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WHO Technical Report Series, No. 957, 2010

Annex 1

WHO good practices for pharmaceutical quality control laboratories

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General considerations

The WHO Expert Committee on Specifications for Pharmaceutical Products adopted in 1999 the guidelines entitled *WHO Good practices for national pharmaceutical control laboratories*, which were published as Annex 3 of the WHO Technical Report Series, No. 902, 2002. As the other guidelines related to laboratory quality assurance have been updated and subsequent inspections for the compliance with the guidelines on good practices for national pharmaceutical control laboratories indicated that some sections were in need of improvement and clarification, it was considered necessary to prepare a revised text.

These guidelines provide advice on the quality management system within which the analysis of active pharmaceutical ingredients (APIs), excipients and pharmaceutical products should be performed to demonstrate that reliable results are obtained.

Compliance with the recommendations provided in these guidelines will help promote international harmonization of laboratory practices and will facilitate cooperation among laboratories and mutual recognition of results.

Special attention should be given to ensure the correct and efficient functioning of the laboratory. Planning and future budgets should ensure that the necessary resources are available inter alia for the maintenance of the laboratory, as well as for an appropriate infrastructure and energy supply. Means and procedures should be in place (in case of possible supply problems) to ensure that the laboratory can continue its activities.

These guidelines are applicable to any pharmaceutical quality control laboratory, be it national, commercial or nongovernmental. However, they do not include guidance for those laboratories involved in the testing of biological products, e.g. vaccines and blood products. Separate guidance for such laboratories is available.

These guidelines are consistent with the requirements of the *WHO guidelines for good manufacturing practices* (*1*) and with the requirements of the International Standard ISO/IEC 17025:2005 (*2*), and provide detailed guidance for laboratories performing quality control of medicines. The guidance specific to microbiology laboratories can be found in the draft working document *WHO guideline on good practices for pharmaceutical microbiology laboratories* (reference QAS/09.297).

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 quality assurance is achieved. The notes given provide clarification of the text or examples; they do not contain requirements which should be fulfilled to comply with these guidelines.

Pharmaceutical quality control testing is usually a matter of repetitive testing of samples of APIs or of a limited number of pharmaceutical products, whereas national quality control laboratories have to be able to deal with a much wider range of pharmaceutical substances and products and, therefore, have to apply a wider variety of test methods. Specific recommendations for national pharmaceutical quality control laboratories are addressed in the following text. Particular consideration is given to countries with limited resources wishing to establish a governmental pharmaceutical quality control laboratory, having recently done so, or which are planning to modernize an existing laboratory.

Quality control laboratories may perform some or all quality control activities, e.g. sampling, testing of APIs, excipients, packaging materials and/or pharmaceutical products, stability testing, testing against specifications and investigative testing.

For the quality of a medicine sample to be correctly assessed:

- The submission of a sample of an API, excipient or pharmaceutical product or a suspected counterfeit material to the laboratory, selected in accordance with national requirements, should be accompanied by a statement of the reason why the analysis has been requested.
- The analysis should be correctly planned and meticulously executed.
- The results should be competently evaluated to determine whether the sample complies with the specifications or other relevant criteria.

National pharmaceutical quality control laboratories

The government, normally through the national medicines regulatory authority (NMRA), may establish and maintain a pharmaceutical quality control laboratory to carry out the required tests and assays to verify that APIs, excipients and pharmaceutical products meet the prescribed specifications. Large countries may require several pharmaceutical quality control laboratories which conform to national legislation, and appropriate arrangements should, therefore, be in place to monitor their compliance with a quality management system. Throughout the process of marketing authorization and postmarketing surveillance, the laboratory or laboratories work closely with the NMRA.

A national pharmaceutical quality control laboratory provides effective support for an NMRA acting together with its inspection services. The analytical results obtained should accurately describe the properties of the samples assessed, permitting correct conclusions to be drawn about the quality of the samples of medicines analysed, and also serving as an adequate basis for any subsequent administrative regulations and legal action.

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 and approved by the relevant government authority for marketing authorization or validated analytical procedures developed by the laboratory; and
— investigative testing of suspicious, illegal, counterfeit substances or products, submitted for examination by medicine inspectors, customs or police.

To ensure patient safety, the role of the national pharmaceutical quality control laboratory should be defined in the general pharmaceutical legislation of the country in such a way that the results provided by it can, if necessary, lead to enforcement of the law and legal action.

Glossary

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

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.

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*).

Note: It is normally established on samples of the material to be examined that have been prepared to quantitative accuracy. Accuracy should be established across the specified range of the analytical procedure. It is generally acceptable to use a "spiked" placebo which contains a known quantity or concentration of a reference substance.

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 (see Part three, sections 18.7–18.11).

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 (see Part three, section 15).

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 (*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 (*3*).

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 (*4*).

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.

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.

Note: Selection and purchase of a new instrument should follow a conscious decision process, based on the needs of the technical management. When designing a new laboratory facility, the design specification and the requirements for services should be agreed between the management team and the agreed suppliers and documented.

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 (*1*).

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.

management review

A formal, documented review of the key performance indicators of a quality management system performed by top management.

manufacturer

A company that carries out operations such as production, packaging, testing, repackaging, labelling and/or relabelling of pharmaceuticals (*1*).

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 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

Non-negative parameter characterizing the dispersion of quantity values being attributed to a measurand (analyte), based on the information used (*4*).

metrological traceability

Property of a measurement result whereby the result can be related to a reference through a documented, unbroken chain of calibrations, each contributing to the measurement uncertainty (*4*).

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 (*5*).

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 (*6*, *7*).

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).

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 (*8*).

Note: Pharmacopoeial chemical reference substances are considered to be primary reference substances. In the absence of a pharmacopoeial reference substance, a manufacturer should establish a primary reference substance.

qualification of equipment

Action of proving and documenting that any analytical equipment complies with the required specifications and performs suitably for its intended purpose (see Part two, section 12).

quality control

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

quality management system

An appropriate 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 (see Part one, section 2).

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 (see Part one, section 1.3(j)).

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 (see Part one, sections 2.1–2.2).

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 (*4*).

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 (*8*).

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 (*8*).

Note: Often referred to as an "in-house" working standard.

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.

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.

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 (*4*, *9*, *10*).

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.

validation of an analytical procedure

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

verification of an analytical procedure

Process by which a pharmacopoeial method or validated analytical procedure is demonstrated to be suitable for the analysis to be performed.

verification of performance

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

Part One. Management and infrastructure

1. Organization and management

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 legally responsible.

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

1.3 The laboratory should:

(a) have managerial and technical personnel with the authority and resources needed to carry out their duties and to identify the occurrence of departures from the quality management system or the procedures for performing tests and/or calibrations, validation and verification, and to initiate actions to prevent or minimize such departures;

(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 the quality of their work;

(c) have a policy and procedure in place to ensure confidentiality of
— information contained in marketing authorizations,
— transfer of results or reports,
— and to protect data in archives (paper and electronic);

(d) 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 or the NMRA in the case of a national pharmaceutical quality control laboratory), and the relationships between management, technical operations, support services and the quality management system;

(e) 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;

(f) ensure the precise allocation of responsibilities, particularly in the designation of specific units for particular types of medicines;

(g) nominate trained substitutes/deputies for key management and specialized scientific personnel;

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

(i) have management which has overall responsibility for the technical operations and the provision of resources needed to ensure the required quality of laboratory operations;

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

(k) ensure adequate information flow between staff at all levels. Staff are to be made aware of the relevance and importance of their activities;

(l) ensure the traceability of the sample from receipt, throughout the stages of testing, to the completion of the analytical test report;

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

(n) have appropriate safety procedures (see Part four).

1.4 The laboratory should maintain a registry with the following functions:

(a) receiving, distributing and supervising the consignment of the samples to the specific units; and
(b) keeping records on all incoming samples and accompanying documents.

1.5 In a large laboratory, it is necessary to guarantee communication and coordination between the staff involved in the testing of the same sample in different units.

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 laboratory management should ensure that its policies, systems, programmes, procedures and instructions are described to the extent necessary to enable the laboratory to assure the quality of the test results that it generates. The documentation used in this quality management system should be communicated, available to, and understood and implemented by, the appropriate personnel. The elements of this system should be documented, e.g. in a quality manual, for the organization as a whole and/or for a laboratory within the organization.

Note: Quality control laboratories of a manufacturer may have this information in other documents than a quality manual.

2.2 The quality manual 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,
  (ii) a commitment to establishing, implementing and maintaining an effective quality management system,
  (iii) the laboratory management's commitment to good professional practice and quality of testing, calibration, validation and verification,
  (iv) the laboratory management's commitment to compliance with the content of these guidelines,
  (v) 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;

(b) the structure of the laboratory (organizational chart);
(c) the operational and functional activities pertaining to quality, so that the extent and the limits of the responsibilities are clearly defined;
(d) outline of the structure of documentation used in the laboratory quality management system;
(e) the general internal quality management procedures;
(f) references to specific procedures for each test;
(g) information on the appropriate qualifications, experience and competencies that personnel are required to possess;
(h) information on initial and in-service training of staff;
(i) a policy for internal and external audit;
(j) a policy for implementing and verifying corrective and preventive actions;
(k) a policy for dealing with complaints;
(l) a policy for performing management reviews of the quality management system;
(m) a policy for selecting, establishing and approving analytical procedures;
(n) a policy for handling of OOS results;
(o) a policy for the employment of appropriate reference substances and reference materials;
(p) a policy for participation in appropriate proficiency testing schemes and collaborative trials and the evaluation of the performance (applicable to national pharmaceutical quality control laboratories, but may be applied by other laboratories); and
(q) a policy to select service providers and suppliers.

2.3 The laboratory should establish, implement and maintain authorized written SOPs including, but not limited to, administrative and technical operations, such as:

(a) personnel matters, including qualifications, training, clothing and hygiene;
(b) the change control;
(c) internal audit;
(d) dealing with complaints;
(e) implementation and verification of corrective and preventive actions;
(f) the purchase and receipt of consignments of materials (e.g. samples, reagents);

(g) the procurement, preparation and control of reference substances and reference materials (*8*);
(h) the internal labelling, quarantine and storage of materials;
(i) the qualification of equipment (*11*);
(j) the calibration of equipment;
(k) preventive maintenance and verification of instruments and equipment;
(l) sampling, if performed by the laboratory, and visual inspection;
(m) the testing of samples with descriptions of the methods and equipment used;
(n) atypical and OOS results;
(o) validation of analytical procedures;
(p) cleaning of laboratory facilities, including bench tops, equipment, work stations, clean rooms (aseptic suites) and glassware;
(q) monitoring of environmental conditions, e.g. temperature and humidity;
(r) monitoring storage conditions;
(s) disposal of reagents and solvent samples; and
(t) safety measures.

2.4 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 and to apply corrective and preventive actions, if necessary. The audits should be carried out by trained and qualified personnel, who are independent of the activity to be audited. The quality manager is responsible for planning and organizing internal audits addressing all elements of the quality management system. Such audits should be recorded, together with details of any corrective and preventive action taken.

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

(a) reports on internal and external audits or inspections and any follow-up required to correct any deficiencies;
(b) the outcome of investigations carried out as a result of complaints received, doubtful (atypical) or aberrant results reported in collaborative trials and/or proficiency tests; and
(c) corrective actions applied and preventive actions introduced as a result of these investigations.

3. Control of documentation

3.1 Documentation is an essential part of the quality management system. The laboratory should establish and maintain procedures

to control and review all documents (both internally generated and from external sources) 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.

3.2 The procedures should ensure that:

(a) each document, whether a technical or a quality document, has a unique identifier, version number and date of implementation;
(b) appropriate, authorized SOPs are available at the relevant locations, e.g. near instruments;
(c) documents are kept up to date and reviewed as required;
(d) any invalid document is removed and replaced with the authorized, revised document with immediate effect;
(e) a revised document includes references to the previous document;
(f) old, invalid documents are retained in the archives to ensure traceability of the evolution of the procedures; any copies are destroyed;
(g) all relevant staff are trained for the new and revised SOPs; and
(h) quality documentation, including records, is retained for a minimum of five years.

3.3 A system of change control should be in place to inform staff of new and revised procedures. The system 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 by a signature that they are aware of applicable changes and their date of implementation.

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.

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

Note: The generally accepted retention period of shelf-life plus one year for a pharmaceutical product on the market and 15 years for an investigational product is recommended, unless national regulations are more stringent or contractual arrangements do not require otherwise.

4.3 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 facilities that provide a suitable environment that will prevent modification, damage or deterioration and/or loss. The conditions under which all original records are stored should be such as to ensure their security and confidentiality and access to them should be restricted to authorized personnel. Electronic storage and signatures may also be employed but with restricted access and in conformance with requirements for electronic records (*12–16*).

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.

5. Data-processing equipment

5.1 Detailed recommendations are provided in Appendix 5 to Annex 4 of the *Fortieth report of the WHO Expert Committee on Specifications for Pharmaceutical Preparations*: Supplementary guidelines in good manufacturing practice: validation. Validation of computerized systems (*12*).

5.2 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:

(a) computer software developed by the user is documented in sufficient detail and appropriately validated or verified as being suitable for use;

(b) procedures are established and implemented for protecting the integrity of data. Such procedures should include, but are not limited to, measures to ensure the integrity and confidentiality of data entry or collection and the storage, transmission and processing of data. In particular, electronic data should be protected from unauthorized access and an audit trail of any amendments should be maintained;
(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 and calibration data;
(d) procedures are established and implemented for making, documenting and controlling changes to information stored in computerized systems; and
(e) electronic data should be backed up at appropriate regular intervals according to a documented procedure. Backed-up data should be retrievable and stored in such a manner as to prevent data loss.

Note: For further guidance on validation of data-processing equipment, refer to documents published by the International Society for Pharmaceutical Engineering (*13, 14*), US Food and Drug Administration (*15*), European Commission (*16*) and the Official Medicines Control Laboratories Network of the Council of Europe (*17*).

6. Personnel

6.1 The laboratory should have sufficient personnel with the necessary education, training, technical knowledge and experience for their assigned functions.

6.2 The technical management should ensure the competence of all personnel operating specific equipment, instruments or other devices, who are performing tests and/or calibrations, validations or verifications. Their duties also involve the evaluation of results as well as signing analytical test reports and certificates of analysis (see Part three, sections 18.7–18.11 and 19).

6.3 Staff undergoing training should be appropriately supervised and should be assessed on completion of the training. Personnel performing specific tasks should be appropriately qualified in terms of their education, training and experience, as required.

6.4 The laboratory personnel should be permanently employed or under contract. The laboratory should ensure that additional technical and key support personnel who are under contract are supervised and

sufficiently competent and that their work is in accordance with the quality management system.

6.5 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.

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

(a) a head of laboratory (supervisor), who should have qualifications appropriate to the position, with extensive experience in medicines analysis and laboratory management in a pharmaceutical quality control laboratory in the regulatory sector or in industry. The head of laboratory is responsible for the content of certificates of analysis and analytical testing reports. This person is also responsible for ensuring that:
  (i) all key members of the laboratory staff have the requisite competence for the required functions and their grades reflect their responsibilities,
  (ii) the adequacy of existing staffing, management and training procedures is reviewed periodically,
  (iii) the technical management is adequately supervised;

(b) the technical management who ensure that:
  (i) procedures for performing calibration, verification and (re-) qualification of instruments, monitoring of environmental and storage conditions are in place and are conducted as required,
  (ii) regular in-service training programmes to update and extend the skills of both professionals and technicians are arranged,
  (iii) the safekeeping of any materials subject to poison regulation or to the controls applied to narcotic and psychotropic substances (see Part one, section 7.12) kept in the workplace is under the supervision of an authorized person,
  (iv) national pharmaceutical quality control laboratories regularly participate in suitable proficiency testing schemes and collaborative trials to assess analytical procedures or reference substances;

(c) analysts, who should normally be graduates in pharmacy, analytical chemistry, microbiology or other relevant subjects,

with the requisite knowledge, skills and ability to adequately perform the tasks assigned to them by management and to supervise technical staff;

(d) technical staff, who should hold diplomas in their subjects awarded by technical or vocational schools; and

(e) a quality manager (see Part one, section 1.3(j)).

7. Premises

7.1 The laboratory facilities are to be of a suitable size, construction and location. These facilities are to be designed to suit the functions and operations to be conducted in them. Rest and refreshment rooms should be separate from laboratory areas. Changing areas and toilets should be easily accessible and appropriate for the number of users.

7.2 The laboratory facilities should have adequate safety equipment located appropriately and measures should be in place to ensure good housekeeping. Each laboratory should be equipped with adequate instruments and equipment, including work benches, work stations and fume hoods.

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.

7.4 Special precautions should be taken and, if necessary, there should be a separate and dedicated unit or equipment (e.g. isolator, laminar flow work bench) to handle, weigh and manipulate highly toxic substances, including genotoxic substances. Procedures should be in place to avoid exposure and contamination.

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

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 Microbiological testing, if performed, should be contained in an appropriately designed and constructed laboratory unit. For further guidance see the draft working document *WHO guideline on good*

practices for pharmaceutical microbiology laboratories (reference QAS/09.297).

7.8 If in vivo biological testing (e.g. rabbit pyrogen test) is included in the scope of the laboratory activities then the animal houses should be isolated from the other laboratory areas with a separate entrance and air-conditioning system. The relevant guidance and regulations are to be applied (*18*).

Laboratory storage facilities

7.9 The storage facilities should be well organized for the correct storage of samples, reagents and equipment.

7.10 Separate storage facilities should be maintained for the secure storage of samples, retained samples (see Part three, section 20), reagents and laboratory accessories (see Part two, sections 10.13–10.14), reference substances and reference materials (see Part two, section 11). Storage facilities should be equipped to store material, if necessary, under refrigeration (2–8°C) and frozen (-20°C) and securely locked. All specified storage conditions should be controlled, monitored and records maintained. Access should be restricted to designated personnel.

7.11 Appropriate safety procedures should be drawn up and rigorously 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, such as hydrochloric acid, nitric acid, ammonia and bromine. Self-igniting materials, such as metallic sodium and potassium, should also be stored separately. 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.

7.12 Reagents subject to poison regulations or to the controls applied to narcotic and psychotropic substances should be clearly marked as required by national legislation. They should be kept separately from other reagents in locked cabinets. A designated responsible member of staff should maintain a register of these substances. The head of each unit should accept personal responsibility for the safekeeping of any of these reagents kept in the workplace.

7.13 Gases also should be stored in a dedicated store, if possible isolated from the main building. Wherever possible gas bottles in the laboratory are to be avoided and distribution from an external gas

store is preferred. If gas bottles are present in the laboratory they should be safely secured.

Note: Consideration should be given to the installation of gas generators.

8. Equipment, instruments and other devices

8.1 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.

8.2 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).

8.3 Equipment, instruments and other devices, including those used for sampling, should meet the laboratory's requirements and comply with the relevant standard specifications, as well as being verified, qualified and/or calibrated regularly (see Part two, section 12).

9. Contracts

Purchasing services and supplies

9.1 The laboratory should have a procedure for the selection and purchasing of services and supplies it uses that affect the quality of testing.

9.2 The laboratory should evaluate suppliers of critical consumables, supplies and services which affect quality of testing, maintain records of these evaluations and list approved suppliers, which have been demonstrated to be of a suitable quality with respect to the requirements of the laboratory.

Subcontracting of testing

9.3 When a laboratory subcontracts work, which may include specific testing, it is to be done with organizations approved for the type of activity required. The laboratory is responsible for periodically assessing the competence of a contracted organization.

9.4 When a laboratory performs testing for a customer and subcontracts part of the testing, it should advise the customer of the arrangement in writing and, if appropriate, gain his or her approval.

9.5 There should be a written contract which clearly establishes the duties and responsibilities of each party, defines the contracted work and any technical arrangements made in connection with it. The contract should permit the laboratory to audit the facilities and competencies of the contracted organization and ensure the access of the laboratory to records and retained samples.

9.6 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.

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

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

Part two. Materials, equipment, instruments and other devices

10. Reagents

10.1 All reagents and chemicals, including solvents and materials used in tests and assays, should be of appropriate quality.

10.2 Reagents should be purchased from reputable, approved suppliers and should be accompanied by the certificate of analysis, and the material safety data sheet, if required.

10.3 In the preparation of reagent solutions in the laboratory:

(a) responsibility for this task should be clearly specified in the job description of the person assigned to carry it out; and
(b) prescribed procedures should be used which are in accordance with published pharmacopoeial or other standards where available. Records should be kept of the preparation and standardization of volumetric solutions.

10.4 The labels of all reagents should clearly specify:

(a) content;
(b) manufacturer;
(c) date received and date of opening of the container;
(d) concentration, if applicable;
(e) storage conditions; and
(f) expiry date or retest date, as justified.

10.5 The labels of reagent solutions 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, as justified; and
(d) concentration, if applicable.

10.6 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; and
(e) standardization factor.

Note: The laboratory should ensure that the volumetric solution is suitable for use at the time of use.

10.7 In the transportation and subdivision of reagents:

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

Visual inspection

10.8 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.

10.9 Reagents that appear to have been tampered with should be rejected; however, this requirement may exceptionally be waived if the identity and purity of the reagent concerned can be confirmed by testing.

Water

10.10 Water should be considered as a reagent. The appropriate grade for a specific test should be used as described in the pharmacopoeias or in an approved test when available.

10.11 Precautions should be taken to avoid contamination during its supply, storage and distribution.

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

Storage

10.13 Stocks of reagents should be maintained in a store under the appropriate storage conditions (ambient temperature, under refrigeration or frozen). The store should contain a supply of clean bottles, vials, spoons, funnels and labels, as required, for dispensing reagents from larger to smaller containers. Special equipment may be needed for the transfer of larger volumes of corrosive liquids.

10.14 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.

11. Reference substances and reference materials

11.1 Reference substances (primary reference substances or secondary reference substances (*8*)) are used for the testing of a sample.

Note: 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.

11.2 Reference materials may be necessary for the calibration and/or qualification of equipment, instruments or other devices.

Registration and labelling

11.3 An identification number should be assigned to all reference substances, except for pharmacopoeial reference substances.

11.4 A new identification number should be assigned to each new batch.

11.5 This number should be marked on each vial of the reference substance.

11.6 The identification number should be quoted on the analytical worksheet every time the reference substance is used (see Part three, section 15.5). In the case of pharmacopoeial reference substances the batch number and/or the batch validity statement should be attached to the worksheet.

11.7 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 material (e.g. as an infrared reference substance or as an impurity reference substance for thin-layer chromatography);
(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;
(j) 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); and
(k) in the case of secondary reference substances prepared and supplied by the manufacturer, the certificate of analysis.

11.8 A person should be nominated to be responsible for reference substances and reference materials.

11.9 If a national pharmaceutical quality control laboratory is required to establish reference substances for use by other institutions, a separate reference substances unit should be established.

11.10 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.

11.11 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.

Retesting (monitoring)

11.12 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 (how often the container is opened and closed). More detailed information on the handling, storage and retesting of reference substances is given in the *WHO General guidelines for the establishment, maintenance and distribution of chemical reference substances* (*8*).

11.13 The results of these tests should be recorded and signed by the responsible analyst.

11.14 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. For evaluation of outcomes of retrospective checks and consideration of possible corrective actions, risk analysis should be applied.

11.15 Pharmacopoeial reference substances are regularly retested and the validity (current status) of these reference substances is available from the issuing pharmacopoeia by various means, e.g. web sites or catalogues. Retesting by the laboratory is not necessary, provided the reference substances are stored in accordance with the storage conditions indicated.

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

12.1 Each item of equipment, instrument or other device used for testing, verification and/or calibration should, when practicable, be uniquely identified.

12.2 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 when recalibration is due.

12.3 Laboratory equipment should undergo design qualification, installation qualification, operation qualification and performance qualification (for definitions of these terms see the Glossary) (*11*). Depending on the function and operation of the instrument, the design qualification of a commercially available standard instrument may be omitted as the installation qualification, operational qualification and performance qualification may be considered to be a sufficient indicator of its suitable design.

12.4 As applicable, the performance of equipment should be verified at appropriate intervals according to a plan established by the laboratory.

12.5 Measuring equipment should be regularly calibrated according to a plan established by the laboratory (*11*).

12.6 Specific procedures should be established for each type of measuring equipment, taking into account the type of equipment, the extent of use and supplier's recommendations. For example:

— pH meters are verified with standard certified buffer solutions before use;

— balances are to be checked daily using internal calibration and regularly using suitable test weights, and requalification should be performed annually using certified reference weights.

12.7 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 (including any relevant manuals provided by the manufacturer) should be readily available for use by the appropriate laboratory personnel together with a schedule of the dates on which verification and/or calibration is due.

12.8 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 other unique identification;
(c) the qualification, verification and/or calibration required;
(d) the current location, where appropriate;
(e) the equipment manufacturer's instructions, if available, or an indication of their location;
(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; and
(h) a history of any damage, malfunction, modification or repair.

It is also recommended that records should be kept and additional observations made of the time for which the equipment, instruments or devices were used.

12.9 Procedures should include instructions for the safe handling, transport and storage of measuring equipment. On reinstallation, requalification of the equipment is required to ensure that it functions properly.

12.10 Maintenance procedures should be established, e.g. regular servicing should be performed by a team of maintenance specialists, whether internal or external, followed by verification of performance.

12.11 Equipment, instruments and other devices, either subjected to overloading or mishandling, giving suspect results, shown to be defective or outside specified limits, should be taken out of service and clearly labelled or marked. Wherever possible they should not be used until they have been repaired and requalified.

12.12 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.

Note: For further guidance on calibration, verification of performance and qualification of equipment refer to:

- *Procedures for verifying and calibrating refractometers, thermometers used in determinations of melting temperatures and potentiometers for pH determinations and methods for verifying the reliability of scales for ultraviolet and infrared spectrophotometers and spectrofluorometers in* The International Pharmacopoeia (*19*);
- *Specific guidelines for qualification of equipment elaborated by the European Network of Official Medicines Control Laboratories* (*OMCL*) (*20*); and
- *General chapter of the* US Pharmacopeia *on Analytical instrument qualification* (*21*).

13. Traceability

13.1 The result of an analysis should be traceable, when appropriate, ultimately to a primary reference substance.

13.2 All calibrations or qualification of instruments should be traceable to certified reference materials and to SI units (metrological traceability).

Part Three. Working procedures

14. Incoming samples

Sections 14.1–14.3 are applicable to national pharmaceutical quality control laboratories.

14.1 Samples received by a laboratory may be for compliance testing or for investigative testing. Samples for compliance testing include routine samples for control, samples suspected of not complying with the specifications 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 sample is large enough to enable, if required, a number of replicate tests to be carried out (see Part three, section 14.3) and for part of the sample to be retained (see Part three, section 20).

14.2 Samples for investigative testing may be submitted by various sources including customs, police and medicines inspectors. These samples comprise suspicious, illegal or counterfeit substances or products. Usually, the primary objective of investigative testing is to identify the substance or the ingredient in the product and, if sufficient substance or product is available, to estimate the purity or content. Well-documented screening procedures should be in place as well as confirmatory analytical procedures to positively identify 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 (see Part three, section 18.10).

14.3 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; and
— the third for retention in case of dispute.

14.4 If the laboratory is responsible for sampling of substances, materials or products for subsequent testing then it should have a sampling plan and an internal procedure for sampling available to all analysts and technicians working in the laboratory. Samples should be representative of the batches of material from which they are taken and sampling should be carried out so as to avoid contamination and other adverse effects on quality, or mix-up of or by the material being sampled. All the relevant data related to sampling should be recorded.

Note: Guidelines for sampling of pharmaceutical products and related materials were adopted by the WHO Expert Committee on Specifications for Pharmaceutical Preparations at its thirty-ninth meeting (*22*).

Test request

14.5 A standard test request form should be filled out and should accompany 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.

14.6 The test request form should provide or leave space for 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, international nonproprietary name (INN) (if available) and brand name(s);
(d) dosage form and concentration or strength, the manufacturer, the batch number (if available) 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 size of the consignment from which it was taken, when appropriate;
(i) the expiry date (for pharmaceutical products) or retest date (for APIs and pharmaceutical excipients);
(j) the specification to be used for testing;
(k) a record of any further comments (e.g. discrepancies found or associated hazard); and
(l) the required storage conditions.

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

(a) the requirements are adequately defined and the laboratory has the capability and resources to meet them; and
(b) the appropriate tests and/or methods are selected and 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 kept.

Registration and labelling

14.8 All newly delivered samples and accompanying documents (e.g. the test request) 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. If applicable, a unique registration number should also be assigned to any incoming retained sample (see Part three, section 20).

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

14.10 A register should be kept, which may be a record book, a card file or data-processing equipment, 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 was forwarded.

Visual inspection of the submitted sample

14.11 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 fact should be recorded without delay on the test request form. Any queries should be immediately referred back to the provider of the sample.

Storage

14.12 The sample prior to testing, the retained sample (see Part three, section 20) and any portions of the sample remaining after performance of all the required tests should be stored safely, taking into account the storage conditions (*22*, *23*) specified for the sample.

Forwarding to testing

14.13 The specific unit to which the sample is sent for testing is determined by the person responsible.

14.14 The examination of a sample should not be started before the relevant test request has been received.

14.15 The sample should be properly stored until all relevant documentation has been received.

14.16 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.

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

14.18 Testing should be performed as described under Part three, section 17.

15. Analytical worksheet

15.1 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.

Purpose

15.2 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 (see Part three, sections 18.1–18.3).

Use

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

15.4 Analytical worksheets from different units relating to the same sample should be assembled together.

Content

15.5 The analytical worksheet should provide the following information:

(a) the registration number of the sample (see Part three, section 14.9);
(b) page numbering, including the total number of pages (and including annexes);
(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 of the test equipment used (see Part two, section 12.1);
(i) the identification number of any reference substance used (see Part two, section 11.5);
(j) if applicable, the results of the system suitability test;
(k) the identification of reagents and solvents employed;
(l) the results obtained;
(m) the interpretation of the results and the final conclusions (whether or not the sample was found to comply with the specifications), approved and signed by the supervisor; and
(n) any further comments, for example, for internal information (see Part three, section 17.1), or detailed notes on the specifications selected and the methods of assessment used (see Part three, section 15.9), or any deviation from the prescribed procedure, which should be approved and reported, or whether and when portions of the sample were forwarded to other units for special tests and the date on which the results were received.

15.6 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 where the data are available.

15.7 The completed analytical worksheet should be signed by the responsible analyst(s), verified and approved and signed by the supervisor.

15.8 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 (it should not be erased or made illegible) 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. The reason for the change should also be given on the worksheet (suitable procedures should be in place for amending electronic worksheets).

Selection of the specifications to be used

15.9 The specification necessary to assess the sample may be that given in the test request or master production instructions. If no precise instruction is given, the specification in the officially recognized national pharmacopoeia may be used or, failing this, the manufacturer's officially approved or other nationally recognized specification. If no suitable method is available:

(a) the specification contained in the marketing authorization or product licence may be requested from the marketing authorization holder or manufacturer and verified by the laboratory; or
(b) the requirements may be set by the laboratory itself on the basis of published information and any procedure employed is to be validated by the testing laboratory (see Part three, section 16).

15.10 For official specifications the current version of the relevant pharmacopoeia should be available.

Filing

15.11 The analytical worksheet should be kept safely together with any attachments, including calculations and recordings of instrumental analyses.

16. Validation of analytical procedures

16.1 All analytical procedures employed for testing should be suitable for the intended use. This is demonstrated by validation (*24*). Validation

also serves to establish acceptance criteria for system suitability tests which are subsequently employed for the verification of the analytical procedure before analysis.

16.2 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 Table 1 (in the development phase of an analytical procedure, robustness, i.e. 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.

Table 1

Characteristics to consider during validation of analytical procedures

Type of analytical Procedure	Identification	Testing for impurities		Assay
		Quantitative tests	Limit tests	• dissolution (measurement only) • content/potency
Characteristics				
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.

16.3 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. If the pharmacopoeial method is adapted for another use then it should be validated for such a use to demonstrate that it is fit-for-purpose.

16.4 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 analysed contribute to the system. Which system suitability tests are to be applied depends on the type of procedure to be used. System suitability tests are employed for the verification of pharmacopoeial methods or validated analytical procedures and should be performed prior to the analysis. Provided the system suitability criteria are fulfilled the method or procedure is considered to be suitable for the intended purpose.

Note: If a large number of samples is being analysed 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.

16.5 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.

Note: Further guidance on validation of analytical procedures is available in the following:

- *Guideline elaborated by the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH)* (*25*);
- *Guideline elaborated by the European Network of Official Medicines Control Laboratories (OMCL)* (*26*);
- *General chapters of the* US Pharmacopeia *on Validation of compendial procedures and on Verification of compendial procedures* (*27*).

17. Testing

17.1 The sample should be tested in accordance with the work plan of the laboratory after completion of the preliminary procedures. If this is not feasible the reasons should be noted, e.g. in the analytical worksheet (see Part three, section 15), and the sample should be stored in a special place which is kept locked (see Part three, section 14.12).

17.2 Specific tests required may need to be carried out by another unit or by a specialized external laboratory (see Part one, section 9). The responsible person should prepare the request and arrange 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 results of tests performed by subcontractors, these results should be identified as such.

17.3 Detailed guidance on official pharmacopoeial requirements is usually given in the general notices and specific monographs of the pharmacopoeia concerned. 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. Where system suitability criteria are defined in the method they should be fulfilled. Any deviation from the test procedure should be approved and documented.

18. Evaluation of test results

18.1 Test results should be reviewed and, where appropriate, 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 (all test data). 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 (see also Part one, section 2).

18.2 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 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; and
(g) ensure that original sample preparations are not discarded until the investigation is complete.

18.3 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 — no obvious cause can be identified — 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. However, further confirmation using another validated method, if available, may be advised.

18.4 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.

18.5 All individual results (all test data) with acceptance criteria should be reported.

18.6 All conclusions should be entered on the analytical worksheet (see Part three, section 15) by the analyst and signed by the supervisor.

Note: Further guidance on evaluation and reporting of test results is available in the following:

- *Guideline elaborated by the US Food and Drug Administration* (*5*);
- *Guideline elaborated by the European Network of Official Medicines Control Laboratories (OMCL)* (*28*).

Analytical test report

18.7 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; and
(b) based on the analytical worksheet (see Part three, section 15).

18.8 Any amendments to the original analytical test report will require the issue of a new corrected document.

18.9 Pharmacopoeial content limits are set taking into account the uncertainty of measurement, and the production capability and acceptance criteria for an analytical result should be predefined. Under presently applicable rules neither the pharmacopoeias nor the NMRAs require the value found to be expressed with its associated expanded uncertainty for compliance testing. However, when reporting the results of investigative testing, although the primary objective is to identify a substance in the sample, a determination of

its concentration may be also requested, in which case the estimated uncertainty should also be given.

18.10 Measurement uncertainty can be estimated in a number of ways, e.g.:

(a) by preparing an uncertainty budget for each uncertainty component identified in an analytical procedure (bottom-up approach);
(b) from validation data and control charts (*29*); and
(c) from the data obtained from proficiency tests or collaborative trials (top-down approach).

Note: Further guidance can be found in various guidelines (*9*, *10*, *30*, *31, 32*).

Content of the analytical test report

18.11 The analytical test report should provide the following information:

(a) the laboratory registration number of the sample;
(b) the laboratory test report number;
(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) an introduction giving the background to and the purpose of the investigation;
(g) 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;
(h) the results of all the tests performed or the numerical results with the standard deviation of all the tests performed (if applicable);
(i) a discussion of the results obtained;
(j) 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;
(k) the date on which the test(s) was (were) completed;
(l) the signature of the head of the laboratory or authorized person;
(m) the name and address of the original manufacturer and, if applicable, those of the repacker and/or trader;
(n) whether or not the sample(s) complies (comply) with the requirements;
(o) the date on which the sample was received;
(p) the expiry date or retest date, if applicable; and

(q) a statement indicating that the analytical test report, or any portion thereof, cannot be reproduced without the authorization of the laboratory.

19. Certificate of analysis

19.1 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; and
(l) the signature of the head of laboratory or other authorized person.

Note: The *Guideline on model certificate of analysis* was adopted by the WHO Expert Committee on Specifications for Pharmaceutical Preparations at its thirty-sixth meeting (*3*).

20. Retained samples

20.1 Samples should be retained as required by the legislation or 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.

Part four. Safety

21. General rules

21.1 General and specific safety instructions reflecting identified risk, should be made available to each staff member and supplemented regularly as appropriate (e.g. with written material, poster displays, audiovisual material and occasional seminars).

21.2 General rules for safe working in accordance with national regulations and SOPs normally include 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 protective clothing, including eye protection;
(e) special care should be taken, as appropriate, in handling, for example, 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 fully 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 safe handling of cylinders of compressed gases should be observed and staff should be familiar with the relevant colour identification codes;
(j) staff should be aware of the need to avoid working 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.

21.3 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 and particularly in the use of safety containers or baskets to avoid spillage from containers. Warnings, 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. 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.

21.4 Poisonous or hazardous products should be singled out and labelled appropriately, but it should not be taken for granted that all other

chemicals and biologicals are safe. 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. 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.

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Appendix

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

A list of equipment considered by the Committee to be adequate either for a first-stage or medium-sized pharmaceutical quality control laboratory is given in the table. In the case of a medium-sized laboratory, specific sections are devoted to a microbiology unit and pharmacognosy/phytochemistry unit. For a first-stage laboratory testing herbal medicines, the additional equipment recommended is specified in the table.

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

Table

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
Thin-layer chromatography spotter	1
Developing chambers	6 + 1[a]
Atomizers	6

First-stage laboratory (cont.)	
Ultraviolet viewing lamp	1
Disintegration test equipment (1 basket for 6 tablets)	1
Dissolution apparatus	1
Soxhlet extraction apparatus (60 ml)	3 + 1[a]
Micrometer callipers	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

Medium-sized laboratory (cont.)	
Microscope	1 or 2
Equipment for thin-layer chromatography	1
Thin-layer chromatography multispotter	1
Developing chambers	6
Atomizers	6
Ultraviolet viewing lamp	1
Potentiometric titrimeter	1
Micro-Kjeldahl equipment (including fume flasks)	1
Soxhlet extraction apparatus (60 ml)	3
Pycnometers	2
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
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	3 or 4

Medium-sized laboratory (cont.)	
Ultraviolet/visible spectrophotometer, double-beam	1
Infrared spectrophotometer with pellet press	1
Agate mortar with pestle	1
Gas chromatograph (flame ionization, direct and static head space injection)	1
Refractometer	1
Karl Fischer titrators (1 semi-micro and 1 coulometric for micro-determination of water)	2
Oxygen flask combustion apparatus	1
Disintegration test equipment (1 basket for 6 tablets)	1
Dissolution test equipment (for 6 tablets/capsules)	1
Optional items	
Atomic absorption spectrophotometer	1
Spectrofluorometer	1
High-performance liquid chromatograph detectors:	
— fluorescence	1
— diode-array	1
— refractive index	1
— evaporative light scattering (ELSD)	1
— charged aerosol (CAD)	1
— mass spectrometric (MS)	1
Gas chromatograph detectors:	
— conductivity	1
— nitrogen/phosphorous (NPD)	1
— mass spectrometric (MS)	1
Capillary electrophoresis equipment	1
Thin-layer chromatography scanner	1
Crushing strength tester	1
Friability tester	1
Viscometer	1
Ice machine	1
Solvent-recovery apparatus	1
Equipment for microbiology unit	
pH meter	1
Ultraviolet/visible spectrophotometer, single-beam	1
Microscopes (for bacteriology)	2

Medium-sized laboratory (cont.)	
Membrane filter assembly for sterility tests	1
Colony counter with magnifier	1
Laminar air flow unit	1
Hot-air sterilizer	1
Incubators, 60 litres	2 or 3
Anaerobic jar	1
Zone reader	1
Centrifuge	1
Water-bath (thermostatically controlled)	2
Autoclaves (100 litres, top-loading)	2
Refrigerators (340 litres)	2
Deep freeze	1
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 set
Microscope[b]	1
Soxhlet extraction apparatus	2 or 3
Water-bath	1
Heating mantles for flasks	1 or 2
Hot plates with magnetic stirrers	2
Equipment for thin-layer chromatography	1 or 2
Developing chambers	3 or 4
Desiccators	2
Rotary vacuum apparatus	1
Distillation equipment	1
Conical percolators	2 or 3
Apparatus for determination of water content by azeotropic method[b]	1
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 medicinal plant materials*. Geneva, World Health Organization, 1998.
[c] *WHO guidelines for assessing quality of herbal medicines with reference to contaminants and residues*. Geneva, World Health Organization, 2006.