



REPUBLIC OF LEBANON
MINISTRY OF PUBLIC HEALTH

Good Laboratory Practices for Pharmaceutical Quality Control Laboratories in Lebanon



2016
Edition 1

Issued by: Quality Assurance of Pharmaceutical Products Program
Prepared by: Dr. Rita Karam & Dr. Mazen El Kurdi

Table of Contents

Introduction.....	3
Glossary	4
I. Management and Infrastructures.....	10
1. Organization and management	10
2. Quality management system	11
3. Control of documentation	13
4. Records	14
5. Contracts	15
6. Personnel.....	16
7. Premises	18
II. Materials, Reagents, Equipment, Instruments and other Devices	20
8. Reagents.....	20
9. Reference substances, reference materials and reference cultures	22
10. Data – Processing equipment.....	24
11. Calibration, verification of performance and qualification of equipment, instruments and other devices.....	25
III. Working Procedures.....	28
12. Incoming samples	28
13. Analytical worksheet	30
14. Validation of analytical procedures	32
15. Testing.....	34
16. Evaluation of test results.....	35
17. Certificate of analysis	38
18. Retained samples	39
IV. Safety	40
19. General safety rules.....	40
References.....	41

Introduction

The good laboratory practice provide advice on good practices for national pharmaceutical control laboratories involved in the analysis of active pharmaceutical ingredients (APIs), excipients and pharmaceutical products.

These guidelines are consistent with the requirements of the WHO guidelines for good Laboratory practices and with the requirements of the International Standard ISO/IEC 17025:2005, and provide detailed guidance for laboratories performing quality control of medicines.

National pharmaceutical quality control laboratories usually encompass essentially two types of activity:

- Compliance testing of APIs, pharmaceutical excipients and pharmaceutical products employing “official” methods including pharmacopoeial methods, validated analytical procedures provided by the manufacturer or validated analytical procedures developed by the laboratory;
- Investigative testing of suspicious, illegal, counterfeit substances or products, submitted for examination by medicine inspectors, customs or police.

Glossary

The definition given below apply to the terms as used in these guidelines

Acceptance criterion for an analytical result

Predefined and documented indicators by which a result is considered to be within the limit(s) or to exceed the limit(s) indicated in the specification. ^[1]

Accuracy

The degree of agreement of test results with the true value or the closeness of the results obtained by the procedure to the true value. ^[1]

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. ^[1]

Analytical test report

An analytical test report usually includes a description of the test procedure(s) employed, results of the analysis, discussion and conclusions and/or recommendations for one or more samples submitted for testing. ^[1]

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, test procedure applied, calculations made, results and any other relevant information or comments. ^[1]

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. ^[1]

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. ^[1]

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. ^[1]

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. ^[1]

Certified reference material

Reference material characterized by a metrologically valid procedure for one or more specified properties, accompanied by a certificate that provides the value of the specified property, its associated uncertainty and a statement of metrological traceability. ^[1]

Design qualification (DQ)

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. ^[1]

ICH

International Council on Harmonization of technical requirements for registration of pharmaceuticals for human use. ^[8]

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.^[1]

Management review

A formal documented review of the key performance indicators of a quality management system performed by top management.^[1]

Manufacturer

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

Measurement uncertainty

Non-negative parameter characterizing the dispersion of quantity values being attributed to a measurand (analyte), based on the information used.^[1]

Operational qualification (OQ)

Documented verification that the analytical equipment performs as intended over all anticipated operating ranges.^[1]

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.

Performance qualification (PQ)

Documented verification that the analytical equipment operates consistently and gives reproducibility within the defined specifications and parameters for prolonged periods.^[1]

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. ^[1]

Precision

The degree 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 — different days, different analysts or different equipment) and reproducibility (precision between laboratories). ^[1]

Primary reference substance

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. ^[1]

Qualification of equipment

Action of proving and documenting that any analytical equipment complies with the required specifications and performs suitably for its intended purpose. ^[1]

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. ^[1]

Quality management system

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. ^[1]

Quality manager

A member of staff who has a defined responsibility and authority for ensuring that the management system related to quality is implemented and followed at all times. ^[1]

Quality manual

A handbook that describes the various elements of the quality management system for assuring the quality of the test results generated by a laboratory. ^[1]

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. ^[1]

Reference substance

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. ^[1]

Secondary reference substance

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. ^[1]

Signature (signed)

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. ^[1]

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. ^[1]

Standard operating procedure (SOP)

An authorized written procedure giving instructions for performing operations both general and specific. ^[1]

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. ^[1]

USP

United States Pharmacopoeias. ^[6]

Validation of an analytical procedure

The documented process by which an analytical procedure (or method) is demonstrated to be suitable for its intended use. ^[1]

Verification of an analytical procedure

Process by which a pharmacopoeial or validated analytical procedure is demonstrated to be suitable for the analysis to be performed. ^[1]

Verification of performance

Test procedure regularly applied to a system (e.g. liquid chromatographic system) to demonstrate consistency of response. ^[1]

I. Management and Infrastructures

1. Organization and management

1.1. The laboratory or the organization of which it is part shall be an entity that can be held legally responsible.^[2]

1.2. Each test facility management should ensure that these Principles of Good Laboratory Practice are complied with, in its test facility.^[3]

1.3. The laboratory should :

1.3.1. Have managerial and technical personnel with the authority and resources needed to carry out their duties and identify the occurrence of departures from the quality management system or the procedures for performing test and / or calibrations, validation and verification, and to initiate actions to prevent or minimize such departures;^[1]

1.3.2. Have policies and procedures to ensure the protection of its clients confidential information and proprietary rights, including procedure for protecting the electronic transmission of results;^[2]

1.3.3. Define, with the aid of organizational charts, the organization and management structure of the laboratory and the relationships between management, technical operations, support services and the quality management system;^[1]

1.3.4. Specify the responsibility, authority and interrelationships of all personnel who manage, perform or verify work which affects the quality of the tests and/or calibrations, validations and verifications;^[1]

1.3.5. Ensure the traceability of the sample from receipt, throughout the stages of testing, to the completion of the analytical test report;^[1]

1.3.6. Have appropriate safety procedures.^[1]

2. Quality management system

2.1. The laboratory or organization management should establish, implement and maintain a quality management system appropriate to the scope of its activities, including the type, range and volume of testing and/or calibration, validation and verification activities it undertakes. The documentation used in this quality management system should be communicated, available to, understood and implemented by, the appropriate personnel.^{[1][2]}

2.2. There should be a quality manual containing as a minimum:

- 2.2.1. A quality policy statement and overall objectives;
- 2.2.2. The structure of the laboratory (organizational chart) ;
- 2.2.3. Outline of the structure of documentation used in the laboratory quality management system ;
- 2.2.4. The general internal quality management procedures ;
- 2.2.5. References to specific procedures for each test ;
- 2.2.6. Information on the appropriate qualifications, experience and competencies that personnel are required to possess;
- 2.2.7. Information on initial and in-service training of staff;
- 2.2.8. A policy for internal and external audit;
- 2.2.9. A policy for implementing and verifying corrective and preventive actions;
- 2.2.10. A policy for dealing with complaints;
- 2.2.11. A policy for the use of appropriate reference substances and reference materials;
- 2.2.12. A policy to select service providers and suppliers.^[1]

2.3. The quality policy stated in the quality manual shall include a statement of the laboratory management's intentions, the commitment to establishing, implementing and maintaining an effective quality management system and the commitment to good professional practice and quality of testing, calibration, validation and verification; the quality policy should also include a requirement that all personnel concerned with testing and calibration activities within the laboratory familiarize themselves with the documentation concerning quality and the implementation of the policies and procedures in their work;^{[1][2]}

The quality program should be carried out by staff with specific responsibilities for quality, who act as the focus and coordinators for quality matters within the laboratory. ^{[3][5]}

2.4. The laboratory should establish, implement and maintain authorized written SOPs including, but not limited to, administrative and technical operations. ^[1]

2.5. The activities of the laboratory should be systematically and periodically audited (internally and, where appropriate, by external audits or inspections) to verify compliance with the requirements of the quality management system. The audits should be carried out by trained and qualified personnel, who are independent of the activity to be audited. Such audits should be recorded, together with details of any corrective and preventive action taken. ^[1]

2.6. Management review of quality issues should be regularly undertaken (at least annually), including:

- 2.6.1. Reports on internal and external audits or inspections and any follow-up required to correct any deficiencies;
- 2.6.2. The outcome of investigations carried out as a result of complaints received;
- 2.6.3. Corrective actions applied and preventive actions introduced as a result of these investigations. ^[1]

3. Control of documentation

- 3.1. The laboratory should establish and maintain procedures to control and review all documents that form part of the quality documentation. A master list identifying the current version status and distribution of documents should be established and readily available.^{[1][2]}
- 3.2. The procedures should ensure that:
 - 3.2.1. Each document, whether a technical or a quality document, has a unique identifier, version number and date of implementation, and total number of pages.
 - 3.2.2. Appropriate, authorized SOPs are available at the relevant locations, e.g. near instruments;
 - 3.2.3. Documents are kept up to date and reviewed as required;
 - 3.2.4. Any invalid document is removed and replaced with the authorized, revised document with immediate effect;
 - 3.2.5. A revised document includes references to the previous document;
 - 3.2.6. Old invalid documents are retained in the archives to ensure traceability of the evolution of the procedures; any copies are destroyed;
 - 3.2.7. All relevant staff are trained for the new and revised SOPs;
 - 3.2.8. Quality documentation, including records, is retained for a minimum of five years.^[2]
- 3.3. The use of computer based systems is recommended to facilitate the control of documents but care is advised to ensure access to the system is only available to authorized staff.^[5]
- 3.4. Changes to documents shall be reviewed and approved by the same function that performed the original review unless specifically designated otherwise.^[2]
- 3.5. Where practicable, the nature of the change shall be identified in the document or the appropriate attachments.^[2]

4. Records

- 4.1. The laboratory should establish and maintain procedures for the identification, collection, indexing, retrieval, storage, maintenance and disposal of and access to all quality and technical/scientific records.^[1]
- 4.2. All original observations, including calculations and derived data, calibration, validation and verification records and final results, should be retained on record for an appropriate period of time in accordance with national regulations and, if applicable, contractual arrangements, whichever is longer. 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. The records for each test should contain sufficient information to permit the tests to be repeated and/or the results to be recalculated, if necessary. The records should include the identity of the personnel involved in the sampling, preparation and testing of the samples.^[1]
- 4.3. Technical records includes forms, contracts, work sheets, work books, check sheets, work notes, control graphs, test reports, calibration certificates, clients notes, papers and feedback, test reports and calibration certificates to clients.^[2]
- 4.4. Quality management records should include reports from internal (and external if performed) audits and management reviews, as well as records of all complaints and their investigations, including records of possible corrective and preventive actions.^[1]

5. Contracts

- 5.1. The laboratory should have a procedure for the selection and purchasing of services and supplies it uses that affect the quality of testing. Procedure shall exist for the purchase, reception and storage of consumable materials relevant for the tests and calibrations.^{[1][2]}
- 5.2. The laboratory should evaluate suppliers of critical consumables, supplies and services which affect quality of testing, maintain records of these evaluations and list approved supplies.^[1]
- 5.3. The laboratory shall advise and obtain approval from the client, preferably in writing, when the laboratory intends to subcontract to another laboratory specific tests and/or calibrations, or a part of a test and/or calibration.^[2]
- 5.4. When a laboratory subcontracts work, which may include specific testing, it is to be done with organizations approved for the type of activity required.^[1]
- 5.5. There should be a written contract which clearly establishes the duties and responsibilities of each party, defines the contracted work and any technical arrangements. The contract should permit the laboratory to audit the facilities and competencies of the contracted organization.^[1]
- 5.6. The laboratory should maintain a register of all subcontractors that it uses for tests and a record of the assessments of the competence of subcontractors.^{[1][2]}
- 5.7. The laboratory takes the responsibility for all results reported, including those furnished by the subcontracting organization.^[1]

6. Personnel

- 6.1. The laboratory should have sufficient personnel with the necessary education, training, technical knowledge and experience for their assigned functions.^[1]
- 6.2. The laboratory management shall ensure the competency of all who operate specific equipment, who perform tests and / or calibrations, evaluate results and sign test reports and calibration certificates.^[2]
- 6.3. The laboratory shall have a policy and procedures for identifying training needs and providing training of personnel. The training programme shall be relevant to present anticipated tasks of the laboratory.^[2]
- 6.4. The laboratory should maintain current job descriptions for all personnel involved in tests and/or calibrations, validations and verifications. The laboratory should also maintain records of all technical personnel, describing their qualifications, training and experience.^[1]
- 6.5. Competence should be monitored continuously with provision for retraining where necessary. Where a method or technique is not in regular use, the competency of the personnel to perform the test should be verified before testing is undertaken.^[4]
- 6.6. Personnel working in microbiology laboratory should be trained in safe handling of microorganisms.^[4]
- 6.7. The laboratory should have :
- 6.7.1. A head of laboratory who should have qualifications appropriate to the position ;
 - 6.7.2. The technical management who ensure that:
 - 6.7.2.1. Procedures for performing calibration, verification and re-qualification of instruments, monitoring of environmental and storage conditions are in place and are conducted as required;
 - 6.7.2.2. Regular in-service training programmes.
 - 6.7.3. Analysts, who should normally be graduates in pharmacy, analytical chemistry, microbiology or other relevant subjects;



6.7.4. Technical staff, who should hold diplomas in their subjects awarded by technical or vocational schools.^[1]

DRAFT

7. Premises

- 7.1. The laboratory facilities are to be of suitable size, construction and location. These facilities are to be designed to suit the functions and operations to be conducted in them. Changing areas and toilets should be separated from laboratory areas.^[1]
- 7.2. The laboratory facilities should have adequate safety equipment located (e.g. eye wash, safety shower) appropriately and measures should be in place to ensure good housekeeping (e.g. laboratory cleaning records). Each laboratory should be equipped with adequate instruments and equipment, including work benches, work stations and fume hoods.^[1]
- 7.3. The environmental conditions, including lighting, energy sources, temperature, humidity and air pressure, are to be appropriate to the functions and operations to be performed. The laboratory should ensure that the environmental conditions are monitored, controlled and documented and do not invalidate the results or adversely affect the quality of the measurements.^[1]
- 7.4. There should be a separate and dedicated unit or equipment (e.g. isolator, laminar flow work bench) to handle, weigh and manipulate highly toxic or biological substances. Procedures should be in place to avoid exposure and contamination.^[1]
- 7.5. Archive facilities should be provided to ensure the secure storage and retrieval of all documents. Archived design and archived conditions should protect contents from untimely deterioration.^{[1][3]}
- 7.6. 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.
- 7.7. Microbiology laboratory should be appropriately designed to enable appropriate cleaning, disinfection and to minimize the risks of contamination.^[4]
- 7.8. Microbiological testing should be contained in an appropriately designed and constructed laboratory unit.^[1] There should be adequate suitable space for samples, reference organisms, media, testing and records.^[4]

- 7.9. Access to the microbiological laboratory should be restricted to authorized personnel.^[4]
- 7.10. Laboratory activities, such as sample preparation, media and equipment preparation and enumeration of microorganisms, should be segregated by space or at least in time, so as to minimize risks of cross contamination, false-positive results and false-negative results. Sterility testing should always be performed in a dedicated area.^[4]
- 7.11. There should be a documented cleaning and disinfection programme.^[4]
- 7.12. Adequate hand-washing and hand-disinfection facilities should be available.^[4]
- 7.13. The storage facilities should be well organized for the correct storage of samples, reagents, equipment, laboratory accessories, reference substances and reference materials. All specified storage conditions should be controlled monitored and records maintained. Access should be restricted to designated personnel.^[1]
- 7.14. Appropriate safety procedures should be drawn up and implemented wherever toxic or flammable reagents are stored or used. The laboratory should provide separate rooms or areas for storing flammable substances, fuming and concentrated acids and bases, volatile amines and other reagents. Small stocks of acids, bases and solvents may be kept in the laboratory store but the main stocks of these items should preferably be retained in a store separate from the laboratory building.^[1]
- 7.15. Gases also should be stored in a dedicated store, if possible isolated from the main building. If gas bottles are present in the laboratory they should be safely secured.^[1]

II. Materials, Reagents, Equipment, Instruments and other Devices

8. Reagents

- 8.1. All reagents, media and chemicals, including solvents and materials used in tests and assays, should be of appropriate quality.^[1]
- 8.2. Reagents / media should be accompanied by the certificate of analysis, and the material safety data sheet.^[1]
- 8.3. In the preparation of reagent solutions / media in the laboratory:
 - a) Responsibility for this task should be clearly specified in the job description of the person assigned to carry it out;
 - b) Prescribed procedures should be used which are in accordance with published pharmacopoeial or other standards where available e.g. United States Pharmacopeia (USP)^[6], European Pharmacopeia (EP)^[7]. Records should be kept of the preparation and standardization of volumetric solutions.^[1]
- 8.4. The labels of all reagents / media should clearly specify:
 - a) Content;
 - b) Manufacturer;
 - c) Date received and date of opening of container;
 - d) Concentration if applicable
 - e) Storage conditions
 - f) Expiry date or retest date as justified.^[1]
- 8.5. The labels of reagent solution prepared in the laboratory should clearly specify:
 - a) Name
 - b) Date of preparation and initials of technician or analyst;
 - c) Expiry date or retest date;
 - d) Concentration.^[1]
- 8.6. The labels for volumetric solutions prepared in the laboratory should clearly specify:
 - a) Name
 - b) Molarity (or concentration)

- c) Date of preparation and initials of technician / analyst;
 - d) Date of standardization and initials of technician / analyst
 - e) Standardization factor.^[1]
- 8.7. Reagents that appear to have been tampered with should be rejected.^[1]
- 8.8. Water should be considered as a reagent. The appropriate grade for a specific test should be used as described in the pharmacopoeias.^{[1][6][7]}
- 8.9. The quality of the water should be verified regularly to ensure that the various grades of water meet the appropriate specifications.^[1]
- 8.10. Stocks of reagents and media should be maintained in a store under the appropriate storage conditions (ambient temperature, under refrigeration or frozen).^[1]
- 8.11. The person in charge of the store is responsible for looking after the storage facilities and their inventory and for noting the expiry date of chemicals and reagents. Training may be needed in handling chemicals safely and with the necessary care.^[1]
- 8.12. Media used in microbiology may be prepared in-house or purchased either partially or fully prepared. Growth promotion and other suitable performance tests (Recovery of 50–200% should be demonstrated; inhibition or suppression of non-target organisms; pH, volume and sterility) should be done on all media on every batch and on every shipment. Where the supplier of fully prepared media is qualified and provides growth promotion certification per batch of media and transportation conditions have been qualified, the user may rely on the manufacturer's certificate with periodic verification of his or her results.^[4]
- 8.13. Shelf-life of prepared media under defined storage conditions shall be determined and verified.^[4]
- 8.14. The expiry date of reagents /solutions may be extended on the basis of documented evaluation or analysis.^[3]

9. Reference substances, reference materials and reference cultures

- 9.1. Reference substances (primary reference substances or secondary reference substances) are used for the testing of a sample.^[1]
- 9.2. Reference materials may be necessary for the calibration and/or qualification of equipment, instruments or other devices.^{[1][4]}

Pharmacopoeial reference substances should be employed when available and appropriate for the analysis. When a pharmacopoeia reference substance has not been established then the manufacturer should use its own reference substance.^[1]
- 9.3. Reference cultures are required for establishing acceptable performance of media, for validating methods, for verifying the suitability of test methods and for assessing or evaluating ongoing performance.^[4]
- 9.4. An identification number should be assigned to each batch of reference substances.^[1] This number should be marked on each vial of the reference substance.^[4]
- 9.5. The identification number should be quoted on the analytical worksheet every time the reference substance is used. In the case of pharmacopoeial reference substance the batch number and / or the batch validity statement should be attached to the worksheet.^[1]
- 9.6. The 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 substance or
 - g) the location of storage in the laboratory, and any special storage conditions;
 - h) expiry date or retest date;
 - i) certificate (batch validity statement) of a pharmacopoeial reference substance

- and a certified reference material which indicates its use, the assigned content, if applicable, and its status (validity);
- j) in the case of secondary reference substances prepared and supplied by the manufacturer, the certificate of analysis.^[1]
- 9.7. A person should be nominated to be responsible for reference substances and reference materials.^[1]
- 9.8. In addition a file should be kept in which all information on the properties of each reference substance is entered including the safety data sheets.^[1]
- 9.9. For reference substances prepared in the laboratory, the file should include the results of all tests and verifications used to establish the reference substances and expiry date or retest date; these should be signed by the responsible analyst.^[1]
- 9.10. All reference substances prepared in the laboratory or supplied externally should be retested at regular intervals to ensure that deterioration has not occurred. The interval for retesting depends on a number of factors, including stability of the substance, storage conditions employed, type of container and extent of use; the results of these tests should be recorded and signed by the responsible analyst.^[1]
- 9.11. In the case that the result of retesting of a reference substance is non-compliant, a retrospective check of tests performed using this reference substance since its previous examination should be carried out.^[1]
- 9.12. Pharmacopoeial reference substances are regularly retested and their validity is available from the issuing pharmacopoeia by various means, (e.g. web sites or catalogues). Retesting by the laboratory is not necessary, where same storage conditions are followed.^[1]

10. Data – Processing equipment

10.1. For computers, automated tests or calibration equipment, and the collection, processing, recording, reporting, storage or retrieval of test and/or calibration data, the laboratory should ensure that:

10.1.1. Computer software developed by the user is documented and appropriately validated;

10.1.2. Procedures are established and implemented for protecting the integrity of data;

10.1.3. Electronic data should be backed up at appropriate regular intervals according to a documented procedure. Backed-up data should be retrievable and sorted in such a manner as to prevent data loss. ^[1]

11. Calibration, verification of performance and qualification of equipment, instruments and other devices

- 11.1. Equipment, instruments and other devices should be designed, constructed, adapted, located, calibrated, qualified, verified and maintained as required by the operations to be carried out in the local environment. The user should purchase the equipment from an agent capable of providing full technical support and maintenance when necessary.^[1]
- 11.2. The laboratory should have the required test equipment, instruments and other devices for the correct performance of the tests and/or calibrations, validations and verifications (including the preparation of samples and the processing and analysis of test and/or calibration data).^[1]
- 11.3. Each item of equipment, instrument or other device used for testing, verification and/or calibration should, be uniquely identified and labeled.^{[2][4]}
- 11.4. All equipment, instruments and other devices (e.g. volumetric glassware and automatic dispensers) requiring calibration should be labelled, coded or otherwise identified to indicate the status of calibration and the date of recalibration.^[1]
- 11.5. The performance of equipment should be verified at appropriate intervals according to a plan established by the laboratory.^[1]
- 11.6. Measuring equipment should be regularly calibrated according to a plan established by the laboratory.^[1]
- 11.7. Specific procedures should be established for each type of measuring equipment, taking into account the type of equipment and the extent of use. For example:
- pH meters are verified with standard certified buffer solutions before use. Conductivity meters, oxygen meters, pH meters and other similar instruments should be verified regularly or before each use. The buffers used for verification purposes should be stored in appropriate conditions and should be marked with an expiry date;^{[1][4]}
 - balances are to be checked daily using suitable test weights, and requalification should be performed annually using certified reference

weights.^{[1][4]}

- For incubators, water –bath and ovens, the stability of temperature, the uniformity of temperature distribution and the time required to reach equilibrium conditions should be established initially and documented.^[4]
- For autoclaves, initial validation should include performance studies for each operating cycle and each load configuration used in practice.^[4]

11.8. Only authorized personnel should operate equipment, instruments and devices. Up-to-date SOPs on the use, maintenance, verification, qualification and calibration of equipment, instruments and devices should be available for use by the appropriate laboratory personnel.^[1]

11.9. Records should be kept of each item of equipment, instrument or other device used to perform testing, verification and/or calibration. The records should include at least the following:

- a) the identity of the equipment, instrument or other device;
- b) the manufacturer's name and the equipment model, serial number or and code number;
- c) the qualification, verification and/or calibration required;
- d) the current location, where appropriate;
- e) the equipment manufacturer's instructions;
- f) the dates, results and copies of reports, verifications and certificates of all calibrations, adjustments, acceptance criteria and the due date of the next qualification, verification and/or calibration;
- g) the maintenance carried out to date and the maintenance plan;
- h) A history of any damage, malfunction, modification or repair.^{[1][2]}

11.10. Procedures should include instructions for the safe handling, transport and storage of measuring equipment.^{[1][2]}

11.11. Maintenance of essential equipment should be carried out at predetermined intervals in accordance with a documented procedure. The maintenance is followed by verification of performance.^{[1][4]}

11.12. Equipment, instruments and other devices, shown to be defective or outside specified limits, should be taken out of service and clearly labelled or marked.

They should not be used until they have been repaired and requalified.^{[1][2]}

11.13. When the equipment, instruments and other devices are outside the direct control of the laboratory for a certain period or have undergone major repair, the laboratory should requalify the equipment to ensure its suitability for use.^{[1][2]}

11.14. The temperature measurement devices should be of appropriate quality to achieve the required accuracy and their calibration should be traceable to national or international standards for temperature.^[4]

11.15. Volumetric equipment should be verified (automatic dispensers, mechanical hand pipettes and disposable pipettes) and then regular checks are done to ensure that the equipment is performing within the required specification. Equipment should be checked for the accuracy of the delivered volume against the set volume and the precision of the repeat deliveries should be measured.^[4]

11.16. No initial verification is necessary for certified glassware.^[4]

III. Working Procedures

12. Incoming samples

12.1. It is important that the sample is large enough to enable a number of replicate tests to be carried out.^[1]

12.2. It is common for a sample to be taken and divided into three approximately equal portions for submission to the laboratory:

- one for immediate testing;
- the second for confirmation of testing if required;
- the third for retention in case of dispute.^[1]

12.3. Transport and storage of samples for microbiological testing should be under conditions that maintain the integrity of the sample. Testing of the samples should be performed as soon as possible after sampling. The storage conditions should be monitored and records kept.^[4]

12.4. A standard test request form should be filled out and should accompany each sample submitted to the laboratory. The test request form should provide the following information:

- a) the name of the institution or inspector that supplied the sample;
- b) the source of the material;
- c) a full description of the medicine, including its composition, and brand name;
- d) dosage form and concentration or strength, the manufacturer, the batch number and the marketing authorization number;
- e) the size of the sample;
- f) the reason for requesting the analysis;
- g) the date on which the sample was collected;
- h) the expiry date (for pharmaceutical products) or retest date (for APIs and pharmaceutical excipients);
- i) the standards / specifications to be used for testing;
- j) the required storage conditions;
- k) condition of the sample on receipt;

1) characteristics of the sampling operation (sampling date / sampling condition).^{[1][4]}

12.5. All newly delivered samples and accompanying documents should be assigned a registration number. Separate registration 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.^[1]

12.6. A label bearing the registration number should be affixed to each container of the sample.^[1]

12.7. A register should be kept, which may be a record book, in which the following information is recorded:

- The registration number of the sample;
- The date of receipt.^[1]

12.8. The sample received should be visually inspected by laboratory staff to ensure that the labelling conforms to 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 fact should be recorded without delay on the test request form. Any queries should be immediately referred back to the provider of the sample.^[1]

12.9. The sample prior to testing, the retained sample and any portions of the sample remaining after performance of all the required tests should be stored safely, taking into account the storage conditions specified for the sample.^[1]

12.10. There should be a written procedure for the retention and disposal of samples. If sample integrity can be maintained it may be appropriate that samples are stored until the test results are obtained. Laboratory sample portions that are known to be contaminated should be decontaminated prior to being discarded.^[4]

13. Analytical worksheet

- 13.1. The analytical worksheet 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 is to be complemented by the raw data obtained in the analysis.^[1]
- 13.2. A separate analytical worksheet should usually be used for each numbered sample or group of samples.^[1]
- 13.3. The analytical worksheet should provide the following information:
- a) the registration number of the sample;
 - b) page numbering including the total number of pages;
 - c) the date of the test request;
 - d) the date on which the analysis was started and completed;
 - e) the 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;
 - h) the identification number of any reference substance used;
 - i) if applicable, the results of the system suitability test;
 - j) the identification of reagents and solvents employed;
 - k) the results obtained;
 - l) the interpretation of the results and the final conclusions approved and signed by the supervisor;
 - m) any further comments.^[1]
- 13.4. 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 where the data are available.^[1]
- 13.5. The completed analytical worksheet should be signed by the responsible analyst(s), verified and approved and signed by the supervisor.^[1]



- 13.6. When a mistake is made in an analytical worksheet or when data or text need to be amended, the old information should be deleted by putting a single line through it and the new information added alongside. All such alterations should be signed by the person making the correction and the date of the change inserted.^[1]
- 13.7. The specification necessary to assess the sample may be that given in the test request or recognized national pharmacopoeia may be used.^[1]
- 13.8. The analytical worksheet should be kept safely together with any attachments, including calculations and recordings of instrumental analyses.^[1]

DRAFT

14. Validation of analytical procedures

14.1. Validation is the confirmation by examination and the provision of effective evidence that the particular requirements for a specific intended use are fulfilled.^[2]

14.2. All analytical procedures employed for testing should be suitable for the intended use. This is demonstrated by validation.^[1]

14.3. Validation should be performed according to a 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 the below Table.^[1]

Type of analytical Procedure	Identification	Testing for impurities		Assay
		Quantitative tests	Limit tests	<ul style="list-style-type: none"> • dissolution (measurement only) • content/potency
Characteristics				
Accuracy	-	+	-	+
Precision				
Repeatability	-	+	-	+
Intermediate precision	-	+	-	+
Specificity	+	+	+	+
Detection limit	-	- ^b	+	-
Quantitation limit	-	+	-	-
Linearity	-	+	-	+
Range	-	+	-	+

14.4. Pharmacopoeial methods are considered to be validated for the intended use as prescribed in the monograph(s). However, the laboratory should also confirm that, for example, for a particular finished pharmaceutical product (FPP) examined for the first time, no interference arises from the excipients present, or that for an API, impurities coming from a new route of synthesis are adequately differentiated.^[1]

14.5. For microbiology, the test method to be used by a laboratory for testing of a specific product needs to be shown to be suitable for use in recovering bacteria,

yeast and mould in the presence of the specific product. Potentially inhibitory effects from the sample should be taken into account when testing different types of sample. The results should be evaluated with appropriate statistical methods, e.g. as described in the national, regional or international pharmacopoeias.^[4]

14.6. System suitability testing is an integral part of many analytical procedures. The tests are based on the fact that the equipment, electronics, analytical operations and samples to be analyzed contribute to the system. System suitability tests are employed for the verification of pharmacopoeial methods or validated analytical procedures and should be performed prior to the analysis. If a large number of samples are being analyzed in sequence, then appropriate system suitability tests are to be performed throughout the sequence to demonstrate that the performance of the procedure is satisfactory. Verification is not required for basic pharmacopoeial methods such as (but not limited to) pH, loss on drying and wet chemical methods.^[1]

14.7. A major change to the analytical procedure, or in the composition of the product tested, or in the synthesis of the API, will require revalidation of the analytical procedure.^[1]

14.8. Test methods should be validated / verified according to international standards e.g. ICH^[8], USP chapter <1225> and <1226>.^[6]

15. Testing

- 15.1. The sample should be tested in accordance with the work plan of the laboratory. If this is not feasible, the reasons should be noted in the analytical worksheet, and the sample should be stored in a special place which is kept locked.^[1]
- 15.2. All instructions, standards, manuals and reference data relevant to the work of laboratory shall be maintained current and be made readily available to personnel.^[2]
- 15.3. Detailed guidance on official pharmacopoeial requirements is usually given in the general notices and specific monographs of the pharmacopoeia concerned.^[1]
- 15.4. International, regional or national standards or other recognized specifications that contain sufficient and concise information on how to perform the tests and / or calibrations do not need to be supplemented nor rewritten as internal procedures if these standards are written in a way that they can be used as published by the operating staff in laboratory. The laboratory shall ensure that it uses the latest edition of standard.^[2]
- 15.5. Alternative testing procedures may be used if they are appropriately validated and equivalence to official methods has been demonstrated.^[4]
- 15.6. Test procedures should be described in detail and should provide sufficient information to allow properly trained analysts to perform the analysis in a reliable manner.^[1]
- 15.7. Where system suitability criteria are defined in the method they should be fulfilled.^[1]
- 15.8. Any deviation from the test procedure should be approved and documented.^[1]

16. Evaluation of test results

16.1. Test results should be reviewed and evaluated statistically after completion of all the tests to determine whether they are mutually consistent and if they meet the specifications used. The evaluation should take into consideration the results of all the tests. Whenever doubtful (atypical) results are obtained, they should be investigated. The complete testing procedure needs to be checked according to the internal quality management system.^[1]

16.2. For microbiology, if the result of the enumeration is negative, it should be reported as “not detected for a defined unit” or “less than the detection limit for a defined unit”. The result should not be given as “zero for a defined unit” unless it is a regulatory requirement. Qualitative test results should be reported as “detected/not detected in a defined quantity or volume”. A reported value of “0” may be used for data entry and calculations or trend analysis in electronic data bases.^[4]

16.3. 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 retesting is permitted. The following steps should be followed:

- a) confirm with the analyst or technician that the appropriate procedure(s) was (were) applied and followed correctly;
- b) examine the raw data to identify possible discrepancies;
- c) check all calculations;
- d) check that the equipment used was qualified and calibrated, and that system suitability tests were performed and were acceptable;
- e) ensure that the appropriate reagents, solvents and reference substances were used;
- f) confirm that the correct glassware was used;
- g) ensure that original sample preparations are not discarded until the investigation is complete.^[1]

16.4. The identification of an error which caused an aberrant result will invalidate the result and a retest of the sample will be necessary. Doubtful results can be

rejected only if they are clearly due to an identified error. Sometimes the outcome of the investigation is inconclusive in which case a confirmatory determination is to be performed by another analyst who should be at least as experienced and competent in the analytical procedure as the original analyst. A similar value would indicate an OOS result;^[1]

- 16.5. An SOP should be in place for the conduct of an investigation of an OOS test result. The SOP should give clear guidance on the number of retests allowed (based on sound statistical principles). All investigations and their conclusions should be recorded. In the event of an error, any corrective action taken and any preventive measure introduced should be recorded and implemented.^[1]
- 16.6. All individual results with acceptance criteria should be reported.^[1]
- 16.7. All conclusions should be entered on the analytical worksheet by the analyst and signed by the supervisor.^[1]
- 16.8. The results should be reported normally in a test report and shall include all the information required by the client and necessary for the interpretation of the results.^[2]
- 16.9. The analytical test report is a compilation of the results and states the conclusions of the examination of a sample. It should be :
 - a) issued by the laboratory;
 - b) based on the analytical worksheet.^[1]
- 16.10. The analytical test report should provide the following information:
 - a) The title of the report
 - 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;



- 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;
- j) a discussion of the results obtained;
- k) the name and address of the original manufacturer and, if applicable, those of the repacker and / or trader;
- l) the date on which the sample was received;
- m) the date on which the test(s) was (were) completed;
- n) the signature of the head of the laboratory or authorized person;
- o) whether or not the sample(s) complies (comply) with the requirements / specification;
- p) the expiry date or retest date, if applicable;
- q) a statement indicating that the analytical test report, or any portion thereof, cannot be reproduced without the authorization of the laboratory.^{[1][2]}

17. Certificate of analysis

17.1. A certificate of analysis is prepared for each batch of a substance or product and usually contains the following information:

- a) the registration number of the sample;
- b) date of receipt ;
- c) the name and address of the laboratory testing the sample;
- d) the name and address of the originator of the request for analysis;
- e) the name, description and batch number of the sample where appropriate;
- f) the name and address of the original manufacturer and, if applicable, those of the repacker and/or trader;
- g) the reference to the specification used for testing the sample;
- h) the results of all tests performed (mean and standard deviation, if applicable) with the prescribed limits;
- i) a conclusion as to whether or not the sample was found to be within the limits of the specification;
- j) expiry date or retest date if applicable;
- k) date on which the test(s) was (were) completed;
- l) the signature of the head of laboratory or other authorized person.^[1]

18. Retained samples

18.1. Samples should be retained as required by the originator of the request for analysis. There should be a sufficient amount of retained sample to allow at least two re-analyses. The retained sample should be kept in its final pack.^[1]

DRAFT

IV. Safety

19. General safety rules

- 19.1. Safety data sheets should be available to staff before testing is carried out.^[1]
- 19.2. Smoking, eating and drinking in the laboratory should be prohibited.^[1]
- 19.3. Staff should be familiar with the use of fire-fighting equipment, including fire extinguishers, fire blankets and gas masks.^[1]
- 19.4. Special care should be taken in handling highly potent, infectious or volatile substances; warning, precautions and instructions should be given 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 and especially biologicals such as infectious agents. Peroxide-free solvents should be used.^[1]
- 19.5. Staff should be instructed in the safe handling of glassware, corrosive reagents and solvents.^[1]
- 19.6. Highly toxic and/or genotoxic samples should be handled in a specially designed facility to avoid the risk of contamination.^[1]
- 19.7. All containers of chemicals should be fully labeled and include prominent warnings (e.g. “poison”, “flammable”, “radioactive”, “biohazard”).^[1]
- 19.8. Staff should be aware of the need to avoid working alone in the laboratory.^[1]
- 19.9. First-aid materials should be provided and staff instructed in first-aid techniques, emergency care and the use of antidotes.^[1]
- 19.10. Protective clothing should be available, including eye protection, masks and gloves. Safety showers and eye wash station should be installed.^[1]
- 19.11. Poisonous or hazardous products should be singled out and labeled appropriately.^[1]
- 19.12. There should be a procedure for dealing with spillage.^[4]

19.13. A procedure for the disposal of contaminated materials should be designed to minimize the possibility of contaminating the test environment or materials. It is a matter of good laboratory management and should conform to national/international environmental or health and safety regulations.^[4]

References

1. WHO good practices for pharmaceutical quality control laboratories; technical report series N^o.957.2010;
2. ISO/ IEC 17025:2005 general requirements for the competence of testing and calibration laboratories;
3. OECD good laboratory practice principles;
4. WHO good practices for pharmaceutical microbiology laboratories; technical report series N^o.961.2011;
5. Eurachem / CITAC working group, July 1998;
6. US Pharmacopeia, National Formulary 39;
7. European Pharmacopoeia, 8th Edition;
8. ICH Guidelines: validation of analytical procedures: test and methodology Q2 (R1).