, adequately supported by evidence and issued by authorized personnel;
t. the date on which the sample was received;
u. the expiry date or retest date, if applicable; and
v. a statement indicating that the analytical test report, or any portion thereof, cannot be reproduced without the authorization of the laboratory.

6.10.6 A Certificate of Analysis (CoA) is prepared for each batch of a substance or product. CoA contains the same information as the Analytical Test Report except for (c) & (d). If applicable, the certificate should include information about the expanded uncertainty of the reportable result, the reference to its estimation and an explanation of how the decision rule was applied to determine compliance with specifications.

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

a. Data provided by the customer should be clearly identified.
b. In addition, a disclaimer should be included in the report when the information is supplied by the customer which could compromise the validity of results.
c. Where the laboratory has not been responsible for the sampling stage (e.g., the sample has been provided by the customer), the report should state that the results apply to the sample as received.

6.11 Non - conforming work

6.11.1 The term “non-conforming work” refers to any deviation of the analytical activities from procedures, internal requirements or analytical requirements agreed with the customer, which should be recorded, addressed, and managed. It is a technical and/or analytical deviation. These deviations to the specified limits comprise equipment, environment conditions, internal quality control criteria and system suitability criteria.

6.11.2 Managing non-conforming work follows the same rationale as described in 3.7 and can be treated under the same system, ensuring that:

a. 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;

b. an evaluation is made of the significance of the non-conforming work, including an impact analysis on previous results;

c. a decision is taken on the acceptability of the nonconforming work;

d. where necessary, the customer is notified and work is recalled; and

e. the responsibility for authorizing the resumption of work is defined.

6.11.3 Records of the non-conforming work are retained, as well as all defined actions.

6.11.4 Corrective actions (3.7) should be implemented if the evaluation indicates that there is a remote possibility that the nonconforming work can recur or there is a reasonable doubt about the conformity of the laboratory's operations with its own QMS.

6.11.5 Analysis of the data obtained from nonconforming work should be performed, addressing specifically those issues for which a trend is observed throughout time (e.g., a systematic non-conforming 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 to the identified risks and opportunities, should be reviewed periodically (3.10) and its impact assessed.

6.12 Retained samples

6.12.1 Samples should be retained (6.2.2) as required by the legislation or by the originator of the request for analysis. *(24)*.

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

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

6.12.4 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

7.1.1 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 to oversee the policy and to ensure compliance by all staff.

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

7.1.3 General and specific safety procedures reflecting identified risk should be made available to each staff member. Seminars should be held at pre-defined intervals as specified in QMS documentation.

7.1.4 General rules for safe working in accordance with national regulations and SOPs normally include, but is not limited to the following requirements:

a. safety data sheets should be available to staff before testing is carried out;
b. smoking, eating and drinking in the laboratory should be prohibited;
c. staff should be familiar with the use of fire-fighting equipment, including fire extinguishers, fire blankets and gas masks;
d. staff should wear laboratory coats or other suitable protective clothing, as required, including eye protection;
e. special care should be taken, as appropriate, in handling highly potent, infectious or volatile substances;
f. highly toxic and/or genotoxic samples should be handled in a specially designed facility to avoid the risk of contamination;
g. all containers of chemicals should be appropriately labelled and include prominent warnings (e.g., “poison”, “flammable”, “radioactive”) whenever appropriate;
h. adequate insulation and spark-proofing should be provided for electrical wiring and equipment, including refrigerators;
i. rules on the safe handling of cylinders of compressed gases should be observed and staff should be familiar with the relevant colour identification codes;
j. staff should not work alone in the laboratory; and
k. first-aid materials should be provided and staff instructed in first-aid techniques, emergency care and the use of antidotes.

7.1.5 Protective clothing should be available, including eye protection, masks and gloves. Safety showers should be installed. 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 SOPs for work with violent, uncontrollable or dangerous reactions when handling specific reagents (e.g., mixing water and acids or acetone–chloroform and ammonia), flammable products, 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.

7.1.6 An SOP for the storage and handling of controlled substances complying with applicable national legislation should be available and enforced.

7.1.7 Poisonous or hazardous products should be identified singled out and labelled appropriately.

7.1.8 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, if required by national regulations.

7.1.9 Replacement of toxic solvents and reagents by 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 the table below.

This list does not represent any requirements which should be fulfilled in order to comply with these guidelines. National medicines regulatory authorities (NRAs) 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
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

First-stage laboratory	
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
Optional items	
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	***Quantity***
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 callipers	1
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

	First-stage laboratory	
	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
	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 micro-determination 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
	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

First-stage laboratory	
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
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 22 January 2021).

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Appendix 2: Recommendations for the target uncertainty and the maximum admissible uncertainty for normal analytical practice

In order to effectively apply the concept of uncertainty to compliance testing in the pharmaceutical sector, the following key recommendations should be formulated (see 6.7, the pharmacopoeial decision rule):

a. recommendations for the target uncertainty for pharmacopoeial tests,

b. recommendations for the maximum admissible 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)*:

a. 1.0 % for volumetric titration of the conjugate acids, non-aqueous and acid-base titrations;

b. 1.5 % for redox and argentometric titrations ;

c. 2.0 % for complexometric titrations ;

d. 2.0 % and 3.0 % for ultraviolet spectrophotometry assays, using the reference substance and specific absorbance, respectively;

e. 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)*:

a. 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.

b. 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.

c. for tests Dissolution and Uniformity of Dosage Units, U^{tg} = 3.0%.

d. 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 ADMISSIBLE UNCERTAINTY FOR NORMAL ANALYTICAL PRACTICE

The approach of normal (routine) analytical practice (NAP) establishes the maximum admissible level of uncertainty from standard analytical operations (U_i^{tg}) and reflects the minimum pharmacopoeial requirements that should be met by all laboratories performing compliance testing (see 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 U^{est}) can be as large as the maximum admissible value (NAP recommendations), which can be greater than that achieved during the analytical procedure development/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", i.e., 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 (i.e., 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/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 (e.g., random variability of an analytical signal) and associated with sample preparation operations (weighing, dilution).

The requirements for the maximum admissible 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).

An 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 in such a way 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 in such a way 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 $\%RSD_{max}$ of the analytical signal for assay by separation technique for finished pharmaceutical products with symmetrical assay content limits.

	Number of individual injections $n^{(1)}$						
	2	3	4	5	6	7	8
(UCL – LCL)/2×100[2]	Maximum permitted relative standard deviation (per cent)						
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

(1) it assumes that the same number of repetitive injections is made for the test and reference solutions.
(2) UCL and LCL are upper and lower content limits, respectively.

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 3 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 admissible 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	Target uncertainty, mL	Target uncertainty, %
10 mL	0.05	0.50
20 mL	0.057	0.28
25 mL	0.0575	0.23
50 mL	0.085	0.17
100 mL	0.12	0.12
200 mL	0.2	0.1
250 mL	0.2	0.08
500 mL	0.35	0.07
1000 mL	0.5	0.05

Table 3. Target uncertainties specific to NAP due to the use of transfer pipettes ISO Class A of various volumes.

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

Table 4. Target uncertainties specific to NAP due to the use of graduated pipettes ISO Class A of different volumes.

Graduated pipette volume	Target uncertainty, mL	Target uncertainty, %(1)
0.5 mL	0.0061	1.23
1.0 mL	0.0074	0.74
2.0 mL	0.012	0.62
5.0 mL	0.037	0.74
10.0 mL	0.062	0.62
25.0 mL	0.123	0.49

(1) 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 in order 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 admissible uncertainty).

For the initial reproduction of the analytical procedure in 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 API is provided in Appendix 3.

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World Health Organization

Appendix 3: Examples of the uncertainty estimation on 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)*. It means the laboratory can adequately 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 admissible uncertainty associated with standard analytical operations can be found in the Ph. Eur. *(5)*, Table 1 and the State Pharmacopoeia of Ukraine (SPhU) *(6)*. The recommendations for maximum admissible 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 and/or measurements). This allows mitigating 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; interference of excipients on measurements, and so on) 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 admissible 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:

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

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_o 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 – the coefficient for converting the concentration into a reportable result (in the 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 combine uncertainties from individual sources of variability directly 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/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)*.

Quantities grouped under formula term *K* (group 4) are usually conversion factors and, therefore, are not sources of variation. Otherwise, their contribution to the combined uncertainty should be evaluated.

<u>1. An example of uncertainty estimation for NAP compliance for a chromatographic assay of API.</u>

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% (Annex 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. 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 below:

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

*0.2 mg is the recommended target uncertainty for the weighing operation (normal analytical practice recommendation, Appendix 2);

Appendix 2, table 2; * Appendix 2, table 4.

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

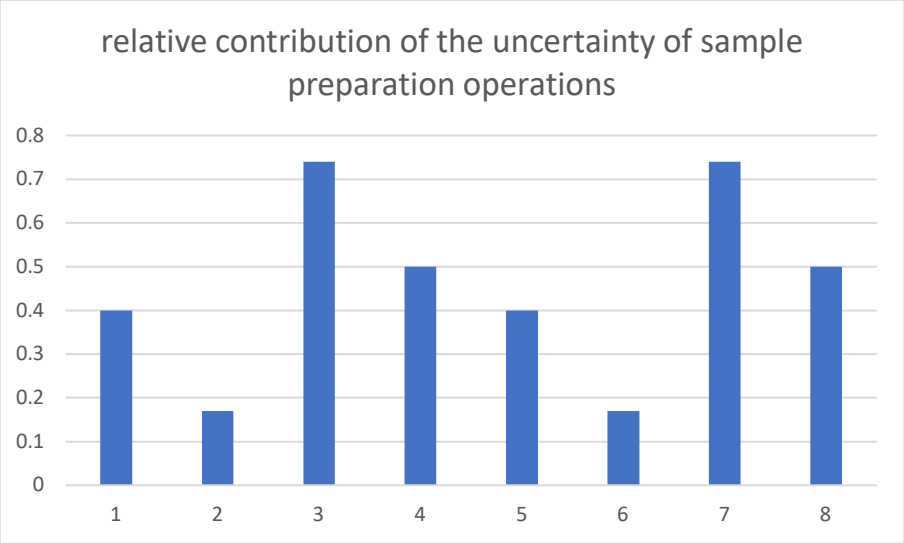
The uncertainty for sample preparation according to NAP recommendations (U_{SP}^{tg}) can be estimated as follows:

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

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 on the diagram: X-axis shows the number of the sample preparation operation (No 1-8); Y-axis shows associated uncertainty (%).



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

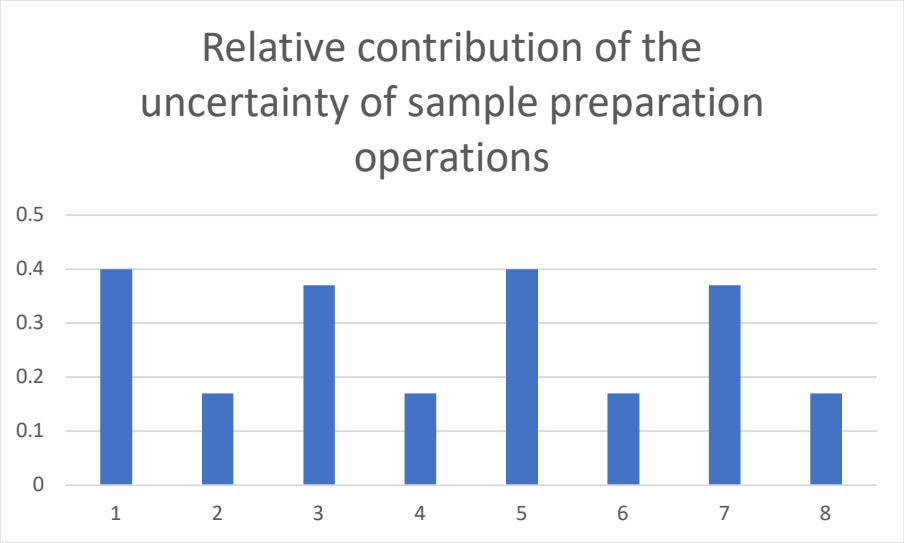
Operations of the second dilution No 3 and 7 (taking an aliquot of 1.0 mL) need optimization first, and then operations No 4 and 8 (dilution to 10.0 mL).

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 follows:

The 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 the diagram below.



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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